Reduction of Organic Functional Groups Using Hypophosphites

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Université Libanaise

École Doctorale
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THÈSE POUR OBTENIR LE GRADE DE DOCTEUR
DE L'UNIVERSITÉ DE LYON ET DE L'UNIVERSITÉ LIBANAISE

En Chimie

École Doctorale de Chimie-École Doctorale des Sciences et Technologies

Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS)
Laboratoire de Catalyse, Synthèse et Environnement (CASYEN)
Laboratoire de Chimie Médicinale et des Produits Naturels (LCMPN)

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Présentée par Rim MOUSELMANI

Le 07 Novembre 2018

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”وَقُل رَّبِّ زِدْنِي عِلْمًا “

“Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world.”

Louis PASTEUR

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To my reason of being, my daughter Malika, you are my deepest motivation!

Abstratct/Resumé

Reduction of organic functional groups using hypophosphites

Recently, requirements in chemistry are changing fast, since sustainable development has retained more attention. Green chemistry principles have promoted chemists to develop chemical products and processes that reduce or eliminate hazardous substances. The research work described in this thesis is focused on the development of new reducing systems using hypophosphites as substitutes for traditional toxic reducing agents.

In order to achieve this goal, aromatic nitriles were reduced into the corresponding aldehydes by the formation of hydrogen gas and nickel nanoparticles upon combining a nickel precursor with calcium hypophosphite in the presence of base in a biphasic medium. Moreover, aromatic nitriles were reduced into primary amines using calcium hypophosphite and the heterogeneous catalyst palladium on carbon. The nature of the metal catalyst, additives, solvents, temperature, and concentrations were studied in details.

On the other hand, the well-known direct reductive amination of aliphatic and aromatic ketones was done for the first time using heterogeneous palladium on carbon, and ammonium hypophosphite which acts as a source of ammonia and as a reducing agent at the same time. During optimization different parameters were studied.

Réduction des groupes fonctionnels organiques utilisant des hypophosphites

Récemment, les exigences en chimie ont évolué rapidement, car le développement durable a retenu plus d'attention. Les principes de la chimie verte ont encouragé les chimistes à développer des produits chimiques et des procédés qui réduisent ou éliminent les substances dangereuses. Les travaux de recherche décrits dans cette thèse portent sur le développement de nouveaux systèmes réducteurs en utilisant des hypophosphites comme substituts aux agents réducteurs toxiques traditionnels.

Pour atteindre cet objectif, les nitriles aromatiques ont été réduits en aldéhydes correspondants par la formation du gaz de l'hydrogène et de nanoparticules de nickel en combinant un précurseur de nickel avec de l'hypophosphite de calcium en présence d'une base dans un milieu biphasique. De plus, les nitriles aromatiques ont été réduits en amines primaires en utilisant de l'hypophosphite de calcium et le catalyseur hétérogène palladium sur le carbone. La nature du catalyseur métallique, les additifs, les solvants, la température et les concentrations ont été étudiés en détail.

D'autre part, l'amination réductrice directe des cétones aliphatiques et aromatiques a été réalisée pour la première fois en utilisant du palladium hétérogène sur du carbone et de l'hypophosphite d'ammonium qui agit comme une source d'ammoniac et un agent réducteur en même temps. Au cours de l'optimisation, des différents paramètres ont été étudiés.

DISCIPLINE : Chimie

KEY-WORDS: Reduction, calcium hypophosphite, ammonium hypophosphite, nitrile, aldehyde, ketone, primary amine, reductive amination, nickel, palladium.

MOTS-CLES: Réduction, hypophosphite de calcium, hypophosphite d'ammonium, nitrile, aldéhyde, cétone, amine primaire, amination reductrice, nickel, palladium.

List of Abbreviations

Aq.	Aqueous	**DES**	Deep eutectic solvent
AcOH	Aceticacid	**DIPEA**	N,N-Diisopropylethylamine
Ac_2O	Acetic anhydride	**DME**	Dimethoxyethane
Ar	Aromatic	**DMC**	Double metal cyanide
Abs.	Absolute	**DIBAL-H**	Diisobutylammonium hydride
acac	acetylacetonate	**DCE**	Dichloroethane
Boc_2O	di-tert-butyldicarbonate	**dppe**	1,2-bis(diphenylphosphino) ethane
BER	Borohydride exchange resin	**d**	Days
BQC	2,2'-biquinoline-4,4'-dicarboxylicacid dipotassium salt	**DCM**	Dichloromethane
Bu	Butyl	**DRA**	Direct Reductive Amination
biPyr	2,2'-bipyridine	**EtOH**	Ethanol
Bmim	1-butyl-3-methyl imidazolium	**Et**	Ethyl
Conv.	Conversion	**EDG**	Electron donating group
CO	Carbonyl	**EWG**	Electron withdrawing group
cod	1,5-cyclooctadiene	**Equiv.**	Molar equivalent
CTH	Catalytic Transfer Hydrogenation	***ee***	Enantiomeric excess
$CDCl_3$	Deuterated chloroform	**Et_2O**	Diethylether
CPME	Cyclopentylmethylether	**EDTA**	Ethylenediaminetetraacetic acid
Cp	Bis(cyclopentadienyl)	**GC**	Gas Chromatography
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene	**h**	Hours
CBSA	Carbon-based solid acid	**HIPAs**	Heteropolyacids
CTFSA	2-choloro-1,1,2,2-tetrafluoro ethane-1-sulfinamide	**HMPA**	Hexanethyl phosphoramide
Cat.	Catalyst	**Hmim**	1-methyl imidazolium
DPPF	1,2-bis-(diphenylphosphino)	***i*-Pr**	Isopropyl

	ferrocene
IL	Ionic liquid
KHMDS	Potassium hexamethyldisilazane
KOH	Potassium hydroxide
LW	Leuckart-Wallach
mol%	Molar percentage
min	Minutes
MCM-41	Mobil Composition of Matter
MeOH	Methanol
MW	Microwave
MS	Molecular Seives
M	Molar
NiNPs	Nickel nanoparticles
$NaBHEt_3$	Sodium triethyl borohydride
n-BuOH	n-Butanol
NHS	N-heterocyclic carbene
OTf	Triflate
OAc	Acetate
OEt	Ethoxy
Pt/C	Platinum on carbon
Ph	Phenyl
Pd/C	Palladium on carbon
PCy_3	Tricyclohexylphosphine
PPh_3	Triphenylphosphine
PMHS	Polymethylhydrosiloxane
PS	Polymer supported
PtO	Platinum Oxide
Pyr	Pyridine
PEMB	5-ethyl-2-methyl pyridine
$Pic\text{-}BH_3$	α-picoline-borane
Ppyz	Piperazine
Red-Al	Sodium bis (2-methoxyethoxy) aluminium hydride
rt	Room temperature
Raney-Co	Raney cobalt
RA	Reductive Amination
Raney-Ni	Raney Nickel
[S]	Concentration of substrate in the considered solvent
$ScCO_2$	Super critical carbon dioxide
SET	Single Electron Transfer
sec	Second
sec.	Secondary
***t*-BuO-**	Tert-butoxide
TBAC	Tetrabutylammonium chloride
TDA	Tris(dioxa-3,6-heptyl)amine
THF	Tetrahydrofuran
TMDS	1,1,3,3-tetramethyldisiloxane
TBAF	Tetra-n-butylammonium fluoride
TMSCl	Trimethylsilylchloride
TPPTS	Tris sodium salt of trisulfonated triphenylphosphine
Ts-DPEN	*N*-tosyl-1,2-diphényl-1,2-éthylènediamine
UV	Ultraviolet
Wt.%	Weight percentage
1,2,3-TMP	1,2,3-trimethoxypropane
2-MeTHF	2-methyltetrahydrofuran

borane

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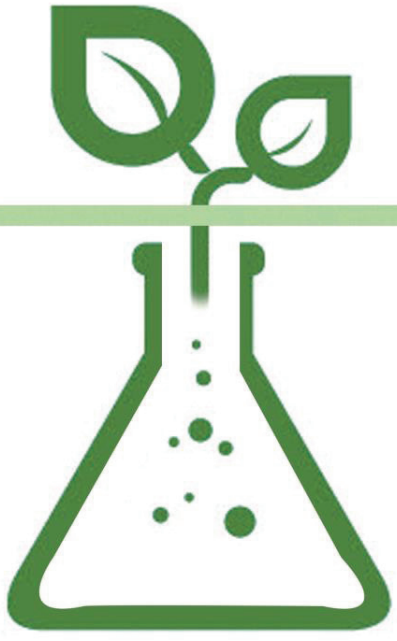
General Introduction



GENERAL INTRODUCTION

The knowledge of chemistry over the last two centuries has contributed to all major advances. Advances in medicine through drug discovery, the role of chemistry in hygiene, building, electronics, cosmetics, perfumes, energy, transportation, and agriculture. Industrialization has led to the development of mass consumption with ever-increasing volumes of products produced. On the other hand, the increase in population has led to greater demand of products, thus reducing resources and increasing pollution. Organic chemistry is currently dependent on the supply of oil and metals. However, the scarcity of these resources leads to an increase in the price of raw materials.

Twenty years ago it was clear that a new paradigm for efficiency in organic synthesis was needed. The introduction of the principles of clean or green chemistry and the underlying concepts of waste minimization, E factors, and atom efficiency provided an answer to this need. Now, twenty years later these concepts are accepted in academic and industrial circles on a worldwide basis. Industrial and academic research has focused on these concepts for the substantial reductions in waste generation by replacing outdated processes employing stoichiometric reagents with greener catalytic alternatives. The next phase of designing a more efficient and sustainable chemical industry will be the successful application of these green catalytic technologies in the efficient synthesis of organic chemicals from renewable resources.[1]

These new principles were applied in the development of new tools for the reduction of organic functional groups, one of the most important transformations in chemical industries, which requires the use of hazardous substances, such as aluminum and boron hydrides ($LiAlH_4$, DIBAL-H, Red-Al, $NaBH_4$, etc.), which are used in large scale by the chemical industries (2000 to 3000 tons per year), as a source of hydrides in reduction reactions. These hydrides are the subject of numerous books, chapters, reviews and are taught in both theoretical and practical courses in universities and schools. However, despite their efficiency in terms of selectivity and yields, there exist several drawbacks:

- They can potentially release hydrogen in a violent manner.
- They can react violently with water and air.
- The solvents used are often ethers (THF, glymes, diethyl ether, etc.) which are toxic and flammable.[2]
- Hydrolysis of aluminum and boron hydrides is highly exothermic with hydrogen production, which causes safety problems.
- Salts produced during hydrolysis,[3] such as borates or aluminum derivatives are potentially toxic and often considered to be partly responsible for Alzheimer's disease.[4]
- The salts resulting from the hydrolysis are difficult to separate from the products of the reaction, especially in the case of aluminum salts. A large amount of solvents are required to wash these salts generating significant waste.[5]

Therefore, with respect to green chemistry principles, they no longer meet the ecological, economic or social demands and their replacement is an objective.

Catalytic hydrogenation using molecular hydrogen is often preferred for ecological and economic reasons as the amount of waste produced is much lower (principles 2 and 8 of green chemistry). However, using this type of reducing agent is limited by the lack of selectivity, and the harsh reaction conditions (high temperatures and pressures) which require using special and expensive equipment. Reductions using isopropanol as hydrogen donor and solvent at the same time are in equilibrium, shifting the reaction in one direction needs large dilution.

In recent years, hydrosilanes (with a Si-H bond), derived from silicon and whose ultimate waste is silica, have been developed as an interesting alternative to conventional reduction methods. Alkyl-, alkoxy-, and chlorosilanes such as $PhSiH_3$, $(OEt)_3SiH$ and $HSiCl_3$ were the first studied because they have the advantage of being commercial and easy to prepare. Activated by transition metals or fluorides, they have been used for the reduction of several organic functions. However, despite interesting results, the cost of hydrosilanes, their low vapor pressure, their flammability and their toxicity limit their use on an industrial scale. In addition, some can generate, by

redistribution, silane (SiH_4) which is a dangerous, toxic, pyrophoric and explosive gas.[6]

These drawbacks can probably be overcome by using hydrosiloxanes (having Si-O-Si bonds). In our laboratory, polymethylhydrosiloxane (PMHS) and 1,1,3,3-tetramethyldisiloxane (TMDS) were activated by transition metals to reduce a wide variety of organic functions, but these reducers remain too expensive.[7]

In our laboratory, during studies dedicated to finding cleaner reducing agents, it was discovered that hypophopshites can selectively reduce some organic functional groups.[8] Actually, hypophosphites are produced on a very large scale, at low price and are known to be non-toxic. Moreover the byporoducts of these reagents are phosphorous derivatives, which are widely used as fertilizers.[9]

It was proved that a mixture of sodium hypophosphite and phosphinic acid in the presence of Pd/C in a biphasic water/2-MeTHF system, was able to reduce aromatic and aliphatic nitro groups to anilines and amines. On the other hand, aromatic ketones were selectively reduced into arylmethylenes or alcohols with hypophosphites and Pd/C depending on the selected conditions. An enantioselective version has also been demonstrated, allowing the reduction of (hetero) aromatic ketones.[10]

These encouraging results are part of the reason for our interest to study the reducing activity of these reagents in the reduction of other functional groups.

Achieving the aim of this PhD project will prove again the efficiency of hypophosphites as air stable, easy to handle, inexpensive and non-toxic reducing agents. Moreover, it will open the path for the reduction of a wide variety of organic functional groups.

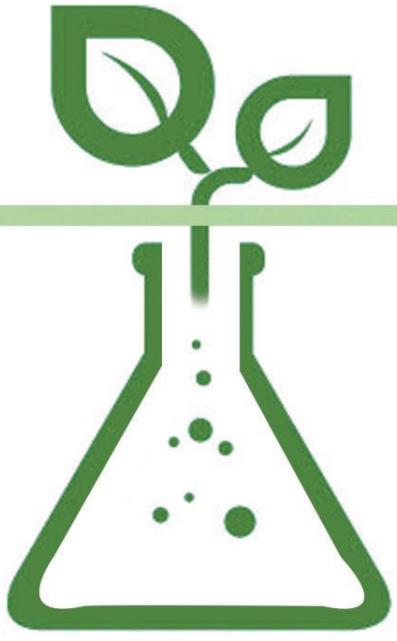
The work of this PhD presented in this thesis is composed of two main parts, briefly explained in the paragraph that follows:

Part one will discuss the reduction of nitriles using calcium hypophosphite and is divided into two distinct sections, the reduction of nitriles into aldehydes and into amines. At the beginning we will discuss general concepts and different methods present in literature for these two reactions. Then, our investigated two methods will be explained. Briefly, in method 1 we associate calcium hypophosphite with nickel acetate in a biphasic medium to produce aldehydes from nitriles. In method 2, the transformation of nitriles into primary amines was performed using calcium hypophosphite in the presence of Pd/C in aqueous medium.

In part two, we present another type of reaction, namely the reductive amination of ketones using ammonium hypophosphite. Similarly, different methodologies present in literature will be discussed, followed by our investigated methodology, where we associate ammonium hypophosphite with Pd/C in n-BuOH.

Part I: Reduction of Nitriles

Using Calcium Hypophosphite

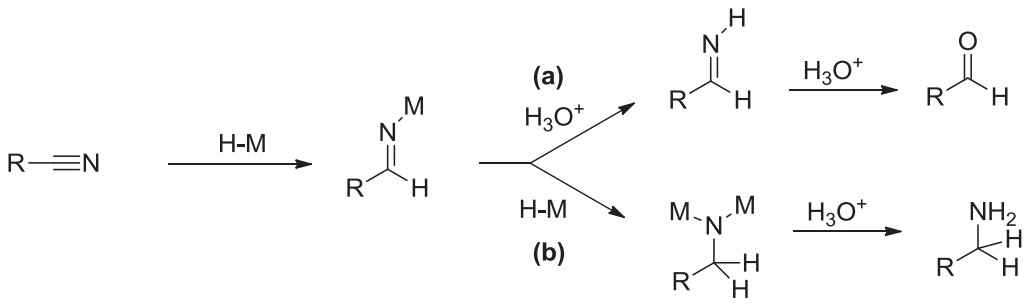


PART I. REDUCTION OF NITRILES USING CALCIUM HYPOPHOSPHITE

1. Introduction

With increasing demand for generic procedures for solution phase chemistry and a broad range of commercially available nitriles, it became desirable to devise an improved protocol for the reduction of surprisingly unreactive cyano group.[11] It has been less investigated so far compared to reductions of C=C, C=O, C=N, and NO_2 bonds. This is primarily due to the high redox potential of nitriles compared to other carboxylic acid derivatives and the low C-CN bond dissociation energy, which leads to undesired reductive decynations, side reactions *via* fragmentation to aklyl radicals and cyanide anions; and the instability of imine/ iminium intermediates under the reaction conditions, which resulted in alcoholysis, transimination or reductive polymerization pathways.[12]

We are interested in two possible pathways: **(a)** reduction of nitrile to imine which can be hydrolyzed to give the aldehyde; **(b)** Reduction of the intermediate imine into amine (scheme 1). The selectivity depends on the nature of the reducing agent, nature of catalyst and on the experimental conditions (temperature, time, solvent, additives, etc.).



Scheme 1. General reaction mechanism for the reduction of nitriles.

Although many methods exist today to selectively reduce this function, the search for new processes that are more environmentally friendly, less expensive, more selective and efficient for industrial development is still very important.

In this part, five sections will be discussed. The first debates the different methods from literature for the reduction of nitriles towards aldehydes and amines, the next two will present the work that was carried out in the laboratory for the reduction of nitriles into aldehydes and amines. The fourth will be a conclusion as well will discuss the future perspectives. Finally, the experimental work will be discussed in addition to the characterization data of the isolated products.

2. Bibliographic data

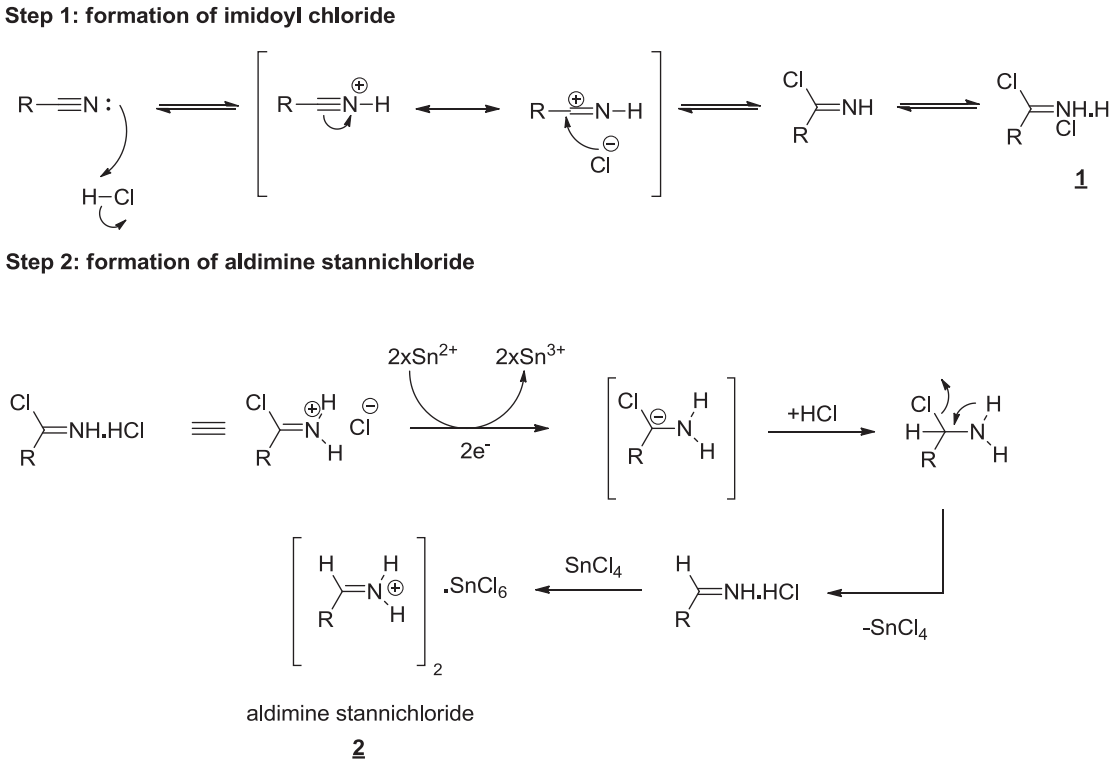
2.1. Reduction of nitriles into aldehydes

Rarely available in nature except in the singular structure of sugars, aldehydes are important intermediates in organic synthesis, but their chemoselective access is a challenging task, because the reaction requires to be stopped at the intermediate imine which is too reactive as mentioned before. Nevertheless selective methods have been found.

2.1.1. Stephen Reduction

Henry Stephen is one of the first researchers who described the reduction of nitriles into aldehydes in 1925.[13] He observed that when aromatic or aliphatic nitriles are added to a solution of stannous chloride (or tin chloride, $SnCl_2$) in saturated diethylether which is then saturated with dry hydrogen chloride, the corresponding imine hydrochloride is obtained. This latter salt, after hydrolysis in warm water, released the corresponding aldehyde in good yield. This conversion of nitriles into aldehydes by the combination of tin chloride/ HCl gas in an organic solvent is known as the " Stephen Reduction".

The Stephen Reduction takes place in three steps (Scheme 2): (1) the nitrile is dissolved in an inert solvent and the solution is then saturated with gaseous hydrochloric acid at 0ºC. The reaction between nitrile and the acid gives an imidoyl chloride **1**. (2) A solution of $SnCl_2$/ HCl in the reaction solvent is then added and reacted with imidoyl chloride **1** to give an aldimine stannichloride **2** which precipitates in the reaction medium. (3) Hydrolysis of this complex in hot water releases the corresponding aldehyde.



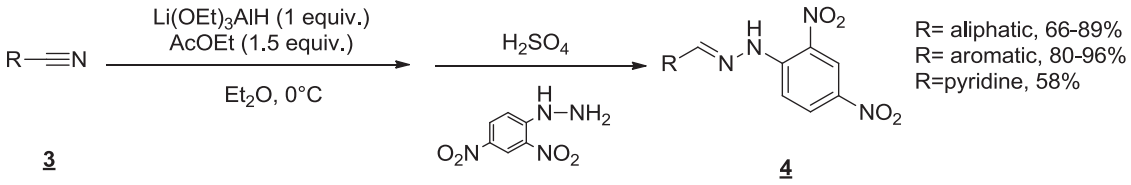
Scheme 2. Mechanism of Stephen reduction. [13]

This method is applicable for the reduction of aromatic nitriles leading to average yields of the corresponding aldehydes. Moreover, the yields with aliphatic nitriles are even lower. The reaction is sensitive to steric hindrance and the tolerance to other functional groups is low.

2.1.2. Reduction of nitriles to aldehydes using aluminum hydrides

Lithium Aluminum hydride, $LiAlH_4$, is known to be not efficient for the selective reduction of nitriles towards aldehydes, since it is highly reactive and it reacts rapidly on the intermediate imine rather than on nitrile leading to the formation of amine as the major product. [14] However, by replacing some of the hydrides with suitable substituents, the selectivity changes towards the aldehyde. A series of lithium aluminum (alkoxy) hydrides such as $Li(OEt)_2AlH_2$, $Li(MeO)_3AlH$, $Li(n\text{-}PrO)_3AlH$, and $Li(n\text{-}BuO)_3AlH$ were studied by H. C. Brown. [15] The best results were obtained with $Li(OEt)_3AlH$. Using this

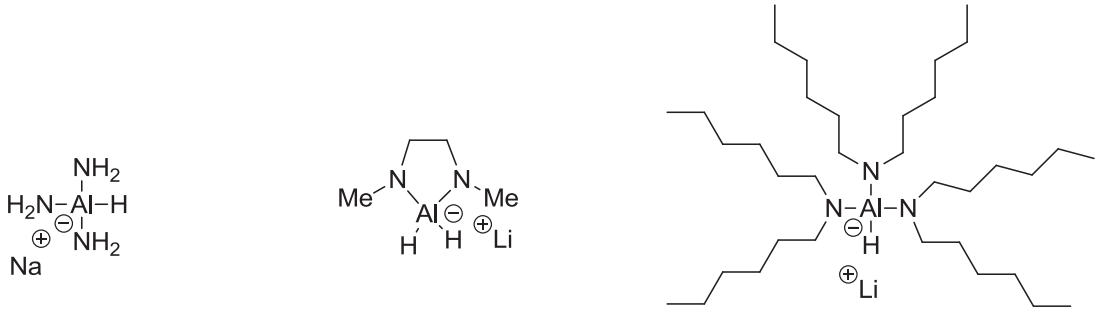
reagent, aromatic and aliphatic nitriles **3** have been reduced to the corresponding aldehydes and isolated as hydrazones **4** in higher yields (scheme 3). [15b]



3 **4**

Scheme 3. Reduction of nitriles **3** by $Li(OEt)_3AlH$ and the formation of aldehydes in the form of hydrazones **4**. [15b]

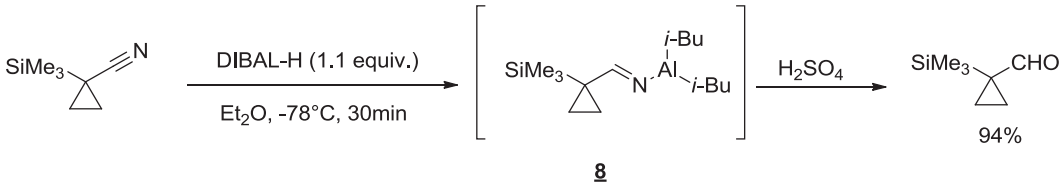
Aluminum, lithium or sodium (amino) hydrides such as $Na(NH_2)_3AlH$ **5**,[16] $Li[MeN(CH_2)_2NMe]AlH_2$ **6** [17] and $Li[(C_6H_{13})_2N]_3AlH$ **7** [18] were developed by N.M Yoon and J. S. Cha to reduce aromatic nitriles to aldehydes at room temperature (Figure 1).



5 **6** **7**

Figure 1. Structures of aluminum (amino) hydrides **5**, **6** and **7**. [16, 17, 18]

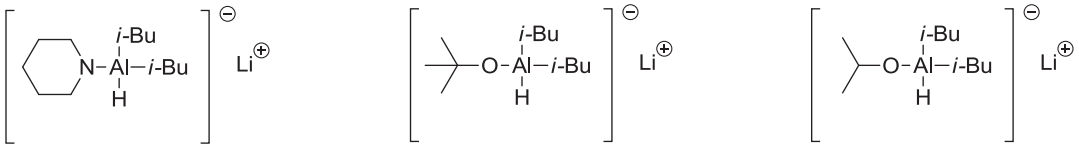
DIBAL-H has also been used for the successful reduction of nitriles into aldehydes. In a medium containing the nitrile at a very low temperature and in stoichiometric amounts, it leads to iminoaluminate **8**, which is finally hydrolyzed to the aldehyde (scheme 4). [19] This method is efficient and applicable on a variety of nitriles including aromatic, aliphatic, α,β-unsaturated nitriles and different derivatives of cyclopropane nitriles. [20]



8

Scheme 4. Example of the selective reduction of nitriles by DIBAL-H. [19]

Recently, new derivatives of DIBAL-H have been developed by D. K. An and his group for the reduction of nitriles at room temperature. From these derivatives Li[($C_5H_{10}N$)(*i*-Bu)$_2$AlH] **9** [21a] Li[(O*t*-Bu)(*i*-Bu)$_2$AlH] **10** [21b] and Li[(O*i*-Pr)(*i*-Bu)$_2$AlH] **11** (figure 2). [21c]

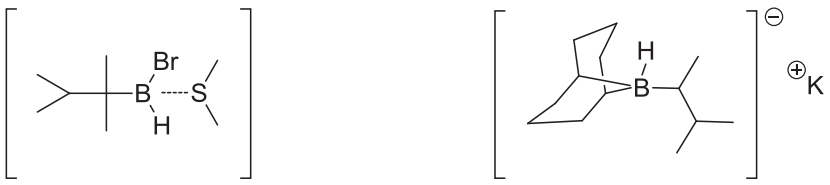


(LDBPA) **9** (LDDBA) **10** (LDBIPA) **11**

Figure 2. Derivatives of DIBAL-H developd by D. K. An.[21]

2.1.3. Reduction of nitriles into aldehydes using boron hydrides

Thexylbromoborane-methyl sulfide **12** (Figure 3) developed by J. S. Cha and his group,[22a] is able to reduce selectively nitriles into aldehydes. The yields of aldehydes are good in the aliphatic series. However, the yields of the aromatic series vary with substituents and the ring itself. On the other hand potassium 9-sec-amyl-9-boratabicyclo-[3,3,1] nonane **13** (Figure 3) developed by the same group, has the capability to reduce only aromatic nitriles in THF at room temperature.[22b]

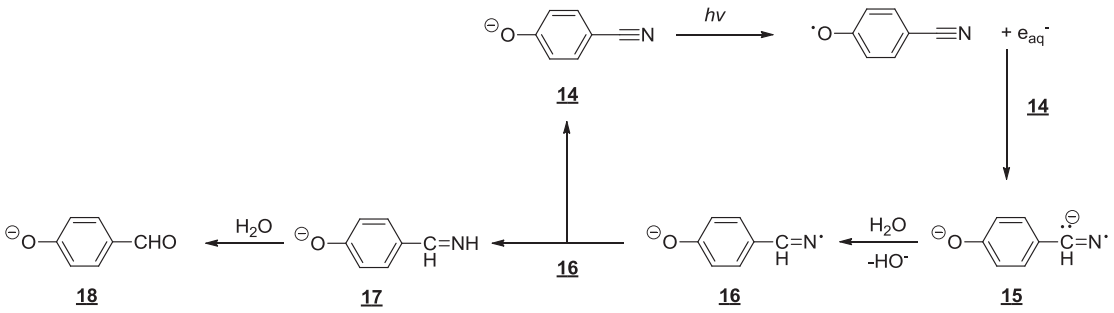


12 **13**

Figure 3. Structures of Thexylbromoborane-methyl sulfide **12** and potassium 9-sec-amyl-9-boratabicyclo-[3,3,1] nonane **13** developed by J. S. Cha.[22]

2.1.4. Reduction of nitriles into aldehydes using hydrated electrons

J. P. Ferris et al. have reported the convenient reduction of nitriles to aldehydes in aqueous media by photochemically generated hydrated electrons.[23] Substituted cyanophenols in the ortho, para and meta positions are the best substrates since they produce electrons themselves. They have demonstrated that the photo-excitation of the ion phenolate **14** gives a hydrated electron. Then it has been suggested that the radical species **15** is formed by the addition of the hydrated electron to the cyanophenolate **14**, followed by a rapid proton transfer. The two radical intermediates **16** are supposed to rearrange giving the starting nitrile **14** and the aldimine **17** which hydrolyze to give the aldehyde **18** in moderate yields (scheme 5). For different substrates, the presence of iodide anion is necessary as it is the source of electrons in the reaction medium. However, the yields remain low.

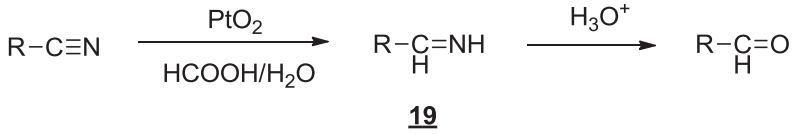


Scheme 5. Reduction of 4-hydroxybenzonitrile **14** to 4-hydroxybenzaldehyde **18** by photochemically generated hydrated electrons.[23]

2.1.5. Reduction of nitriles into aldehydes using aqueous formic acid

Aromatic nitriles can be reduced to the corresponding aldehydes using platinum (IV) oxide in aqueous formic acid with good to excellent yields.[24] Formic acid not only serves as a solvent, but also as a hydrogen source in the reaction. Reaction of formic

acid with platinum oxide liberates hydrogen and carbon dioxide,[25] and leads to formation of more reactive platinum species capable of reducing nitrile to the corresponding aldimine **19** which is rapidly hydrolyzed to aldehyde (scheme 6).



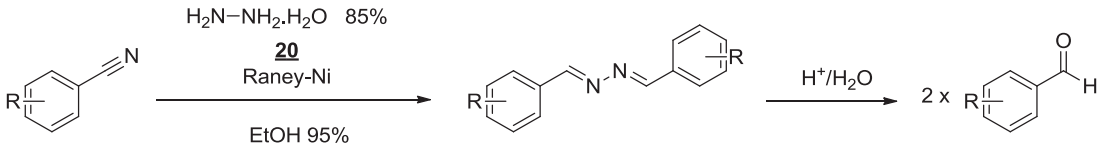
19

Scheme 6. Pathway of reduction of nitrile to aldehyde by platinum(IV) oxide in aqueous formic acid via the intermediate aldimine **19**.[24]

Moreover, for example 4-methoxy benzonitrile was converted to 4-methoxy benzaldehyde by refluxing with Raney nickel in 75% formic acid.[26]

2.1.6. Reduction of nitriles into aldehydes using hydrazine hydrate and Raney nickel

Hydrazine hydrate and Raney nickel are an effective combination to act as a reducing system. Raney nickel has been associated with different organic and inorganic compounds for this purpose as well. For the reduction of nitriles into aldehydes, in the presence of hydrazine hydrate **20**, benzonitrile derivatives **21** were converted to aldazines **22**, which are then hydrolyzed to aldehydes **23** (Scheme 7).[27]



21 **22** **23**

Scheme 7. Reduction of substituted benzonitriles **21** to aldehydes **23** by the reducing system H_2N-NH_2 **20**/ Raney-Ni via aldazines **22**.[27]

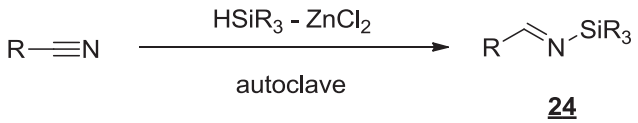
In this reaction system, hydrazine hydrate acts as a reducing agent (reduction of nitrile to imine) and as a reactant where it condenses on the imine to yield the aldazine.

2.1.7. Reduction of nitriles into aldehydes over Ru and Pt- loaded zeolites

Bifunctional zeolite catalysts can be used in the reductive hydrolysis of aromatic nitriles. For example benzaldehyde is produced selectively using Ru-H-beta catalyst, higher conversion is obtained with Pt-loading over NH_4-beta.[28] The reaction passes via the intermediate aldimine.

2.1.8. Reduction of nitriles into aldehydes using hydrosilanes

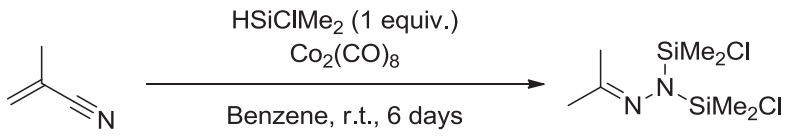
The catalytic hydrosilylation is a suitable tool for the selective reduction of nitriles. It exhibits improved chemo- and regioselectivity under milder conditions compared to conventionally used reducing agents mentioned before. In 1966, R. Calas et al. studied the action of trialkylhydrosilane in the presence of zinc chloride on various nitriles.[29] The major product in the reaction was N-silylimine **24** which is a protected form of aldehyde. Reactions were carried out under reflux and better yields were obtained in an autoclave. Under these conditions aliphatic nitriles bearing α-H give better yields than those having no hydrogen at this position (Scheme 8). On the other hand, yields were low with aromatic nitriles.



24

Scheme 8. Formation of N-silylimine **24** by the reaction of trialkylhydrosilane with nitrile in the presence of $ZnCl_2$.[29]

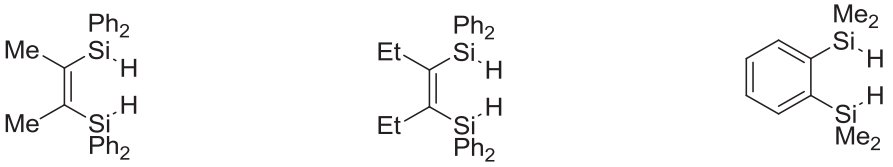
In 1970, A. J. Chalk reported the hydrosilylation of α,β-unsaturated nitriles using dimethylchlorosilane $HSiClMe_2$ in the presence of dicobalt octacarbonyl $Co_2(CO)_8$.[30] For example, with acrylonitrile, the α-adduct was the only product due to the reaction on the carbon-carbon double bond, whereas with methylacrylonitrile **25**, 1,4-addition took place to give the N,N-disilylenamine **26** in 20% yield after 6 days (Scheme 9).



25 **26**

Scheme 9. Hydrosilylation of methacrylonitrile **25** by the $HSiClMe_2/Co_2(CO)_8$ system.[30]

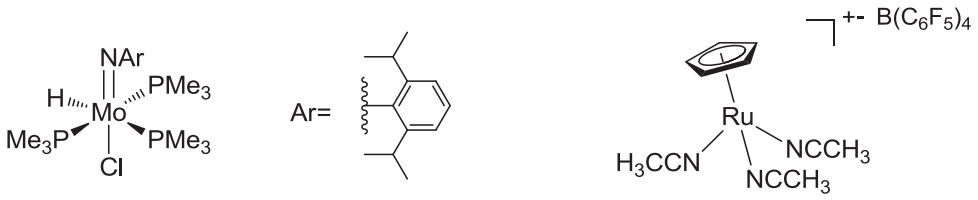
In the 1980's, R. J. P. Corriu studied the combination of bis-silanes **27**, **28** or **29** (Figure 4) and $Fe(CO)_5$ for the stoichiometric hydrosilylation of aliphatic nitriles into N,N-disilylenamines under UV-irradiation.[31] Bis-silanes were also associated with nickel,[32a] platinum,[32b] and rhodium[32c] catalysts to reduce nitriles bearing α-H into cyclic N-silylenamines and aromatic nitriles into cyclic N-silylimines. Moreover, ruthenium,[33a,b] tungsten,[33c,d] and molybdenum[33d,e] complexes bearing Si-H moiety have been designed for the stoichiometric hydrosilylation of nitriles but few examples have been published and yields were low to moderate.



27 **28** **29**

Figure 4. Structures of Bis-silanes developed by Corriu group.[31]

Recently, Nikinov and co-workers reported two complexes of molybdenum and ruthenium to catalyze the reduction of nitriles into imines (Figure 5). The molybdenum complex **30** catalyzed slowly the hydrosilylation of benzonitrile in the presence of $PhSiH_3$,[34a] so that the conversion was complete after 13 days. The cationic ruthenium complex $[Cp(iPr_3P)Ru(NCCH_3)_2][B(C_6F_5)_4]$ **31** with Me_2PhSiH shows better activity,[34b] since it allowed the reduction of aliphatic and aromatic nitriles into N-silylimines at room temperature in good to excellent yields, while preserving any other functional group including ketone, aldehyde, nitro, ether, ester groups and carbon-carbon double bond as well.

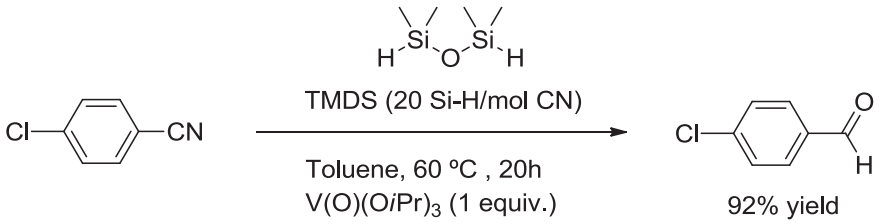


30 **31**

Figure 5. Molybdenum and ruthenium complexes developed by Nikonov.[34]

2.1.9. Reduction of nitriles into aldehydes using hydrosiloxanes

Hydrosiloxanes have been considered as a safer alternative for hydrosilanes. Recently our lab reported the first reducing system employing 1,1,3,3-tetramethyldisiloxane (TMDS) activated by an oxovanadium(V) complex, triisopropoxyvanadium(V) oxide, to reduce nitriles into aldehydes.[35] The reaction proceeds in toluene at 60 ºC with both aromatic and aliphatic nitriles to give the corresponding aldehydes in moderate to good yields (Scheme 10).

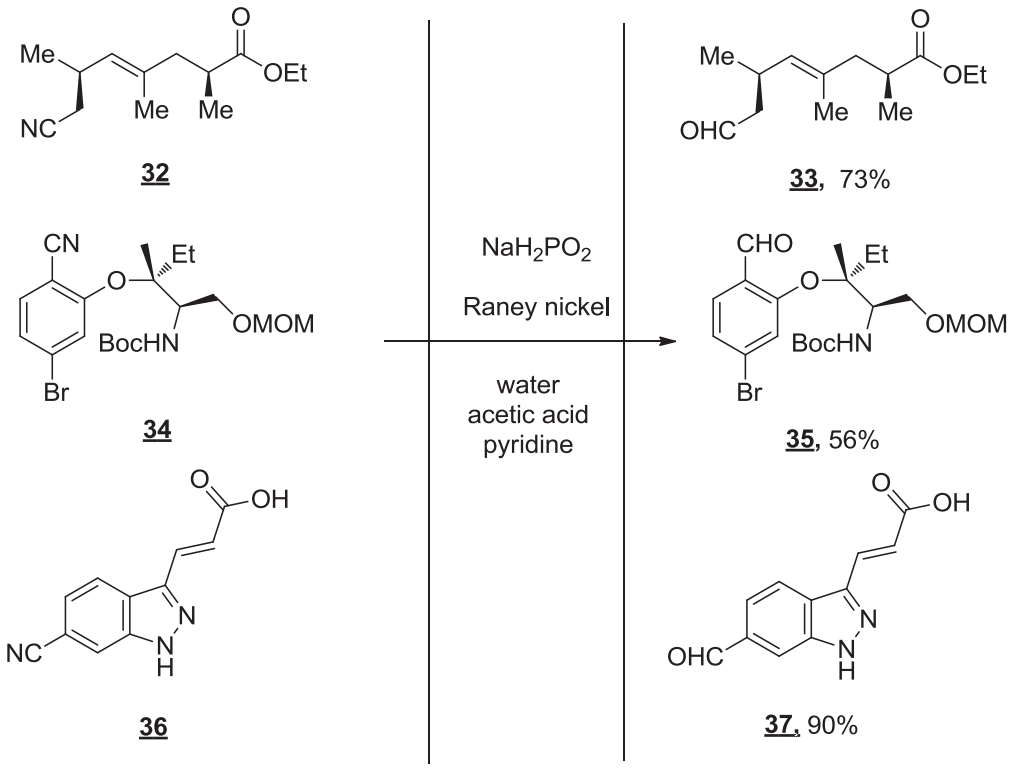


Scheme 10. Example of the reduction of nitriles to aldehydes by TMDS.[35]

2.1.10. Reduction of nitriles to aldehydes by hypophopshites

In the sixties, Staskun was the first to report the reduction of nitriles into aldehydes with hypophosphites and Raney-nickel as a catalyst in water/acetic acid/ pyridine solution (Scheme 11).[36] These conditions were thereafter widely applied to the reduction of aliphatic,[37] aromatic[38] and heteroaromatic[39] nitriles. As an example, Gosh used these conditions to reach compound **33**, which was an intermediate in the total synthesis of (+)-

Jasplakinolide.[40] The chemoselectivity of this reaction is well represented by the reduction of compound **34** into **35** for which no dehalogenation was observed.[41] Moreover, the reduction could be performed in the presence of a heteroaromatic ring, as in the transformation of **36** to **37** with 90% yield.[42]



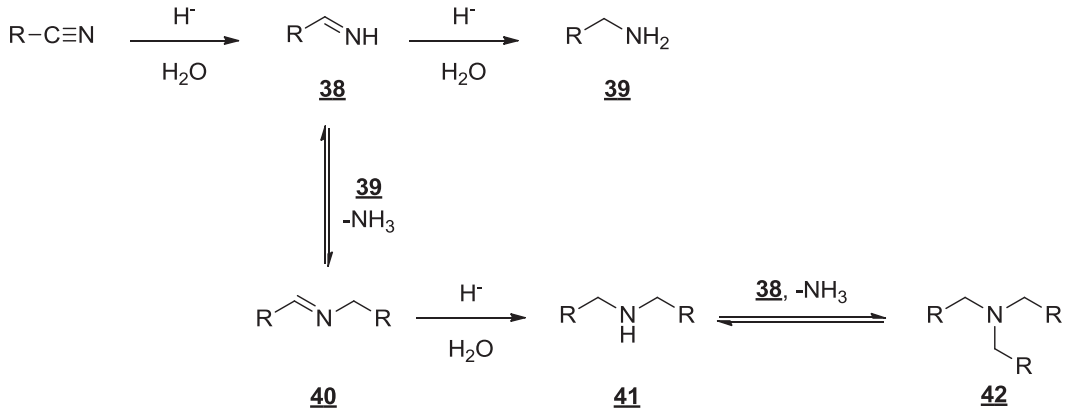
Scheme 11. Examples of the reduction of nitriles to aldehydes by hypophosphites.[40, 41, 42]

2.2. Reduction of nitriles into amines

Amines are valuable compounds that are present in many agrochemicals and drugs. In addition, many other industrially relevant products, such as dyes, detergents, solvents, additives or antifoaming agents contain amines in their structure.[43] More specifically, primary amines are highly relevant, owing to their straightforward functionalization.[44]

The reduction of nitrile to primary amine is usually accompanied with the formation of secondary and tertiary amines as by-products of the reaction (Scheme 12). The formation of the secondary amine **41** is due to the nucleophilic attack of the amine **39** previously

formed on the intermediate imine **38**. The elimination of ammonia leads to the secondary imine **40**, which is then reduced to the secondary amine **41**. Furthermore, the latter secondary amine **41** can also react with the imine **38** to result in the tertiary amine **42** in the same manner.

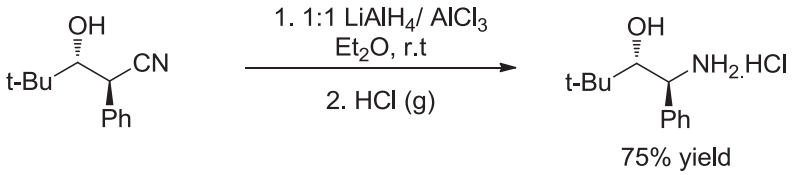


Scheme 12. Reduction of nitriles to amines and possible side reactions.

The selectivity of the respective amines depends on the structure of the substrate, the nature and the amount of the catalyst, basic and acidic additives, the reaction medium, and other reaction parameters. Among these factors, the nature of the catalyst appears to be the most important for determining the selectivity. Apparently, there are two possibilities to improve the chemoselectivity towards the primary amine: (1) a low concentration of the imine **38** is desirable to suppress formation of the secondary amine **41** and (2) the equilibrium between **38** and **40** should be shifted towards **39** by the addition of ammonia or an appropriate base.[45]

2.2.1. Reduction of nitriles into amines using aluminum hydrides

Among the metal hydrides used for the reduction of nitriles to amines are aluminum hydrides such as $LiAlH_4$, $NaAlH_4$, AlH_3 and Red-Al.[46] For example, P. R. Carlier and his group have reported the reduction of β-hydroxy nitrile **43** to the corresponding γ-amino alcohol **44** using $LiAlH_4/AlCl_3$ system (Scheme 13).[47]

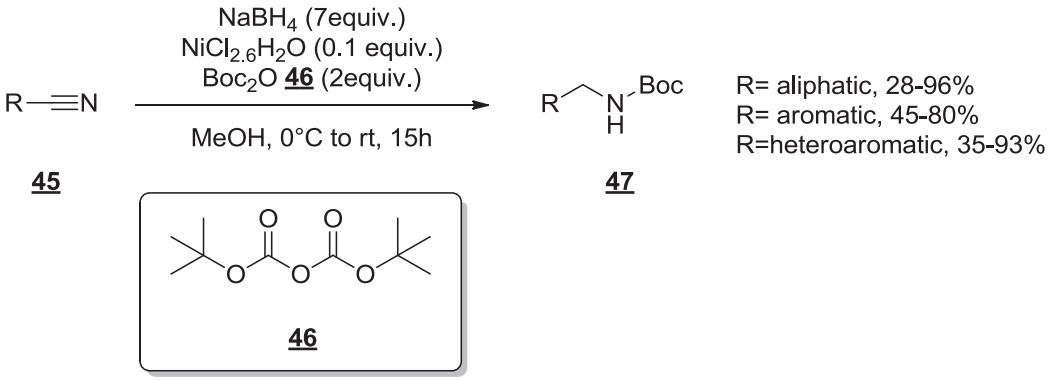


43 **44**

Scheme 13. Reduction of β-hydroxy nitrile **43** developed by P. R. Carlier.[47]

2.2.2. Reduction of nitriles into amines using boron hydrides

Borohydrides are also effective in reducing nitriles to amines. Diborane B_2H_6 has found numerous applications in reductions, where it works particularly well in the presence of $NiCl_2$.[48] The milder sodium borohydride is generally not strong enough to reduce cyano group, however, its behavior change upon association with transition metal salts, such as nickel,[49] and cobalt.[50] For example, in the presence of catalytic amount of nickel chloride, $NaBH_4$ reduces aromatic, aliphatic and (hetero) aromatic nitriles **45** to amines at r.t. in methanol. The addition of di-*tert*-butyl dicarbonate reagent (Boc_2O) **46** in the medium leads to the isolation of protected primary amines **47** (Scheme 14).[49c]



Scheme 14. Reduction of nitriles **45** in the presence of $NaBH_4$.[49c]

B. Singaram and his group developed another class of boron hydrides, the N,N-dialkylaminoborohydrides, such as $LiMe_2NBH_3$ **48** and $LiPyrrBH_3$ **49** (Figure 6), were able to reduce nitriles into the corresponding amines by refluxing in THF.[51] However,

these aminoboranes are not able to reduce nitriles in the presence of other functional groups including aldehydes, ketones, epoxides and esters.

$LiMe_2NBH_3$ **48** $LiPyrrBH_3$ **49**

Figure 6. Structures of N,N-dialkylaminoborohydrides developed by B. Singaram.[51]

2.2.3. Reduction of nitriles into amines by catalytic hydrogentation

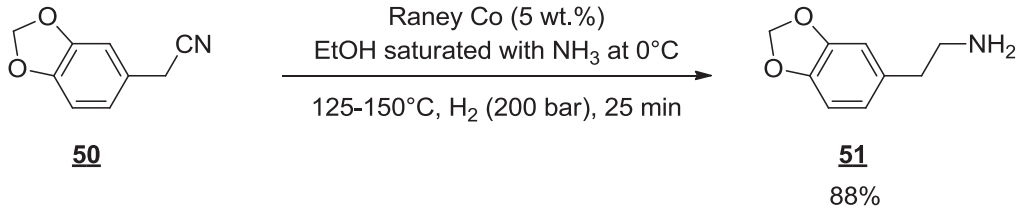
Catalytic hydrogenations are of great importance in organic synthesis and play a key role in the production of numerous bulk products and intermediates in the chemical industry. From an ecological point of view, reductions using molecular hydrogen as reducing agent represent one of the most efficient and atom-economical transformations.[52] In general, heterogeneous catalysts are well established in the hydrogenation of non-demanding polar functional groups, which often takes place at high temperatures and/or pressures.[53] The complementary development of well-defined homogeneous complexes that allow for selective reduction under milder conditions also constitute a cutting-edge endeavor in modern catalyst design.[54]

2.2.3.1.Heterogeneous catalysis

2.2.3.1.1. Raney Nickel and cobalt catalysts

Among various metallic catalysts, nickel and cobalt have been widely used for the hydrogenation of nitriles to primary amines. In general, cobalt catalysts are supposed to be more selective than nickel in the formation of primary amines, although nickel catalysts are usually more active than cobalt ones.[55] For example the reduction of nitrile **50** gave amine **51** in 88% yield after 25 min. using Raney cobalt in ethanol-ammonia at

125-150°C and under 20 Mpa (200 bar) (Scheme 15).[56] Recently in 2016, Beller group developed a new heterogeneous cobalt catalyst system supported on α-Al_2O_3 for the reduction of aromatic as well as aliphatic nitriles to primary amines under mild conditions.[57]



50 **51**

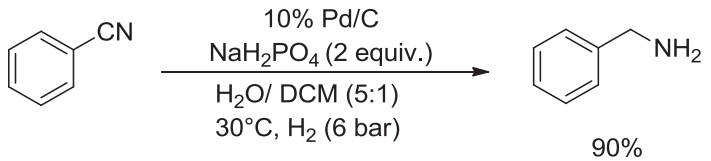
88%

Scheme 15. Reduction of nitrile **50** to primary amine **51** by heterogeneous catalytic hydrogenation using Raney-Co.[56]

With respect to Raney nickel, the most widely used reaction at the industrial level is the reduction of adiponitrile in the presence of Raney nickel to give either 1,5-hexanediene,[58] (synthesis of nylon-6,6) or 6-aminohexanenitrile,[59] (synthesis of caprolactam, precursor of nylon-6).

2.2.3.1.2. Palladium catalysts

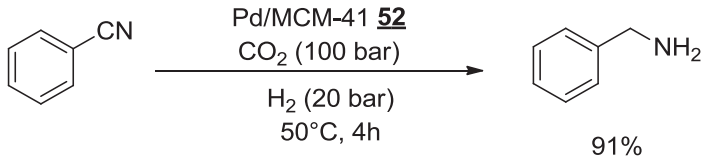
Heterogeneous catalytic hydrogenation of nitriles over palladium catalyst is also effective to obtain high yields of primary amines. For example in 2005, the group of Hegedîs reported the liquid phase heterogeneous catalytic hydrogenation of benzonitrile to benzylamine under mild reaction conditions (30°C, 6 bar) over Pd/C in a mixture of two immiscible solvents H_2O/DCM and in the presence of sodium dihydrogen phosphate NaH_2PO_4 (Scheme 16).[60]



90%

Scheme 16. Hydrogenation of benzonitrile using Pd/C.[60]

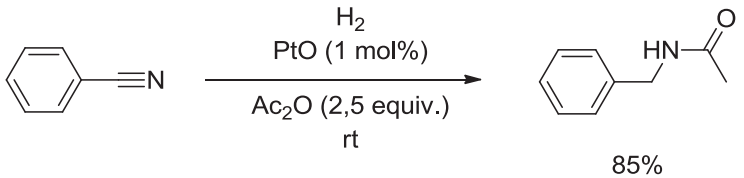
In 2010, Suzuki and his group explored for the first time the reduction of benzonitrile to benzylamine in 91% selectivity using 2 Mpa H_2 (20 bar) in super critical carbon dioxide ($scCO_2$) over palladium catalyst **52** (Scheme 17).[61] By tuning the CO_2 pressure, it is possible to obtain benzylamine or dibenzylamine. For instance, at lower pressure, CO_2 acts as a protecting agent, leading to the formation of primary amine. However, at higher pressure, the yield of primary amine as well as the solubility of the imine intermediate in CO_2 increases, which leads to more interaction between the two, resulting in high selectivity of the dibenzyl amine. This process has been extended to the hydrogenation of a series of different nitriles.



Scheme 17. Hydrogenation of benzonitrile in $scCO_2$.[61]

2.2.3.1.3. Platinum catalysts

Another precious metal which has been used in the heterogeneous catalytic hydrogenation of nitriles into amines is platinum. For example, when the hydrogenation takes place in the presence of platinum oxide, adding HCl or acetic anhydride to the medium make it possible to trap the previously formed primary amine and thus improving the selectivity of the reaction (Scheme 18).[62]

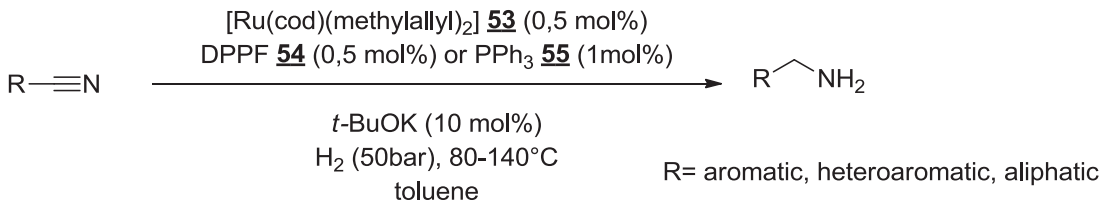


Scheme 18. Hydrogenation of benzonitrile by heterogeneous catalytic hydrogenation with PtO.[62]

2.2.3.2. Homogeneous Catalysis

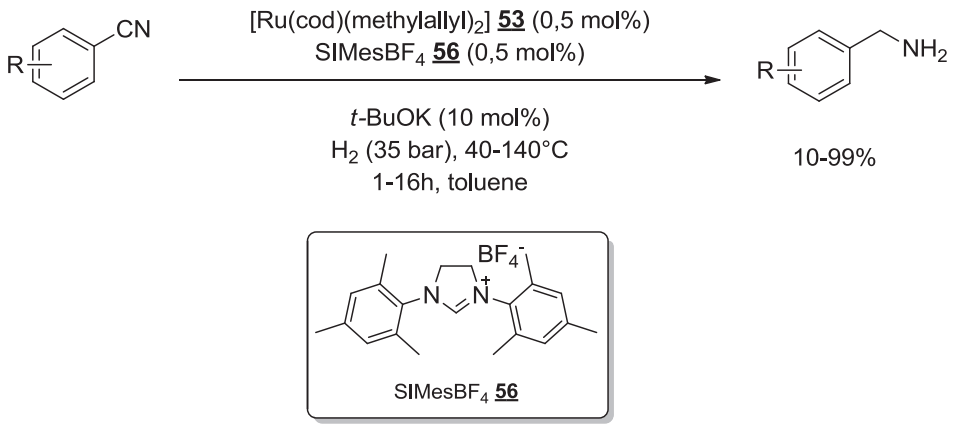
2.2.3.2.1. Ruthenium catalysts

Early studies described the hydrogenation of nitriles with $Fe(CO)_5$ and $Ni(CO)_4$ at high temperature/pressure (~200°C, ~140 bar H_2).[63] Later on, $Ru(PPh_3)_3Cl_2$ and Ru(CO)HCl were later disclosed for this transformation in another industrial patent by Dewhirst, where the reduction proceeds at milder reaction conditions (130°C, 40 bar H_2).[64] In 2002, Hidai and co-workers synthesized amidoruthenium complexes and used them for the selective reduction of benzonitrile in the presence of PCy_3 (PCy_3=tricyclohexylphosphine).[65] Subsequently, Beller's group developed two catalytic systems by applying [Ru(cod)(methylallyl)$_2$] **53** as precursor and DPPF [1,2-bis-(diphenylphosphino)ferrocene] **54** or PPh_3 (triphenylphosphine) **55** as ligand (Scheme 19).[66] Aromatic, heteroaromatic and alkyl nitriles were reduced using these systems.



Scheme 19. Hydrogenation of nitriles using ruthenium/DPPF or PPh_3 systems.[66]

Furthermore, the same group performed the selective hydrogenation of aromatic nitriles by applying a combination of the ruthenium precursor **53** in the presence of $SIMesBF_4$ **56** and additional base (Scheme 20).[67]

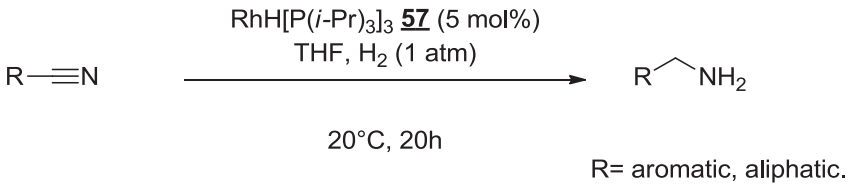


Scheme 20. Hydrogenation of aromatic nitriles using Ru/carbine-catalyzed system.[67]

It should be noted that the presence of base *t*-BuOK increases the selectivity of the reaction towards primary amine and strongly inhibits the formation of secondary amines. Ruthenium hydride complexes were also developed for the reduction of nitriles to amines.[68]

2.2.3.2.2. Rhodium catalysts

In 1979, Yoshida, Okano, and Otsuk explored rhodium(I) hydrides for the first time for the selective hydrogenation of nitriles to the corresponding primary amines under ambient conditions.[69] For example RhH[P(*i*-Pr)$_3$]$_3$ **57** proved to hydrogenate aromatic and aliphatic nitriles to give the corresponding primary amines with excellent yields up to 99% (Scheme 21).

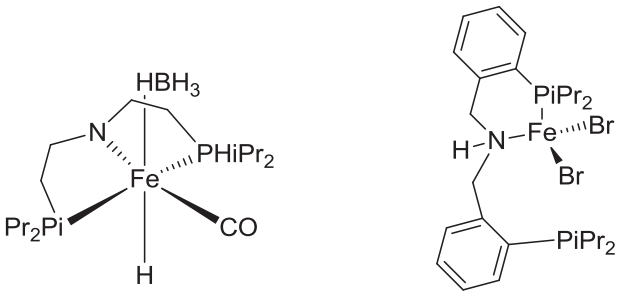


Scheme 21. Hydrogenation of nitriles using rhodium catalyst.[69]

It is noted that complexes with other precious metals including Ir [70] and Re[71] have been used for this type of hydrogenation as well.

2.2.3.2.3. Iron catalysts

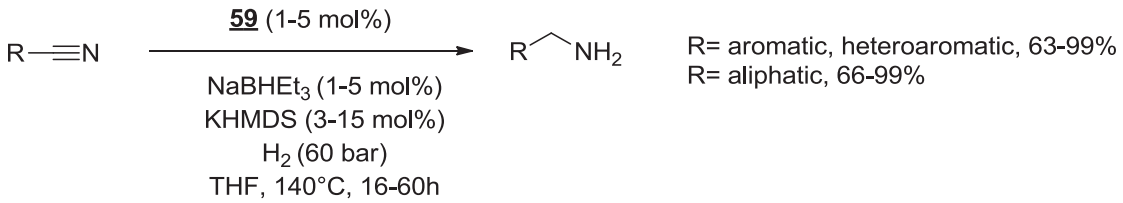
Nowadays one of the major goals in catalysis is the replacement of previously mentioned precious metals by inexpensive and less toxic non-noble metals.[72] In 2014, Beller group reported an aliphatic PNP-pincer based iron catalyst **58** for the hydrogenation of nitriles to primary amines.[73] Two years later, D. Milstein and co-workers developed another novel iron complex **59** (Figure 7) based on a novel PNP pincer ligand as well.[74]



58 **59**

Figure 7. Fe based catalysts for homogeneous hydrogenation of nitriles to primary amines.[73,74]

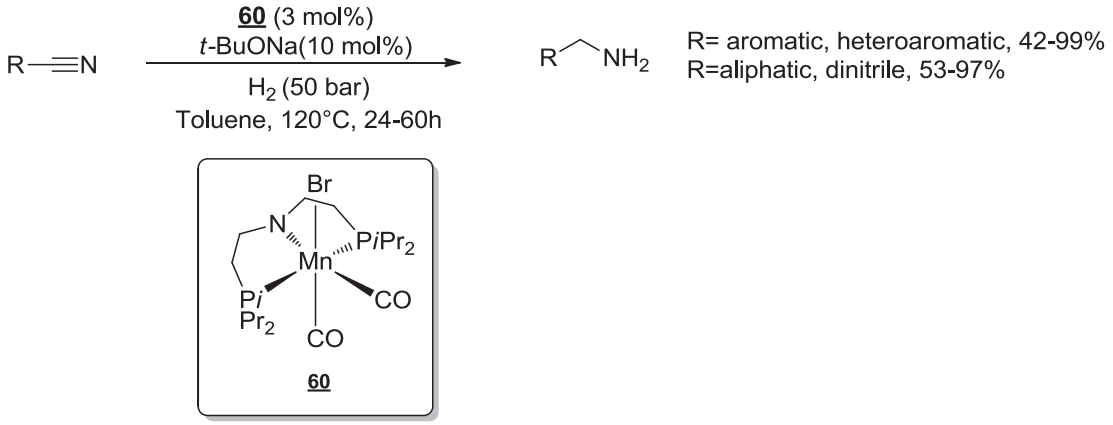
Complex **59** in the presence of $NaBHEt_3$ as a hydride source, and potassium hexamethyldisilazane (KHMDS) as a base, effectively catalyzed the hydrogenation of various heteroaromatic, benzylic and aliphatic nitriles (Scheme 22).[74]



Scheme 21. Hydrogenation of nitriles using iron complex **59**.[74]

2.2.3.2.4. Manganese Complexes

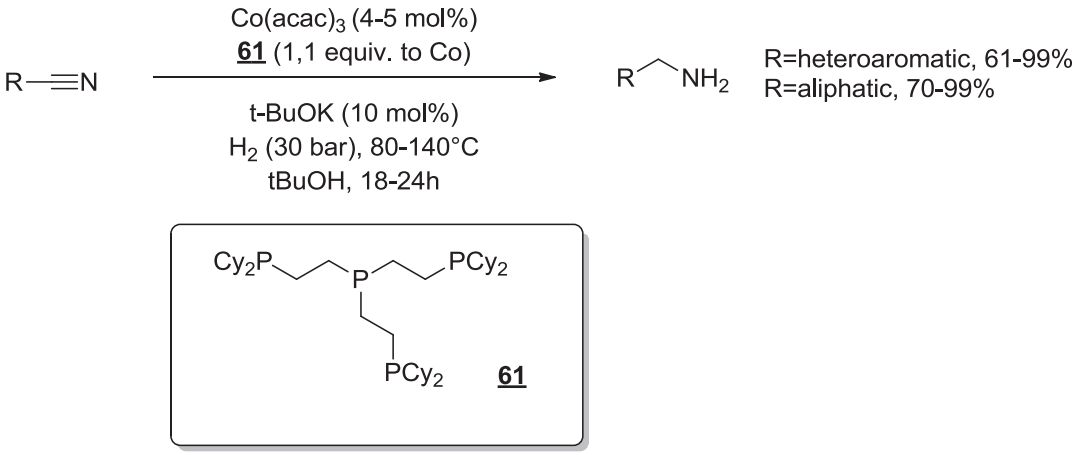
Recently in 2016, Beller group described the synthesis and application of manganese pincer complex **60** in the catalytic hydrogenation of aromatic, aliphatic and dinitriles (Scheme 22).[75]



Scheme 21. Hydrogenation of nitriles and dinitriles using manganese complex **60**.[75]

2.2.3.2.5. Cobalt catalysts

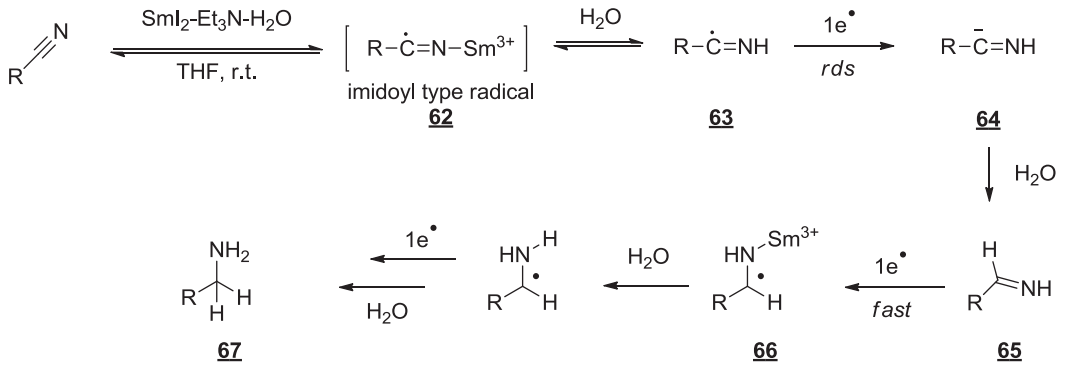
Another non-noble metal is cobalt. In 2017, Beller group developed a new cobalt/tetradentate phosphine catalyst system for the synthesis of primary amines from nitriles.[76] $Co(acac)_3$ in combination with ligand tris[2-(dicyclohexylphosphino) ethyl]phosphine **61** efficiently catalyzed the selective hydrogenation of a wide range of heteroaromatic ($Co(acac)_3$ 4 mol%, 80-120°C, 18h) and aliphatic nitriles ($Co(acac)_3$ 5 mol%, 140°C, 24h) to give the corresponding amines (Scheme 22). Mechanistic investigations indicated a strong dependence on temperature for the formation of the active catalytic species **61**.



Scheme 22. Hydrogenation of nitriles using Co/**61** catalytic system.[76]

2.2.4. Reduction of nitriles to amines by single electron transfer (SET)

Recently, Procter and co-workers described the first reduction of aromatic and aliphatic nitriles to primary amines under single electron transfer conditions using SmI_2 (Kagan's reagent)[77] activated by Lewis base.[78] They demonstrated that the reaction proceeds through the generation of imidoyl-type radicals **62** which was formed in equilibrium with the imine radical **63**. Subsequently, single electron transfer (SET) to the imine radical **63** generated a carbamine anion **64**, which underwent a protonation resulting in the formation of the imine **65**. In the next step, a further SET to the imine **65** led to the formation of an Sm^{3+} intermediate **66** which upon subsequent protonation furnished the final product **67** (Scheme 23).

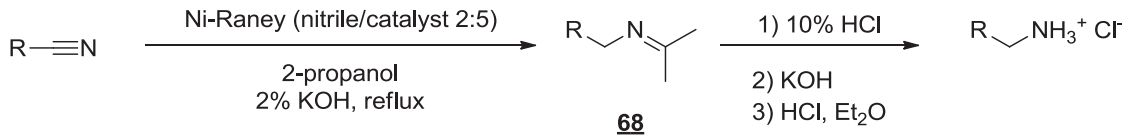


Scheme 23. Electron transfer reduction of nitriles using SmI_2-Et_3N-H_2O.[78]

2.2.5. Reduction of nitriles to amines by catalytic transfer hydrogenation (CTH)

Complementary to catalytic hydrogenations with molecular hydrogen, the use of transfer hydrogenation reagents allows for reductions under ambient conditions without the need for any special high pressure equipment.[79] This is of special interest to organic synthesis as well as fine chemical production in batch processes.

In 2002, D.C. Gowda reported the CTH of nitriles using Raney nickel and hydrazinium monoformate (N_2H_4.HCOOH) as a hydrogen donor in a medium containing methanol at room temperature.[80] Later in 2003, R. C. Mebane and his group described the CTH of aliphatic nitriles to the corresponding primary amines with Raney nickel and 2-propanol as the hydrogen donor in the presence of 2% KOH.[81] In this reaction N-isoproplidene amine **68** formed as a result of the condensation between the primary amine arising from nitrile reduction and acetone resulting from the oxidation of 2-propanol during CTH reaction (Scheme 24). The N-isopropylidene amine **68** is then hydrolyzed to primary amine with dilute HCl and isolated as hydrochloride salt. Actually, the presence of KOH suppresses the reduction of **68** into symmetrical amine.

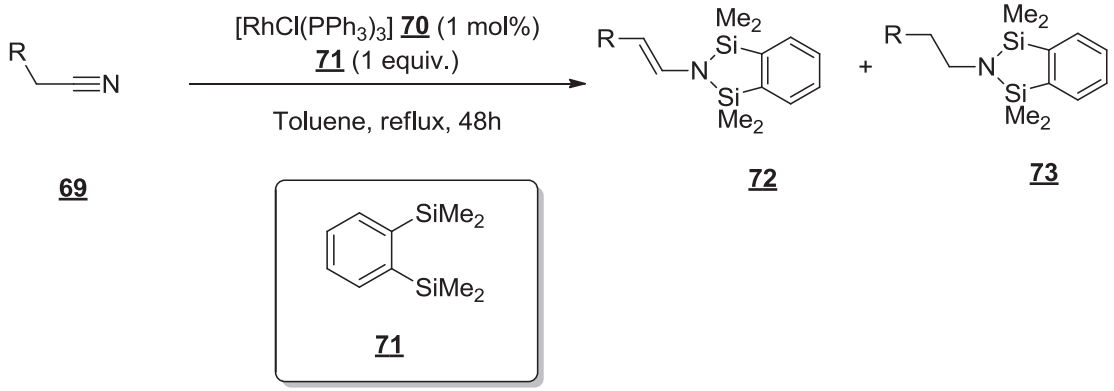


Scheme 24. Catalytic transfer hydrogenation of aliphatic nitriles using 2-propanol/Ni-Raney.[81]

In 2013, Beller and co-workers explored CTH of aromatic and aliphatic nitriles to the corresponding primary amines using 2-butanol as a hydrogen donor.[82] The same group, later studied the CTH of (hetero)aryl nitriles to amines using ammonium formate (NH_4HCO_2) in the presence of Pd/C.[83]

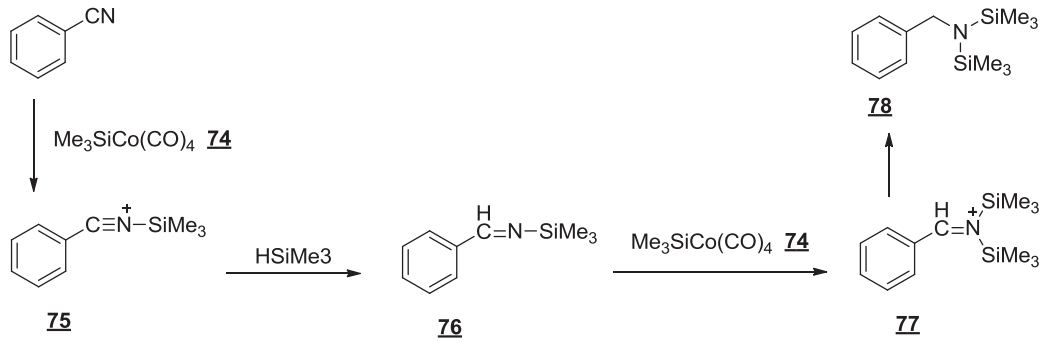
2.2.6. Reduction of nitriles to amines using hydrosilanes

For the first time, Corriu and co-workers reported transition metal catalyzed hydrosilylation of nitriles using Wilkinson's catalyst.[84] In the presence of Wilkinson catalyst [$RhCl(PPh_3)_3$] **70** and 1,2-bis(dimethylsilylbenzene) **71**, aliphatic nitriles **69** were reduced. The reaction leads to a mixture of *trans*-*N,N*-disilylated enamines **72** and *N,N*-disilylated amines **73** (Scheme 25). The ratio between products depends on the nitrile and on the catalyst.



Scheme 25. Hydrosilylation of aliphatic nitriles **69** using silane **71** and Wilkinson's Catalyst.[84]

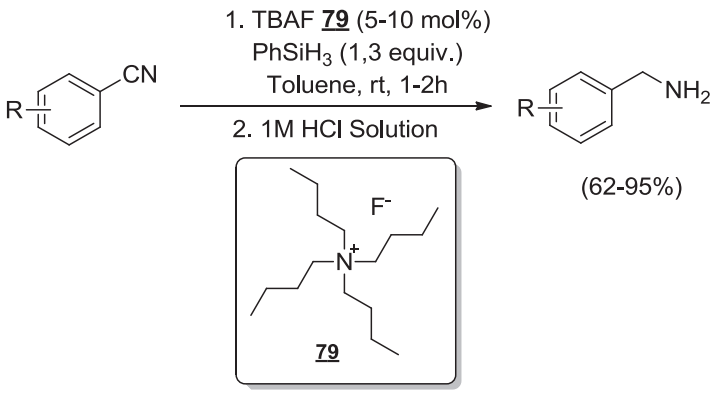
In 1985, T. Murai group developed a system using $HSiMe_3$ (10 equiv.) and $Co_2(CO)_8$ (8 mol%) for the hydrosilylation of aromatic nitriles into *N,N*-disilylamines at 60°C under CO atmosphere (to regenerate the catalyst).[85] $Me_3SiCo(CO)_4$ **74** generated by the reaction of Me_3SiH and $Co_2(CO)_8$ react with nitrile to give *N*-silylnitrilium ion intermediate **75** and $Co(CO)_4^-$. Transfer of hydrogen from a hydrosilane to **75** might occur to form silylimine **76**. The addition of Me_3SiH to **76** in a similar manner would result in the formation of the *N,N*-disilylamine **78** (Scheme 26). The reduction of aliphatic nitriles using this system required higher temperature (100°C) and the addition of triphenylphosphine as a ligand.[86]



Scheme 26. Mechanism of reduction of benzonitrile using $HSiMe_3/Co_2(CO)_8$ system.[85]

Non-supported rhodium nanoparticles show efficiency in the catalytic hydrosilylation of aromatic nitriles in the presence of trimethylsilane.[87] In 2001, platinum,[88] and nickel[89] complexes were also used, however examples are rare. Later in 2011, I. Cabrita and A. C. Fernandes explored the reduction of a wide range of aromatic nitriles bearing different functional groups using $PhSiH_3$ (300 mol%) and $ReIO_2(PPh_3)_2$ (10 mol%) as a catalytic system.[90]

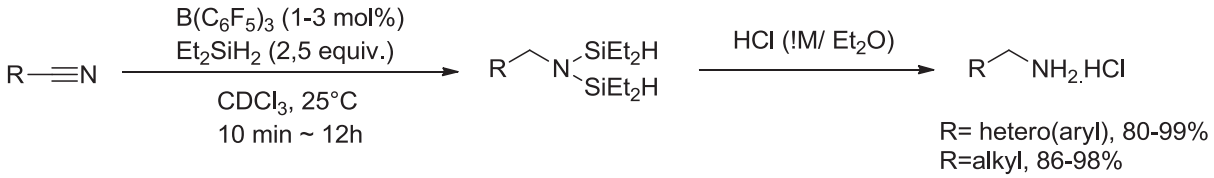
In addition to metal catalysis, a convenient approach is the use of fluoride ions as an activator for the hydrosilylation. Tetra-*n*-butylammonium fluoride (TBAF) is considered to be a useful catalyst candidate since it offers a highly nucleophilic fluoride anion as an activator for the hydrosilylation. For example in 2013, Beller group studied the hydrosilylation of aromatic nitriles using TBAF **79** (Scheme 27).[91]



Scheme 27. Reduction of aromatic nitriles using $PhSiH_3$/TBAF system.[91]

Unfortunately, using this approach to reduce aliphatic nitriles and heterocyclic nitriles such as, 3-thiophene carbonitrile and picolinonitrile did not yield the desired product.

Another example of the metal-free silylative reduction of nitriles is the use of $B(C_6F_5)_3/Et_2SiH_2$ system developed by S. Chang and co-workers (Scheme 28).[92] The use of sterically bulky silane such as Et_3SiH allowed only the partial reduction leading to *N*-silylimines.



Scheme 28. Reduction of aromatic nitriles using $Et_2SiH_2/B(C_6F_5)_3$ system.[92]

2.2.7. Reduction of nitriles to amines using hydrosiloxanes

The most studied hydrosiloxanes are the long-chain polymer polymethylhydrosiloxane (PMHS) **80** and the shortest 1,1,3,3-tetramethyldisiloxane (TMDS) **81** mentioned before in the reduction of nitriles to aldehydes (Figure 8).

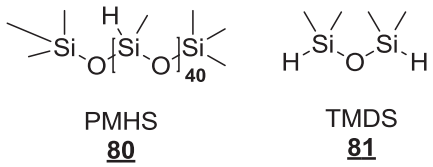
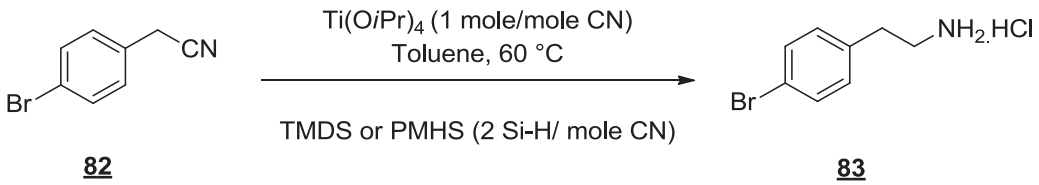


Figure 8. Structures of PMHS **80** and TMDS **81**.

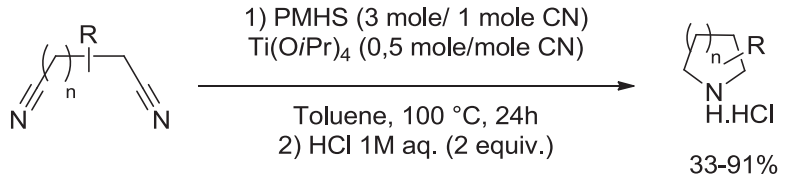
Two efficient systems TMDS-Ti(O*i*Pr)$_4$,[93] and PMHS-Ti(O*i*Pr)$_4$,[93b] were developed in our laboratory for the reduction of aliphatic and aromatic nitriles to the corresponding primary amines. The synthetic approach was straight forward and provided primary amines as hydrochloride salt in almost quantitative yields. For example nitrile **82** was reduced to primary amine **83** in 90% isolated yield using both systems (Scheme 29). However, the reaction with PMHS **80** was faster than in case of TMDS **81**.



82 83

Scheme 29. Reduction of nitrile **82** to primary amine **83** using TMDS or PMHS in the presence of $Ti(OiPr)_4$.[93]

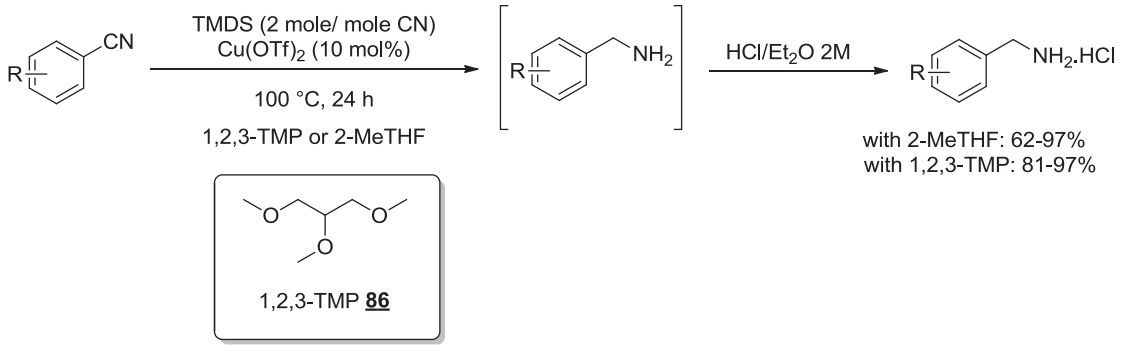
Furthermore, PMHS-$Ti(OiPr)_4$ reducing system reduced dinitriles **84** into the corresponding saturated N-heterocycles **85** (Scheme 30).[93b]



84 85

Scheme 30. Reduction of dinitriles **84** into saturated N-heterocycles **85** with the reducing system PMHS- $Ti(OiPr)_4$.[93b]

Another methodology was developed in our group for the reduction of aromatic nitriles to amines with TMDS **80** in the presence of catalytic quantity of copper triflate ($Cu(OTf)_2$) (Scheme 31).[94]

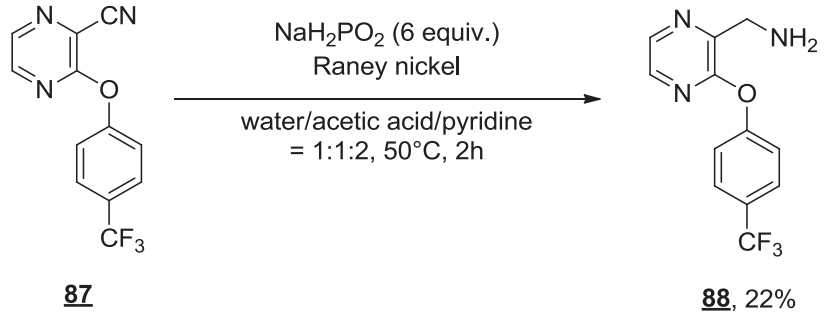


Scheme 31. Reduction of nitriles to primary amines using TMDS and $Cu(OTf)_2$ in 2-MeTHF or in 1,2,3-TMP.[94]

The reaction is highly solvent dependent and the best results were found in 1,2,3-Trimethoxypropane **86** (1,2,3-TMP). Good results were also observed with 2-MeTHF, even if the selectivity for the desired primary amine was sometimes lower.

2.2.8. Reduction of nitriles to amines using hypophosphites

The reduction of nitriles into amines using hypophosphites was mentioned as the result of formation of an undesired product observed by Johnstone during the cleavage of aromatic ethers with sodium hypophopshite and Pd/C.[95] Another example is the reduction of nitrile **87** to primary amine **88** using sodium hypophosphite in the presence of Raney nickel and in a mixture of water/acetic acid/ pyridine, however, the yield was as low as 22% (Scheme 32).[96]



87 **88**, 22%

Scheme 32. Reduction of nitrile **87** to primary amine **88** using sodium hypophosphite.[96]

2.3. Conclusion

Numerous synthetic tools are available in literature for the selective reduction of nitrile function. Aluminum and boron hydrides are effective, but several drawbacks exist such as their use in combination with toxic and flammable solvents, dangerous workup, production of hazardous and toxic metal salts as secondary products, as wellas being substrate dependent.

Molecular hydrogen remains the ideal reducer. Effective and selective homogeneous as well as heterogeneous catalysts have been developed. However, no universal catalyst exists, and no general method is available, so that each type of substrate needs

optimization. Moreover the workup of such reactions requires specific apparatus that holds high pressure.

The single electron transfer and catalytic transfer hydrogenation makes it possible to overcome the limitations of hydrogenation, but these conditions remain ineffective on several substrates.

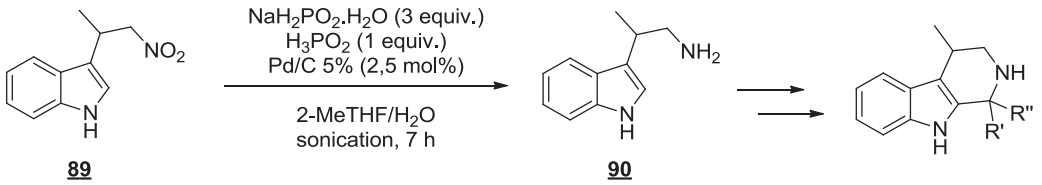
Hydrosilylation reactions have also been reported to convert nitriles to either N-silylimine or to N,N-disilylenamine (protected forms of aldehyde) or to N,N-disilylamine (protected form of amine). Other methods allow the isolation of unprotected amines. However, such methods utilize reagents that are often too expensive, must be used in excess, toxic, flammable, and can release in some cases SiH_4 which is dangerous pyrophoric gas. Another limitation is their use in association with toxic metals and expensive ligands in some cases. These drawbacks can probably be overcome by using hydrosiloxanes, but the limitation in such cases is also the relative high cost of the silicon reagents.

Finally, few examples have been reported for the reduction of nitriles to aldehydes using hypophosphites, and only one example is available for their reduction towards the amine but in a very low yield.

3. Results and discussion

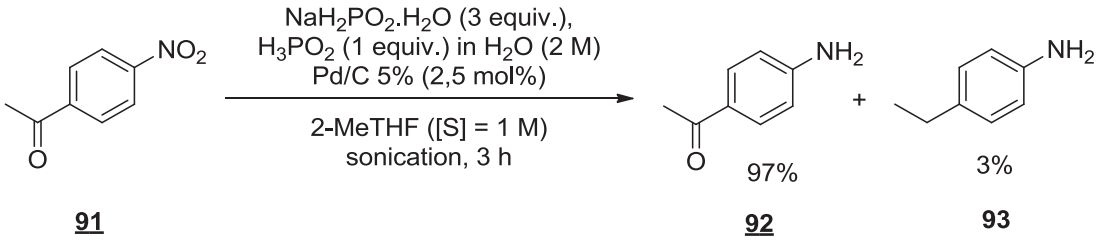
3.1. Previous results in the laboratory

Marc Baron has developed during his PhD work the synthesis of tetrahydro-*β*-carbolines including the reduction of nitroindoles to provide non-natural tryptamines.[8] For example 3-(1-methyl-2-nitro-ethyl)-1*H*-indole **89** was reduced to compound **90** under optimized conditions using sodium hypophosphite ($NaH_2PO_2.H_2O$) and phosphinic acid (H_3PO_2), in combination with 5wt.% Pd/C (2,5 mol%) and in the presence of a biphasic mixture of two solvents 2-MeTHF/water under sonication (Scheme 33).



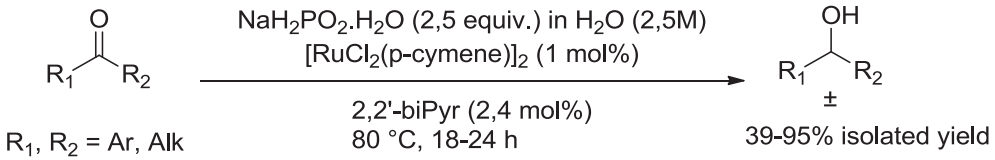
Scheme 33. Reduction of nitroindoles to non-natural tryptamines for the synthesis of tetrahydro-β-carbolines.[8]

The methodology scope was extended to nitro aromatic compounds, providing thus a general method for almost all categories of nitro-containing substrates. For example 4'-nitroacetophenone **91** was reduced to the corresponding amine **92** in 97% yield. Traces of 4-ethylaniline **93** (3% yield) were also observed (Scheme 34).[8]



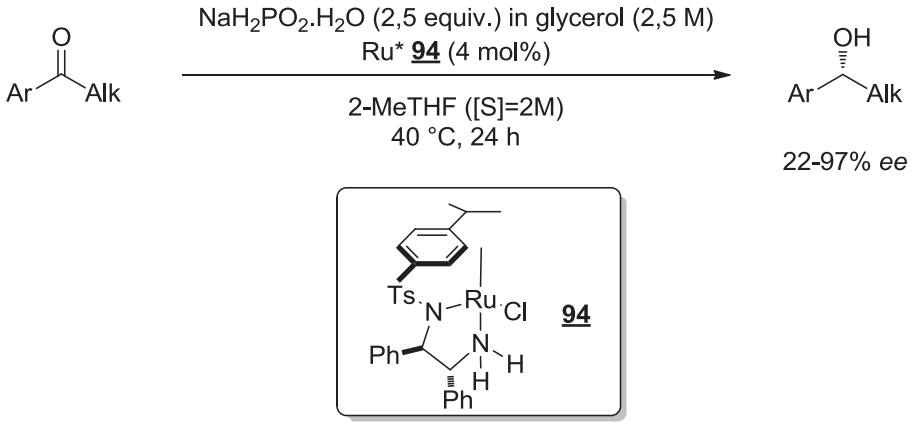
Scheme 34. Reduction of 4'-nitroacetophenone **91** to amine **92** in the presence of $NaH_2PO_2.H_2O$ and Pd/C.[8]

Interested by these results, new methodologies for the selective reduction of ketones to alcohols and alkanes were developed by Carole Guyon during her PhD. The transfer hydrogenation of ketones has been achieved using sodium hypophosphite as a hydrogen donor in the presence of $[RuCl_2(p\text{-cymene})]_2$ (1 mol%) and 2,2'-bipyridine (2,4 mol%) in water at 80°C (Scheme 35), where the corresponding alcohols were isolated in moderate to excellent yields (39-95%).[10]



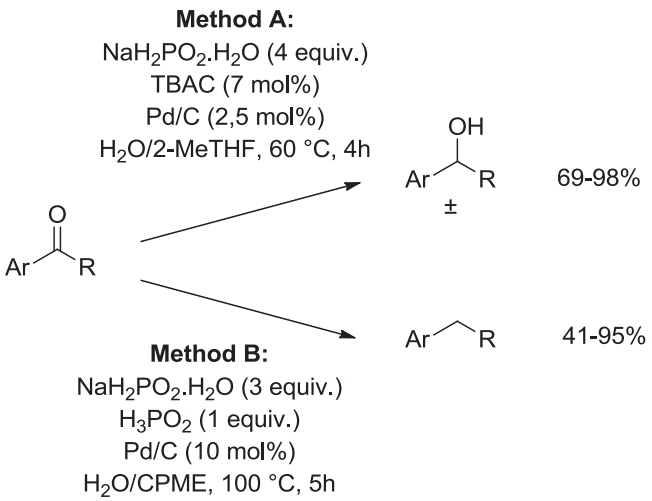
Scheme 35. Reduction of aromatic and aliphatic ketones using sodium hypophosphite.[10]

On the basis of these encouraging results, an enantioselective version has been developed using RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] **94** (4 mol%) as a catalyst, in a glycerol/2-MeTHF biphasic solvent mixture (Scheme 36).[10] The reaction allowed the reduction of (hetero)aromatic ketones to alcohols in moderate to excellent chemo- and enantioselectivities (22-97% *ee*).



Scheme 36. Enantioselective reduction of ketones using sodium hypophosphite.[10]

Moreover, aromatic ketones were reduced either to alcohols or alkanes using hypophosphites with Pd/C.[11] The study of the reaction parameters revealed the importance of the acidity of the reaction medium, the temperature as well as the catalyst loading. The determining factor for the selectivity towards alcohol is the addition of tetrabutylammonium chloride (TBAC) (7 mol%) in the presence of $NaH_2PO_2.H_2O$ (4 equiv.), Pd/C (2,5 mol%) in water/2-MeTHF at 60°C for 4 hours (Scheme 37, method A).



Scheme 37. Commutative reduction of ketones either to alkanes or alcohols.[11]

The deoxygenation reaction to obtain the alkane was maintained in the presence of $NaH_2PO_2.H_2O$ (3 equiv.), H_3PO_2 (1 equiv.), Pd/C (10 mol%) in H_2O/CPME at 100°C for 5h (Scheme 37, method B). The reaction was generally faster in comparison to that using ruthenium catalyst.

3.2. Objective

After obtention of these results, it seems very interesting to study the reductive ability of these types of reagents in the presence of other functionalities. Our aim is to develop easy, versatile and green methods, particularly for the reduction of nitriles into aldehydes and amines. Herein, we report our investigated methodologies in details.

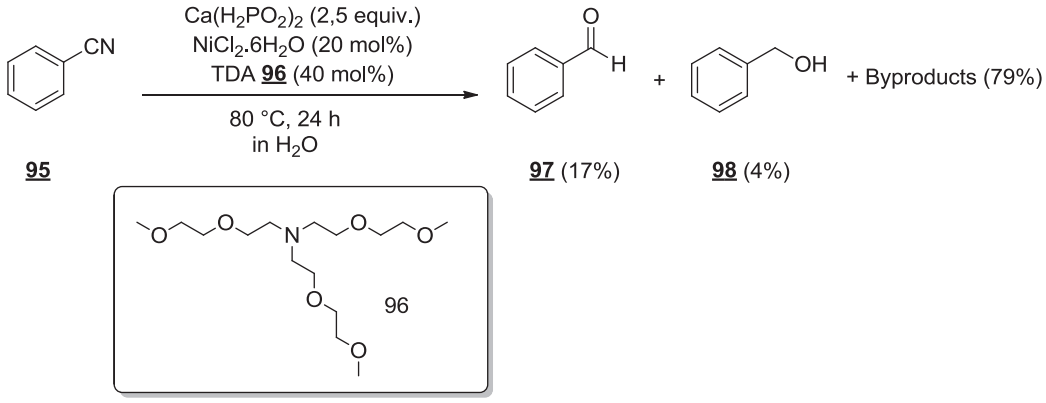
3.3. Reduction of nitriles to aldehydes

3.3.1. Feasibility and optimization of reaction conditions

a. Screening of different hypophosphites

In order to confirm the feasibility of the reduction of the group nitrile by hypophosphite, benzonitrile **95** was used as a model substrate. The first tests were carried out using nickel chloride as a catalyst, since we are interested in using non-precious metal catalysts

due to their abundance and low price. Initially, the reducing activity of different hypophosphites was studied in the presence of an additive tris(dioxa-3,6-heptyl)amine (TDA) **96**, at 80°C in aqueous medium. The use of additives for organic synthesis has become a common tactic to improve the outcome of organic reactions. A first test was carried out at 80°C in H_2O, with 2.5 equiv. of calcium hypophosphite ($Ca(H_2PO_2)_2$) and 20 mol% of the catalyst $NiCl_2.6H_2O$, in addition to 40 mol% of TDA **96**. The reaction progress was followed by GC analysis. In these circumstances, and after 24h we observed 29% conversion of benzonitrile **95**, where aldehyde **97** was obtained in 17%, and benzylalcohol **98** in 4%, with 79% of several unknown byproducts (Scheme 1).



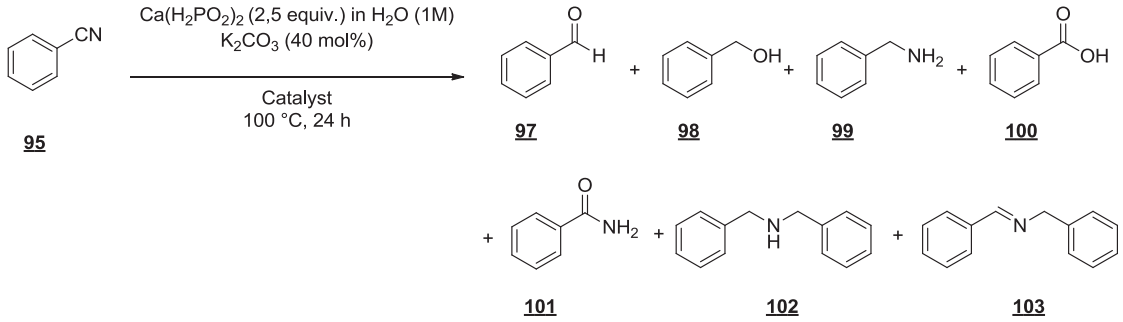
Scheme 38. Reduction of benzonitrile using $Ca(H_2PO_2)_2$/ $NiCl_2.6H_2O$.

In this case it is important to mention that the color of the reaction mixture changes from green which is the color of **Ni(II)** species to dark grey the color of $\mathbf{Ni^{(0)}}$ species. Other hypophosphites were also tested in this reaction including sodium hypophosphite ($NaH_2PO_2.H_2O$), ferric hypophosphite [$Fe(H_2PO_2)_3$] and hypophosphorous acid (H_3PO_2). However, we didn't observe any conversion with no change in the color of the reaction mixture. As a result, $Ca(H_2PO_2)_2$ was the only one to show reactivity in this transformation, so it was choosed for further studies to optimize reaction conditions. On the other hand, the change in the color of the reaction mixture from green to dark grey is an evidence that a reaction took place.

b. Screening of different catalysts

While trying to improve the conversion, we decided to increase the temperature to 100°C, and to use K_2CO_3 as a basic additive instead of TDA in the presence of different metal catalysts (Table 1). As we mentioned before in the bibliographic part, nitriles in reductive conditions can afford several products in different ratios depending on the reaction conditions. Increasing the temperature and using 40 mol% of K_2CO_3 in the presence of $NiCl_2.6H_2O$, makes it possible to increase the conversion up to 68%, and to increase the GC ratio of benzaldehyde **97** to 46% (Table 1, entry 1).

Table 1. Reduction of benzonitrile **95** with $Ca(H_2PO_2)_2$ catalyzed by different metal catalysts.



Entry	Catalyst	Conv. [%][a]	GC ratio [%][a]						
			97	**98**	**99**	**100**	**101**	**102**	**103**
1	$NiCl_2.6H_2O$ (20 mol%)	68	46	12	-	-	11	5	26
2	$CuCl_2.2H_2O$ (20 mol%)	6	-	-	-	-	100	-	-
3	5 wt.% Pd/C (2,5 mol%)	100	-	-	84	-	2	14	-
4	10 wt.% Pd/C (2,5 mol%)	100	-	-	100	-	-	-	-
5	$[RuCl_2(p\text{-cymene})]_2$ (2,5 mol%)	98	-	5	-	30	65	-	-
6	10 wt.% Pt/C (2,5 mol%)	16	-	19	-	81	-	-	-

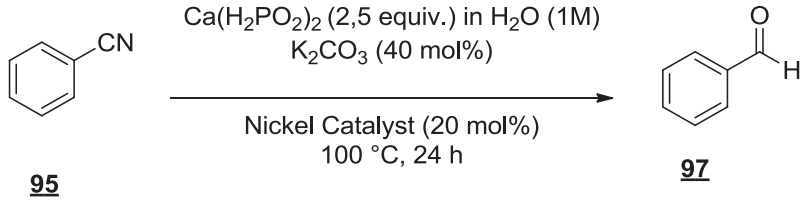
[a] Conv. and GC ratio were determined by gas chromatography.

Other products were also obtained including benzylalcohol **98** (12%) resulting from the over reduction reaction of benzaldehyde **97**, benzamide **101** (11%) obtained from the hydration reaction of benzonitrile **95**, dibenzylamine **102** (5%) and dibenzylimine **103** (26%) resulting from the reductive amination reaction. Another transition metal catalyst copper(II)chloride was evaluated, the results showed a very low conversion of 6%, and benzamide **101** was the only product in this reaction (Table 1, entry 2). The efficiency of noble metal catalysts in this transformation was evaluated as well. In the presence of 2.5 mol% of 5wt.% Pd/C, benzonitrile **95** was completely converted to give 84% of benzylamine **99**, 2% of **101** and 14% of **102** (Table 1, entry 3). The use of the same amount of 10 wt.% Pd/C, led to complete conversion of **95**, giving benzylamine **99** as the sole product in the reaction (Table 1, entry 4). This reaction will be studied in the second section of this part. The use of 2,5 mol% $[RuCl_2(p\text{-cymene})]_2$ showed almost complete conversion of **95** reaching 98%, and promoted the formation of **98**, **100** and 1**01** in 5%, 30% and 65% respectively (Table 1, entry 5). In case of 10 wt.% Pt/C the conversion was low (Table 1, entry 6). Other catalysts were also tested including Mg(II), Fe(II) and Co(II) precursors, however, none of these catalysts displayed any activity in the reduction of benzonitrile **95**.

c. Screening of different nickel catalysts

On the basis of these results, where only nickel catalyst yielded the desired aldehyde **97**, the catalytic activity of different nickel complexes was tested in the same reaction conditions (Table 2). It is noted that only the GC ratio of benzaldehyde **97** is presented in the table, though other products are formed during the reactions. $NiCl_2.6H_2O$ as shown before, gave 68% conversion of benzonitrile **95** and led to the formation of 46% of benzaldehyde **97** after 24h(Table 2, entry 1). 37% conversion was achieved with $NiBr_2$ after the same reaction time, giving 51% of **97** (Table 2, entry 2). Similar conversion was obtained with $NiCp_2$ which gave 62% of **97** (Table 2, entry 3). In contrast $Ni(acac)_2$ was not efficient (Table 2, entry 4). Using $Ni(dppe)Cl_2$, the GC Ratio of benzaldehyde **97** decreased to 28% with lower conversion of the benzonitrile **95** (Table 2, entry 5).

Table 2. Reduction of benzonitrile **95** with $Ca(H_2PO_2)_2$ catalyzed by different nickel complexes.



95 **97**

Entry	Nickel complex	Conv. [%][a]	GC ratio of **97** [%][a]
1	$NiCl_2.6H_2O$	68	46
2	$NiBr_2$	37	51
3	$NiCp_2$	34	62
4	$Ni(acac)_2$	4	-
5	$Ni(dppe)Cl_2$	22	28
6	$Ni(PPh_3)_2Br_2$	51	10
7	$Ni(PPh_3)_4$	68	16
8	$Ni(OAc)_2.6H_2O$	76	68
9	$Ni(cod)_2$	100	6
10[b]	Ni~65 wt.% on Si/Al	62	79

[a] Conv. and GC ratio were determined by gas chromatography; [b] reaction time is 30 minutes.

Phosphine nickel complexes such as $Ni(PPh_3)_3Br_2$ and $Ni(PPh_3)4$, inducing 51% and 68% conversions respectively. However, these two catalysts did not lead to any improvement in the selectivity towards **97** (Table 2, entries 6 and 7). The best result was observed in the presence of $Ni(OAc)_2.4H_2O$, where the conversion of **95** reached 76%, affording 68% of the desired product **97** (Table 2, entry 8). Two **$Ni^{(0)}$** catalysts were evaluated. For example, $Ni(cod)_2$ leads to a complete conversion, but a mixture of products was observed with only 6% of benzaldehyde **97** (Table 2, entry 9). The other tested **$Ni^{(0)}$** catalyst was Ni~65 wt.% on Si/Al, after 24h the conversion was complete, but we didn't obtain benzaldehyde **97**, instead benzylalcohol **98**, benzamide **101** and dibenzylamine

102 were the products in this reaction. It seems that this reaction is too fast, so several reactions were followed. We observed that after 1h the conversion was complete leading to 35% of **97**. After 30 min the conversion reaches 62%, giving 79% of benzaldehyde **97** (Table 2, entry 10). It is clear that Ni~65 wt.% on Si/Al is efficient with high reactivity, however the chemoselectivity should be improved. Moreover, the appearance of a green color at the end of the reaction reveals a lack of stability of this catalyst in these reaction conditions.

This series of experiments revealed that the nature of nickel precursor is very important in determining the conversion and the selectivity towards the desired product. $Ni(OAc)_2.4H_2O$ showed the best reactivity in this reaction.

d. The nature of catalytic species

It is important to mention that a control experiment in the absence of calcium hypophosphite and base did not lead to any conversion, thus confirming that the hypophosphite and the base are crucial for the formation of $\mathbf{Ni^{(0)}}$ species, and eventually for the reduction of nitrile to aldehyde.

A recent work done in 2012 reported the synthesis of nickel nanoparticles (NiNPs) by the reduction of less toxic nickel precursor $Ni(OAc)_2.4H_2O$, using sodium hypophosphite $NaH_2PO_2.H_2O$ under microwave irradiation in the presence of propylene glycol as a solvent (Figure 9).[97] It was mentioned that the formation of NiNPs depended on $[Ni^{2+}]/[NaH_2PO_2]/[NaOH]$ molar ratios. More NaOH leds to an increase in the pH of the reaction solution and thereby to a decrease in the free energy required to form NiNPs as per Nernst equation:

$$Ni^{2+} + 2OH^- + 2H_2PO_2^- \longrightarrow Ni + 2HPO_2^- + 2H_2O.$$

Such decrease in the free energy would have resulted in large number of nuclei and thus particles. On the other hand, higher concentration of $NaH_2PO_2.H_2O$ introduced more phosphorous into the system, thus increasing the chances of Ni-P compounds formation

instead of pure Ni. Here arises the second role of the base in the medium, where it helps in releasing phosphorous species into the system to form pure NiNPs.

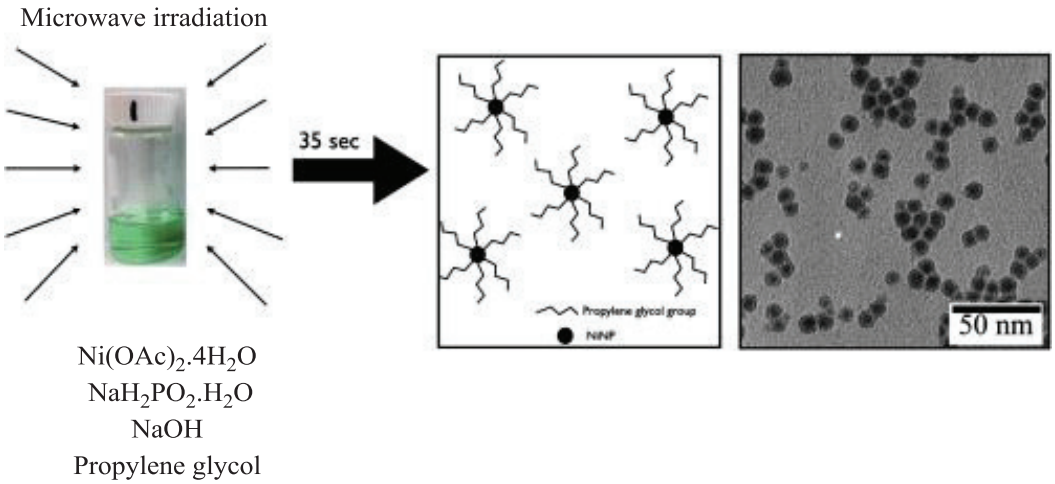


Figure 9. Synthesis of NiNPs using sodium hypophosphite under microwave irradiation.[97]

Moreover, higher molar ratios of NaOH and $NaH_2PO_2.H_2O$, resulted in higher wt.% of P and O, thus confirming the authors hypothesis that Ni particles are covered with HPO_2^- radicals, and supported by Fourier Transform infrared spectroscopy. As similar conditions are encountered in our study, we assumed that the formed **$Ni^{(0)}$** species formed are actually nickel nanoparticles.

e. Screening of basic additives

It is known that the solubility of $Ca(H_2PO_2)_2$ in water is low in comparison to the solubility of other hypophosphite derivatives (Table 3). Therefore lower concentrations of calcium hypophosphite were used in our study. Experiments showed that the amount of $Ca(H_2PO_2)_2$ could be reduced to 1 equiv. instead of 2.5 equivalents with improved conversions.

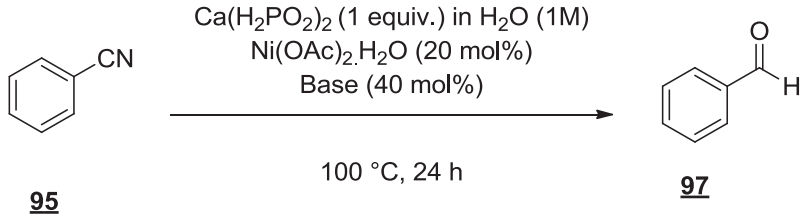
Table 3. Solubility of different hypophosphites in water expressed in percentage by weight of the hypophosphite derivative.

Hypophsophite derivative	Solubility in water (wt.%)
$Ca(H_2PO_2)_2$	13[98]
$NH_4H_2PO_2$	51[99]
NaH_2PO_2	58[100]
H_3PO_2	Very soluble[101]
H_3PO_3	75[101]
Na_2HPO_3	Very soluble[102]

After studying several parameters including the type of hypophosphite, the type of catalyst as well as the reaction temperature, it was important to study the influence of different bases on this transformation. The results of reduction in the presence of 1 equiv. $Ca(H_2PO_2)_2$ (1M in H_2O), 20 mol% $Ni(OAc)_2.4H_2O$ and 40 mol% of base at 100°C for 24h are summarized in Table 4.

A blank experiment was done in the absence of base. After 24h, the color of the reaction persisted at green and no conversion was observed (Table 4, entry 1). This indicated that $\mathbf{Ni^{(II)}}$ species were not reduced to $\mathbf{Ni^{(0)}}$ which is the real catalyst in the reaction. For all other entries with different bases, the color of the solution changes to dark grey indicating the formation of $\mathbf{Ni^{(0)}}$ species. In the presence of K_2CO_3 (Table 4, entry 2), the conversion increased up to 91% after 24h in comparison to entry 8 of table 2 (with 2,5 equiv. of reducing agent). However, lower GC ratio of benzaldehyde **97** was obtained (29%). Na_2CO_3 and $CaCO_3$ showed similar results with high conversions and moderate yield of **97** reaching 40 and 42%, respectively (Table 4, entries 3 and 4). This is an indication that the counter ion has small effect on the selectivity. When acetates were used as bases, benzaldehyde **97** was the sole product in the reaction but with low conversions (Table 4, entries 6 and 7).

Table 4. Reduction of benzonitrile **95** with $Ca(H_2PO_2)_2$ catalyzed by $Ni(OAc)_2.4H_2O$ in the presence of different bases.



95 **97**

Entry	Base	Conv. [%][a]	GC ratio of **97** [%][a]
1	-	-	-
2	K_2CO_3	91	29
3	Na_2CO_3	94	40
4	$CaCO_3$	97	42
5	AcOK	73	89
6	AcONa	18	100
7	$Ca(OAc)_2.H_2O$	12	100
8	DIPEA	100	5

[a] Conv. and GC ratio were determined by gas chromatography.

A reaction with *N,N*-Diidopropylethylamine (DIPEA) was also performed, leading to a complete conversion after 24 h, but only 5% of **97** was detected (Table 4, entry 8). Even after 7h a mixture of different products was observed with 55% of **97**.

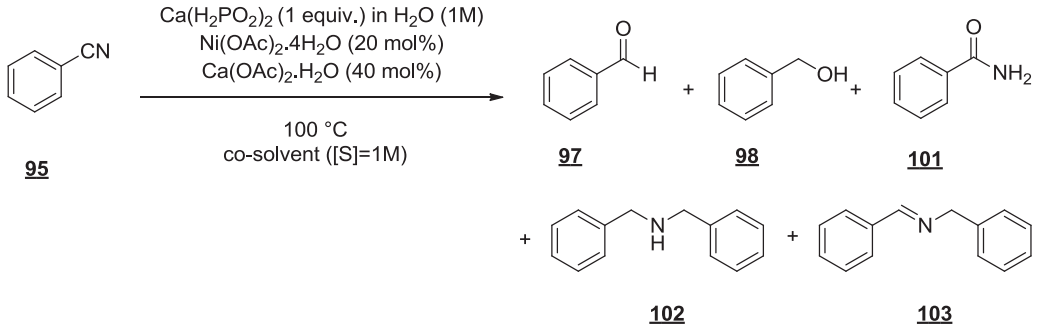
It is clear that the type and strength of base is important to have suitable pH in the reaction medium, leading to changes in conversions and selectivities. On the basis of these results, acetates showed better reactivity in terms of GC ratio towards the desired product, though the conversions were low. The optimization was pursued with $Ca(OAc)_2.H_2O$ as a base.

f. Screening of different co-solvents

We start thinking how it is possible to increase the conversion while keeping the same selectivity. In fact, benzonitrile is slightly soluble in these aqueous conditions (<0.5 g/100 ml at 22 °C). Therefore, in our route for optimization we were interested in using a co-

solvent to the improve the conversion. As a consequence, the reduction of benzonitrile **95** was studied in a mixture of different organic solvents and water over 20 mol% $Ni(OAc)_2.4H_2O$, 40 mol% $Ca(OAc)_2.H_2O$ and in the presence of 1 equiv. of $Ca(H_2PO_2)_2$ (Table 5).

Table 5. Reduction of benzonitrile **95** in the presence of different co-solvents.



Entry	Co-solvent	Time [h]	Conv.[%][a]	GC ratio [%][a]				
				97	**98**	**101**	**102**	**103**
1	MeOH	21	75	91	4	2	3	-
2	EtOH	7	100	100	-	-	-	-
3	n-BuOH	7	42	95	3	2	-	-
4	*tert*-butanol	7	93	74	13	2	11	-
5	CPME	7	64	83	6	-	8	3
6	1,2,3-TMP	7	73	92	8	-	-	-

[a] Conv. and GC ratio were determined by gas chromatography.

The reaction performed in H_2O/MeOH solvent mixture led to an increase in the conversion up to 75% after 21h, but with lower yield of benzaldehyde **97** (91%) (Table 5, entry 1). In this case, side reactions occured and led to the formation of benzylalcohol **98**, benzamide **101** and dibenzylamine **102** as byproducts. This is evidence that the conversion could be improved in the presence of co-solvent. When EtOH was used as a co-solvent, the rate of the reaction was faster; where benzonitrile **95** was completely converted after 7h to benzaldehyde **97** as the sole product (Table 5, entry 2). In this case when, EtOH was added a turbid reaction mixture was obtained which means that ethanol acts as a hydrotrope for the solubilization of benzonitrile in water. Conversely, in H_2O/n-

BuOH solvent mixture, only 42% conversion was reached after 7h with 95% of **97**, traces of **98** and **101** were also observed (Table 5, entry 3). When the reaction with *tert*-butanol and H_2O was performed over 7h, a conversion of 93% was reached with 74% of **97** and **98**, **101** and **102** as byproducts (Table 5, entry 4). Using a less polar solvent such as CPME, 64% of **95** were converted to give 83% of **97** and other byproducts (Table 5, entry 5). In the presence of 1,2,3-TMP, a conversion of 73% was noted after 7h with 92% yield of benzaldehyde **97** (Table 5, entry 6). Over reduction led to the formation of 8% of benzylalcohol **98** as a byproduct. This optimization part reveals the importance of solubilization of the substrate and the reducing agent together in the mixture of solvents.

g. Effect of concentration of $Ca(H_2PO_2)_2$ in water

In order to evaluate the effect of concentration of calcium hypophosphite in water on the reaction, the reduction of benzonitrile **95** was performed using the optimized conditions: 20 mol% $Ni(OAc)_2.4H_2O$, 40 mol% $Ca(OAc)_2.H_2O$, 1 equiv. Of $Ca(H_2PO_2)_2$ in biphasic system of H_2O/EtOH at 100 °C, where $[benzonitrile]_{in\ EtOH}$ = 1 M, and varying concentrations of $Ca(H_2PO_2)_2$ in H_2O. Results are represented in the graph shown in Figure 10. It was observed that the concentration of calcium hypophosphite has an effect on the conversion of **95** rather than on the GC ratio of benzaldehyde **97**. The ideal concentration was 1M, lower concentrations diminished the conversion where it reaches 79% at $[Ca(H_2PO_2)_2]$= 0.4M. When higher concentrations were used, the conversion drops dramatically to 38% at $[Ca(H_2PO_2)_2]$= 2M. It is possible that at higher concentrations, calcium hypophosphite, nickel catalyst and substrate are less soluble.

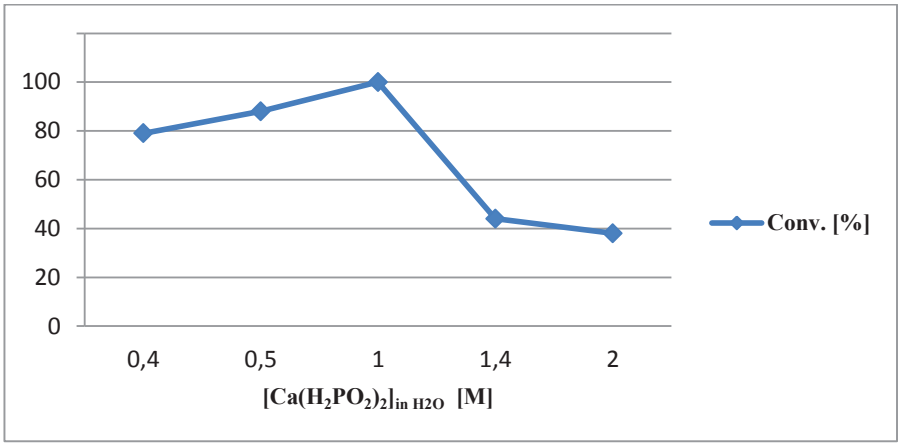


Figure 10. The variation in the conversion of **95** as a function of concentration of $Ca(H_2PO_2)_2$ in water.

h. Effect of concentration of benzonitrile in ethanol

The effect of concentration of benzonitrile in EtOH was also studied and results are represented in Figure 11. As the concentration increases the conversion increases too, till it reaches 100% at 1M. Higher concentration did not lead to any change in conversion.

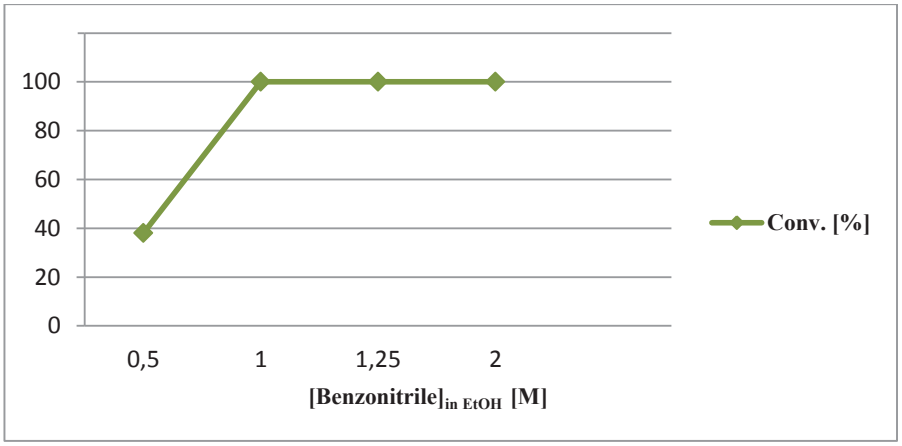
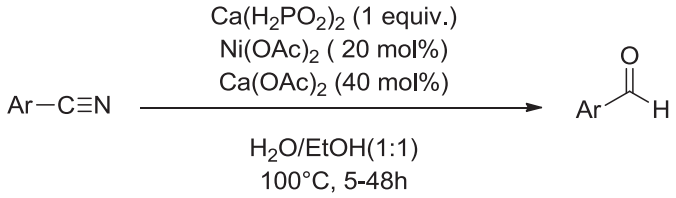


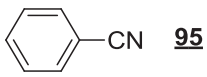
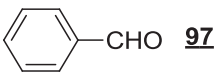
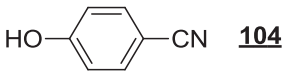
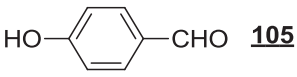
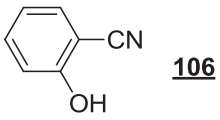
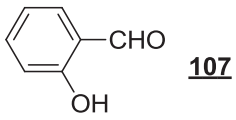
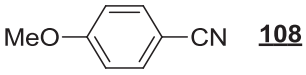
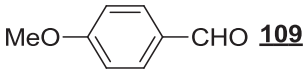
Figure 11. The variation in the conversion of **95** as a function of concentration of benzonitrile in ethanol.

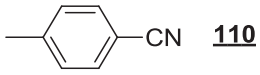
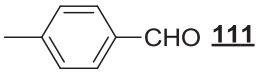
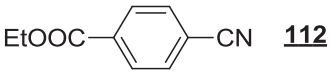
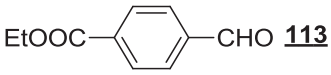
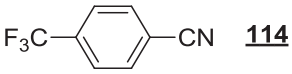
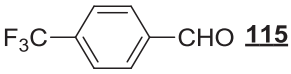
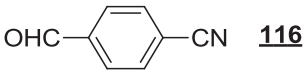
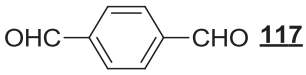
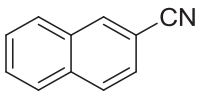
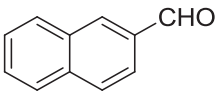
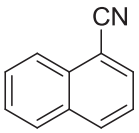
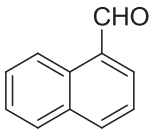
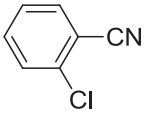
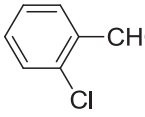
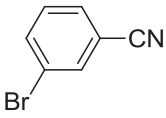
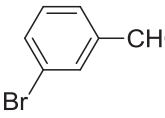
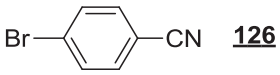
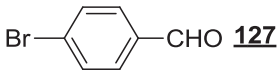
3.3.2. Application of the methodology on different substrates

According to optimization data, the best results were obtained in the presence of calcium hypophosphite (1 equiv.), with 20 mol% $Ni(OAc)_2.4H_2O$ and 40 mol% $Ca(OAc)_2.H_2O$ at 100 °C in H_2O/EtOH solvent mixture for 5-48h depending on the substrate. In order to evaluate the generality of this system, the mentioned conditions were applied to different nitriles. Results are shown in Table 6. In order to avoid the separation of a complex mixture at the end of the reaction, all reactions were performed several times to determine the time needed for complete conversion avoiding the over reduction into alcohol.

Table 6. Reduction of aromatic nitriles to aldehydes.



Entry	Substrate	Aldehyde	Time [h]	Conv. [%][a]	GC ratio [%][a]	Isolated yield [%][b]
1	 **95**	 **97**	7	100	100	50
2	 **104**	 **105**	7	100	93	90
3	 **106**	 **107**	23	93	93	90
4[c]	 **108**	 **109**	26	100	100	97

5	 **110**	 **111**	17	96	98	98
6	 **112**	 **113**	7	100	100	94
7	 **114**	 **115**	5	93	93	84
8	 **116**	 **117**	8	86	90	85
9	 **118**	 **119**	21	91	100	80
10	 **120**	 **121**	48	91	100	85
11	 **122**	 **123**	7	51	57	30
12	 **124**	 **125**	29	82	92	90
13	 **126**	 **127**	23	81	91	90

[a] Conversion and GC ratio of aldehyde were determined by GC; [b] Isolated yield as hydrochloric acid salt; [c] [S] in EtOH= 0.66M.

Benzonitrile **95** was well reduced in 7h into benzaldehyde **97** as mentioned in the optimization section. However, the isolated yield was only 50% due to the high volatility of **97**, which was partially lost during evaporation after treatment of the reaction mixture (Table 6, entry 1). Nitriles bearing an EDG were successfully reduced. For 4-hydroxybenzonitrile **104**, traces of byproducts were observed resulting from the over

reduction, and the corresponding aldehyde 4-hydroxybenzaldehyde **105** was obtained in 93% yield and 90% isolated yield (Table 6, entry 2). However, in case of 2-hydroxybenzonitrile **106**, where the hydroxyl group is at the ortho position, the reaction required 23h, and afforded 2-hydroxybenzaldehyde **107** in 93% yield (Table 6, entry 3). The reduction of 4-methoxybenzonitrile **108** also required also a longer reaction time, where pure aldehyde **109** was obtained with 97% isolated yield after 26h (Table 6, entry 4). *P*-tolunitrile **110** was also reduced to the corresponding aldehyde **111** after 17h in 98% yield (Table 6, entry 5).

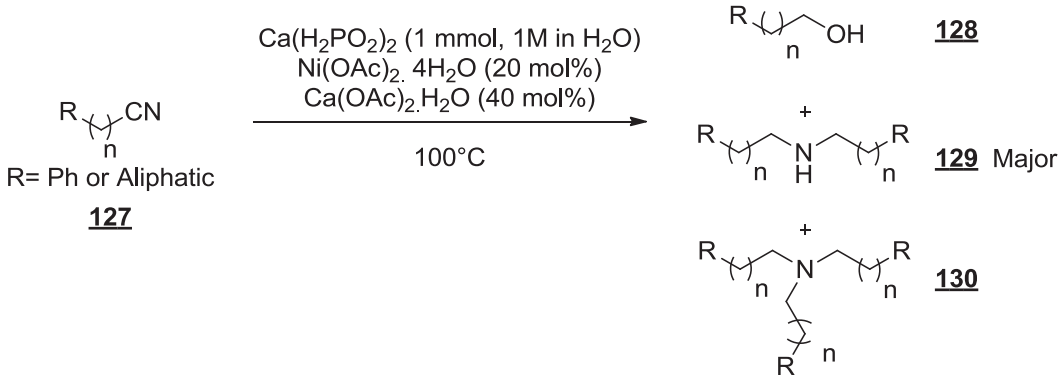
The reduction of substrates containing EWG was also performed. For example, ethyl 4-cyanobenzoate **112** was completely converted after 7h into ethyl 4-formylbenzoate **113** with 94% isolated yield (Table 6, entry 6). In case of 4-(trifluoromethyl) benzonitrile **114**, the reaction was fast,so that after 5h 4-(trifluoromethyl) benzaldehyde **115** was obtained in 93% yield. The alcohol was a byproduct in this reaction (Table 6, entry 7).

With 4-formylbenzonitrile **116**, the conversion was not complete reaching 86% after 8h and giving terephthaldehyde **117** in 85% isolated yield (Table 6, entry 8). As the reaction proceeds, the conversion was complete but with the corresponding alcohol as the major product due to the over reduction. The reaction of naphthaline nitriles **118** and **120** afforded the corresponding aldehydes **119** and **121** in 80 and 85% isolated yields. However the conversions cannot be increased more than 91%, even after long reaction time (Table 6, entries 9 and 10).

The substrate versatility of this method was further demonstrated by the reduction of halogenated aromatic nitriles. For 2-chlorobenzonitrile **122**, only 51% of the nitrile was converted after 7h yielding 57% of 2-cholorobenzaldehyde **123** (Table 6, entry 11). It is noted that several byproducts were observed resulting from the over reduction and dehalogenation reactions. Moreover, it is important to mention that complete conversion cannot be attained even after long reaction time, or upon increasing the amount of hypophosphite, or even upon changing the concentration of nitrile **122** in ethanol. On the other hand, the reduction worked better in the presence of bromine substituents **124** and

126 at *meta* and *para* positions, with high yields reaching 90% of the corresponding aldehydes (Table 6, entries 12 and 13).

Finally, to check the potential of our investigated method, reactions were employed on the more challenging alkyl chain substituted benzonitriles and aliphatic nitriles including hexanenitrile, octanenitrile, phenylacetonitrile and phenylbutyronitrile. Results showed that complete conversion of nitrile **127**, with no selectivity towards the aldehyde. Instead, alcohol **128**, diamine **129** as the major product and triamine **130** were observed as shown in scheme 39.



Scheme 39. Reduction of aliphatic nitrile **127** using our investigated methodology.

3.3.3. Limitations of the methodology

For every method, there exist some limitations. For example, in case of 2-cyanopyridine **131** and 2-aminobenzonitrile **132**, formation of inactive complexes were observed with blue and offwhite colors respectively (Figure 12).

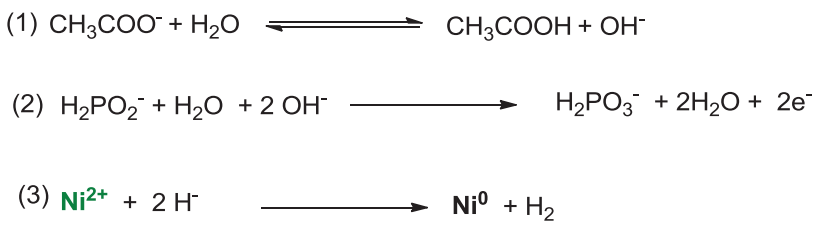
131 **132**

Figure 12. Structures of 2-cyanopyridine **131** and 2-aminobenzonitrile **132**.

On the other hand, with nitro substituted nitriles, Ni^{II} was not reduced to Ni^{0} (no change of color from green to black), thus the reduction did not occur. This was verified by making GC of the reaction mixture. It is expected that nitro group poisons the catalyst. To confirm this hypothesis, a reaction was performed with nitrobenzene in our optimized conditions; in this case Ni^{0} was not formed as well. And as we mentioned in the previous page that the reduction of aliphatic nitriles is considered to be a limitation.

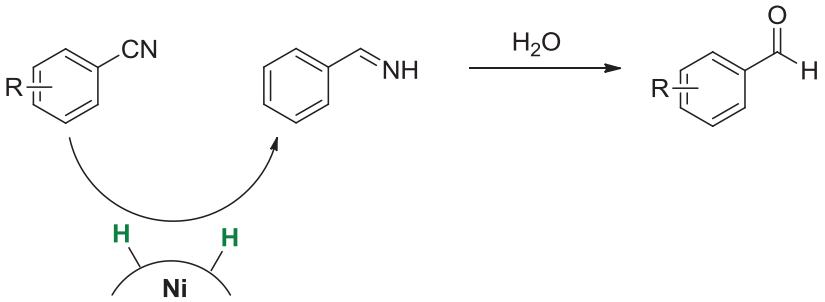
3.3.4. Mechanism

Moving to the mechanistic part, from an experimental point of view, the reduction of nitrile to aldehyde occur when there is modification in the color of the reaction mixture from light green into grey or black. This could be attributed to the reduction of Ni^{II} to Ni^{0} by hypophosphite and the formation of nickel nanoparticles as described in literature.[97] While trying to understand the mechanism, a test was done by heating hypophosphite, nickel catalyst and the base in water at 100°C in a sealed tube. After 30 min, the color changed to black, and when we open to add benzonitrile there was a lot of pressure. As expected, after 7h there was no conversion. Mainly this is due to the loss of hydrogen gas. From these observations we expect to have the redox reactions shown in scheme 40.



Scheme 40. Expected redox reactions.

(1) The base acetate CH_3COO^- deprotonates water to generate OH^-. (2) The interaction between hypophosphite and OH^- leads to the formation of hydride (3) which reduces Ni^{II} to Ni^{0} generating hydrogen gas. The generated hydrogen gas is then adsorbed on the surface of Ni^{0} nanoparticles and could be the real reducing agent that reduces the nitrile into aldehyde via the intermediate imine as shown in scheme 41.



Scheme 41. The reduction of nitrile into aldehye over nickle nanoparticles.

3.3.5. Conclusion and perspectives

In this part, we have shown that the selective reduction of nitrile to aldehyde is possible by calcium hypophosphite in the presence of $Ni(OAc)_2.4H_2O$. After studying the reaction parameters, best results were obtained using 1equiv. of $Ca(H_2PO_2)_2$ as the reducing agent and 0,2 equiv. of $Ni(OAc)_2.4H_2O$ as the catalyst, in the presence of stoichiometric amount of $Ca(OAc)_2.H_2O$ in H_2O/EtOH solvents mixture. In these condtions aromatic nitriles were converted to aldehydes in good to very good yields.

However, limitations have been noted in case of nitriles bearing nitro and amine groups. Moreover, aliphatic nitriles were not reduced to the desired aldehyde as well.

For future perspectives, the mechanism should be studied in details concerning the type of intermediates and species present at each stage of the reaction. Moreover, the method could be improved in order to reduce aliphatic and sterically hindered substrates with better isolated yields and on large scale for industrial applications.

3.4. Reduction of nitriles into amines

3.4.1. Objective

As mentioned in the previous section, where we discussed the reduction of benzonitrile **95** with $Ca(H_2PO_2)_2$ catalyzed by different metal catalysts that the reduction using 10

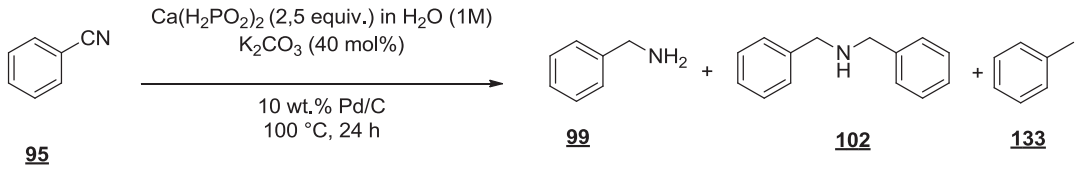
wt.% Pd/C caused the complete conversion of benzonitrile to benzylamine as the sole product (Table 1, entry 4). Interested by these results we went forward for studying this reaction.

3.4.2. Feasibility and optimization of reaction conditions

a. Effect of the amount of catalyst

It was very clear that the efficiency of the reduction highly depends on the type of the catalyst used. At the same time, the amount of catalyst used can change the whole pathway of the reaction as shown in Table 7.

Table 7. Reduction of benzonitrile **95** in the presence of Pd/C.



95 **99** **102** **133**

Entry	10 wt.% Pd/C [mol%]	Conv. [%][a]	GC Ratio [%][a]		
			99	**102**	**133**
1	2.5	100	98	-	2
2	1	100	6	94	-

[a] Conv. and GC ratio were determined by gas chromatography

The reduction of benzonitrile **95** was done in the presence of 2,5 equiv. of $Ca(H_2PO_2)_2$ as the reducing agent, 40 mol% of K_2CO_3 as a basic additive in aqueous medium at 100°C for 24h. Underr these conditions using, 2.5 mol% of 10 wt.% Pd/C as the catalyst, led to the formation of benzylamine **99** in 98% yield and toluene **133** as a byproduct in 2% yield, which can be obtained via hydrogenolysis (Table 7, entry 1). When changing the amount of catalyst to 1 mol%, only 6% of **99** were obtained. The major product was dibenzylamine **102** with 94% yield (Table 7, entry 2). This could be explained by the

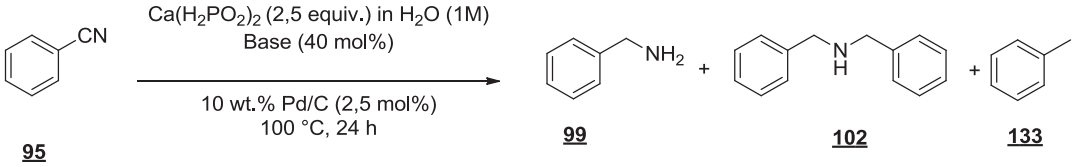
slow kinetics of the reaction when the amount of catalyst is low, so that there is more interaction between the intermediate imine and the produced amine.

Although very good results were obtained, it was very important to study the effect of different parameters on the reaction pathway.

b. Screening of different basic additives

At the beginning, the reaction was performed with the same previous conditions but in the presence of two other t bases (Table 8).

Table 8. Reduction of benzonitrile **95** in the presence of different bases.



95 **99** **102** **133**

Entry	Base	Time [h]	Conv. [%][a]	GC Ratio [%][a]		
				99	**102**	**133**
1	K_2CO_3	24	100	100	-	-
2	DIPEA	5	99	81	13	6
3	$Ca(OAc)_2.H_2O$	16	100	64	29	2

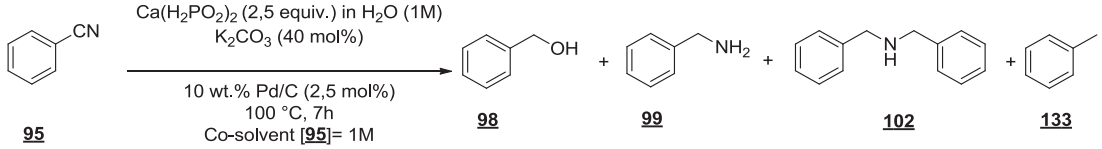
[a] Conv. and GC ratio were determined by gas chromatography

Using the string base DIPEA, the reaction was fast with complete conversion after 5h (Table 8, entry 2). In this case the desired benzylamine **99** was obtained in 81% yield and with **102** and **133** as byproducts. It is noted that even at less reaction time this percentage cannot be increased. Calcium acetate hydrate $Ca(OAc)_2.H_2O$ was also tested. The conversion was complete after 16h, however, only 69% of **99** was obtained (Table 8, entry 3). Thus, the best result was observed with complete conversion and excellent selectivity towards the amine by using K_2CO_3 as the base.

c. Screening of different co-solvents

The effect of the presence of co-solvent in the medium was evaluated next. The results of the reduction of benzonitrile **95** in the mixture of different solvents and water, over 10 wt.% Pd/C (2,5 mol%), in the presence of $Ca(H_2PO_2)_2$ (2,5 equiv.) and K_2CO_3 (40 mol%) at 100°C for 7h are given in Table 9. The concentration of **95** in the organic solvent was 1M.

Table 9. Reduction of benzonitrile **95** in the presence of different co-solvents.



Entry	Co-solvent	Conv. [%][a]	GC Ratio [%][a]			
			98	**99**	**102**	**133**
1	EtOH	99	13	52	10	25
2	n-BuOH	100	-	82	2	16
3	MeOH	88	42	36	16	6
4	2-MeTHF	41	12	71	5	12
5	CPME	100	-	96	-	4

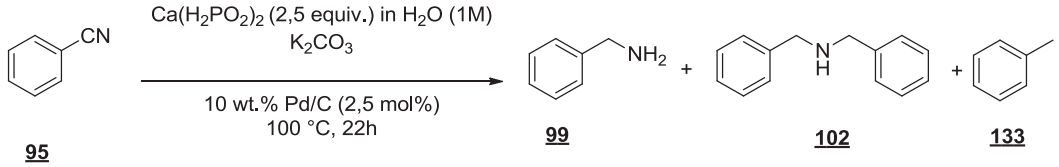
[a] Conv. and GC ratio were determined by gas chromatography

The conversion of **95** was fast and almost complete in H_2O/EtOH solvent mixture, but a mixture of products was obtained with only 52% of the desired benzylamine **99** (Table 9, entry 1). Using H_2O/n-BuOH mixture, the reaction was also faster than that with only water; while complete conversion of **95** was observed after 7h, lower yield of **99** was obtained (Table 9, entry 2). In a mixture of H_2O/MeOH the conversion was not complete after 7h (88%), giving only 36% of **99** (Table 9, entry 3). In the presence of H_2O/2-MeTHF the conversion was the lowest after 7h in comparison to other co-solvents reaching 41% with 71% of **99** (Table 9, entry 4). Using H_2O/CPME mixture, the reaction was very fast leading to a complete conversion after 7h with 96% of **99** and traces of toluene **133** (Table 9, entry 5). According to these results, it is favourable to use a simple system with water as the sole solvent.

d. Effect of the amount of base

Finally, the amount of base necessary for the reduction was investigated. Results are given in Table 10. In general, we noticed that decreasing the amount of potassium carbonate K_2CO_3 does not have any effect on the conversion, whereas it influences the ratio between different products.

Table 10. Influence of the amount of K_2CO_3 on the reduction of benzonitrile **95**.



95 **99** **102** **133**

Entry	K_2CO_3 [mol%]	Conv. [%][a]	GC Ratio [%][a]		
			99	**102**	**133**
1	20	100	95	-	5
2	10	100	92	-	8
3	5	100	86	-	14
4	-	100	86	3	11

[a] Conv. and GC ratio were determined by gas chromatography.

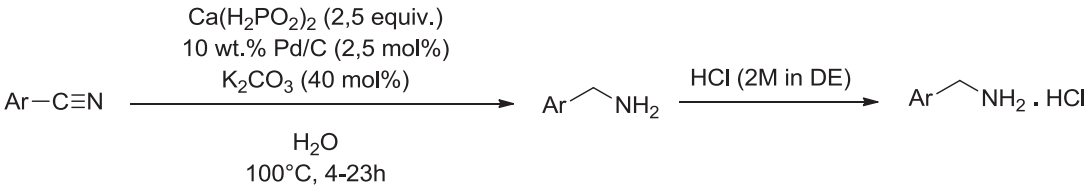
With 20 mol% K_2CO_3, the ratio of **99** decreases to 95% and more toluene **133** was formed (Table 10, entry 1). Going down to 10 mol% K_2CO_3, 92% of **99** and 8% of **133** were formed (Table 10, entry 2). With no base or with 5 mol% (Table 10, entries 3 and 4) similar results were obtained with ratio 86% of **99**. Thus, the base has an important role in shifting the reaction towards primary amine with no byproducts.

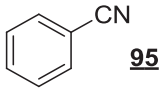
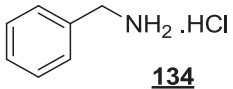
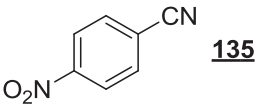
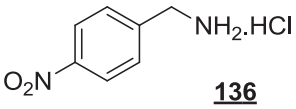
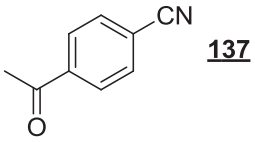
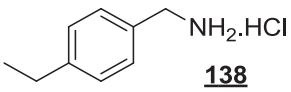
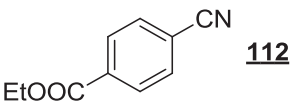
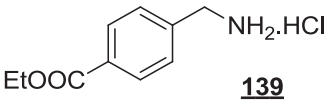
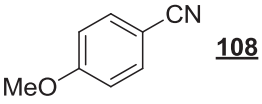
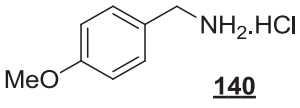
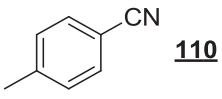
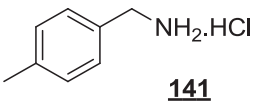
3.4.3. Application of methodology on different substrates

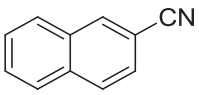
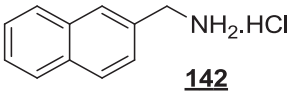
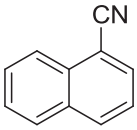
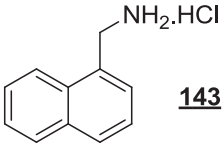
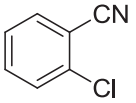
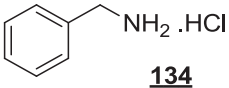
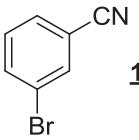
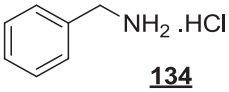
After checking all these parameters, the optimal conditions are now in hand. Using 10 wt.% Pd/C and 2,5 equiv. of $Ca(H_2PO_2)_2$ and 40 mol% K_2CO_3 in aqueous medium at 100°C, we investigated the reduction of 10 different nitriles with excellent chemoselectivity to yield the corresponding primary amines within reaction times ranging from 2-23h. After hydrolysis at room temperature with 2M HCl solution in diethylether,

pure amines were obtained as their hydrochloride salts. The catalytic system displayed a variety of functional group tolerance, so that aromatic nitriles with electron-withdrawing as well as electron-donating substituents were reduced in good to excellent yields (Table 11).

Table 11. Reduction of aromatic nitriles to amines.



Entry	Nitrile	Amine hydrochloride	Time [h]	Conv.[%][a]	GC ratio of amine [%][a]	Isolated yield of salt [%][b]
1	 **95**	 **134**	22	100	98	96
2	 **135**	 **136**	4	100	100	>99
3	 **137**	 **138**	16	100	91	89
4	 **112**	 **139**	4	100	95	93
5	 **108**	 **140**	22	100	96	95
6	 **110**	 **141**	22	100	96	95

7	 **118**	 **142**	23	100	56	56
8[c]	 **120**	 **143**	23	100	55	55
9	 **122**	 **134**	22	100	100	98
10	 **122**	 **134**	22	100	100	97

[a] Conversion and GC Ratio were determined by GC; [b] yield of product isolated as HCl salt; [c] Pd/C 10wt.% (3 mol%, 0.03 mmol), H_2O (3 mL) ([$Ca(H_2PO_2)_2$]= 0.83M).

Benzonitrile derivatives bearing electron-withdrawing substituents at the 4-position such as $–NO_2$ (**135**), -CHO (**137**), and -COOEt (**112**) were quantitatively reduced with calcium hypophosphite and isolated in the form of hydrochloride salts **136**, **138** and **139** respectively (Table 11, entries 2-4). Noting that in case of 4-formyl benzonitrile **137** (Table 11, entry 3), the conversion was complete after only 2h, reducing formyl and cyano groups into hydroxyl and amine groups respectively. However it was not possible to determine the corresponding yield by precipitation due to the presence of hydroxyl group. For that reason, the reaction was kept for 16h so that the hydroxyl group was reduced. Derivatives with electron-donating groups including methoxy (**108**) and methyl groups (**110**), were also reduced successfully after 22 hours, and the salts (**140**) and (**141**) were obtained in excellent yields (Table 11, entries 5-6).

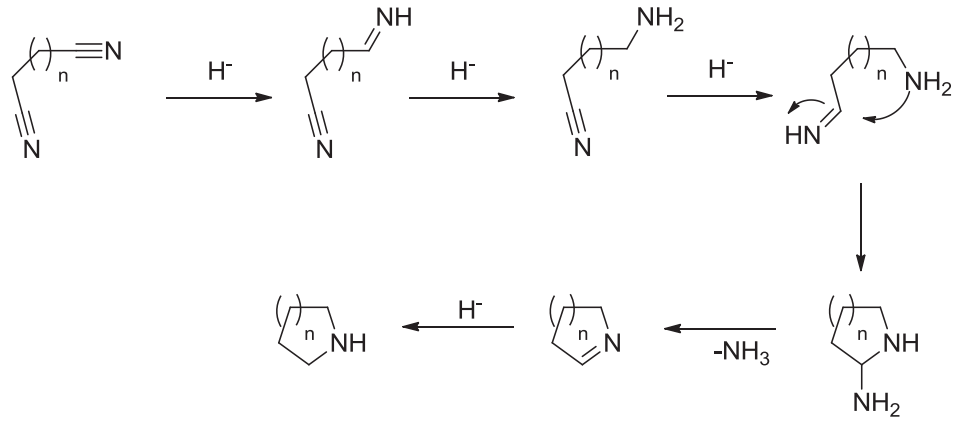
Cyano-naphthalene substrates **118** and **120** with cyano groups at different positions were also reduced. In these cases only a GC ratio of 55-56% of the corresponding amines were

obtained with methylnaphthalenes as byproducts (Table 11, entries7-8). It should be noted that these percentages cannot be increased even at less reaction times, the formation of the amine and methylnaphthalene are in parallel.

Halogenated derivatives were also reduced (Table 11, entries 9-10). In these cases, dehalogenation reactions were observed followed by the reduction of nitrile to amine. Other halogenated derivatives at different positions were reduced giving benzylamine at the end of the reaction.

It is noted that this system is efficient in the cyclization of dinitriles. From literature data, this transformation could be realized by hydrogenation catalyzed by Ni,[103] Rh,[104] Pt [105] and Pd [103f, 105a] catalysts. Other sources of hydrides such as aluminum and boron hydrides or silanes have been used as well. [106,107]

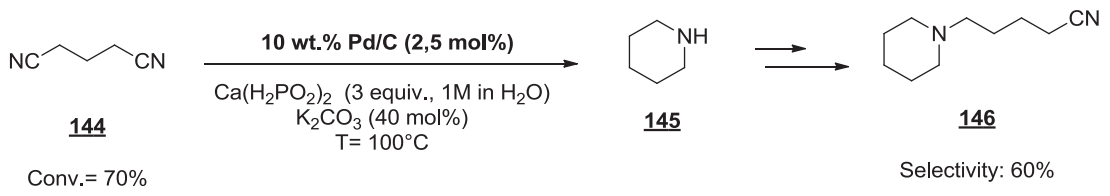
In our laboratory, two systems were reported using TMDS-Ti(O*i*-Pr)$_4$ and PMHS- Ti(O*i*-Pr)$_4$ .These systems were able to reduce dinitriles into the corresponding saturated N-heterocycles, through an intramolecular reductive alkylation reaction as shown in scheme 42.[108]



Scheme 42. Formation of saturated N-heterocycles by reduction of dinitriles.

In our case, glutaronitrile **144** was converted into piperidine **145** then to 5-(piperidin-1-yl)pentanenitrile **146** under similar reaction conditions, where 3 equivalents of the

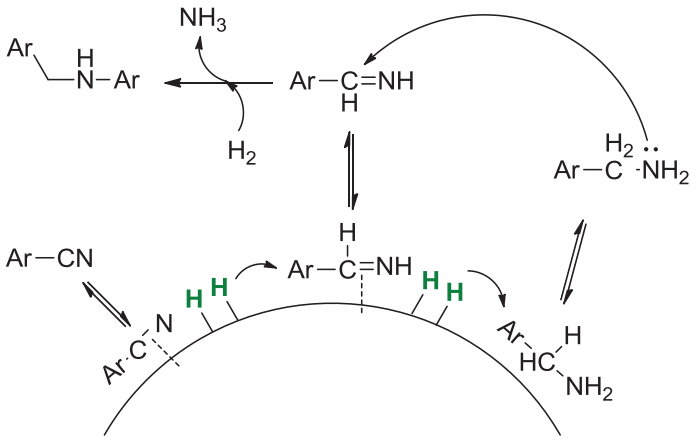
reducing agent $Ca(H_2PO_2)_2$ (Scheme 43). This shows that our system is able to cyclize dinitriles into either N-heterocyclic compounds or into substituted N-heterocyclic compounds. However, the reaction conditions should be optimized. On the other hand some limitations exist, in case of aliphatic nitriles the conversions were very low.



Scheme 43. The cyclization of glutaronitrile **144** into5-(piperidin-1-y)pentanenitrile **146** via intermediate **145**.

3.4.4. Mechanism

Based on our observations, a mechanism was proposed as detailed in Scheme 44. We propose that reactions take place on the surface of heterogeneous palladium and in solution. At the beginning, we suggest that molecular hydrogen is formed during the interaction of base and calcium hypophosphite in water upon heating. Molecular hydrogen then deposits on the surface of Pd/C, where consequence reduction of benzonitrile to benzylamine occur on the surface of the catalyst passing through benzylimine intermediate. To explain the formation of dibenzylamine, we suggest that when there is less catalyst, the concentration of free imine increases in the solution, since there is less adsorption onto the catalyst surface. This benzylimine reacts with the formed benzylamine and produces dibenzylamine and ammonia.



Scheme 44. Proposed mechanism for the reduction of nitrile into amine and diamine.

3.4.5. Conclusion

The comparison of the results obtained with calcium hypophosphite and the results of Johnstone obtained with sodium hypophosphite during the cleavage of aromatic ethers, [95] showed better conversions as well as better yields in our method.

As a result we have demonstrated that our catalytic system $Ca(H_2PO_2)_2$/ Pd/C is efficient for the reduction of variety of aromatic nitriles bearing different functional groups where the amount of catalyst change the whole pathway of the reaction. The advantages of the used system lie in the choice of greener reagents and solvents (H_2O) and the easy workup (mild, simple, and practical).

3.5. Conclusion

In this part, we have developed two methodologies for the reduction of nitriles into aldehydes and amines, using an effective hydrogen donor calcium hypophosphite $Ca(H_2PO_2)_2$.

The reduction of nitriles into aldehydes was done in the presence of $Ni(OAc)_2$ as a catalyst and $Ca(OAc)_2$ as a basic additive in biphasic medium of ethanol/water. Good yields and good selectivities have been observed, however the reaction is restricted only

to aromatic derivatives. More experiments and analysis should be done to improve the substrate versatility and to understand the exact mechanism.

The reduction into amines was done in different conditions, using Pd/C as a catalyst and K_2CO_3 as a basic additive in aqueous medium. With 2,5 mol% of catalyst the amine is the sole product, changing the amount to 1 mol% the diamine is the major one. This system also allowed the formation of 6-membered saturated heterocycle by the reduction of glutaronitrile. Additional optimization and development steps are therefore required for the cyclization of dinitriles.

Finally, these reactions were performed with non-toxic solvents and an inexpensive reducer $Ca(H_2PO_2)_2$. For these reasons these two reducing systems may be of interest in green synthesis.

4. Experimental part

4.1. General information

All reagents were obtained from commercial sources and used as received without any further purification. $CuCl_2$, $Ca(H_2PO_2)_2$ and TDA were purchased from Alfa Aesar®. $Ca(H_2PO_2)_2$ was placed always in desiccators. $Ni(CH_3CO_2)_2.4H_2O$ Assay ≥ 99.0% (KT) was purchased from Fluka. 10% Pd/C, 10% Pt/C, 5% Pd/C, $[RuCl_2(p\text{-cymene})]_2$ and $NiCp_2$ were purchased from Strem Chemicals. $NiBr_2$, Ni $(acac)_2$, $Ni(ph_3P)_2Br_2$, $Ni(ph_3P)_4$, $Ni(cod)_2$, Ni~65 wt. % on Si/Al, 2,2'-bipyridine, K_2CO_3, N,N-diisopropylethylamine, hydrogen chloride solution 2M in diethylether and calcium acetate monohydrate were purchased from Sigma Aldrich. $Ni(dppe)Cl_2$ was purchased from ACROS. $NiCl_2$ was purchased from Laurylab.

The complete references of the used sealed tubes used in the reduction of nitriles into aldehydes are: ACE pressure tubes, Ace-Thred #7, order code (*Z*564564), length (10.2 cm), body O.D. (19 mm), capacity (9 mL), pressure rating (150 PSI or 10.3 bar). The

pressure tube was closed by a front seal Ace O-rings, Silicone (wall 1.78 mm, I.D. 5.3 mm) provided by Sigma Aldrich (ref: 7855-207).

The complete references of the pressure tubes used in the reduction of amines into aldehydes are: ACE pressure tubes, #15 Ace-Thred, order code (CAS: 8648-03), length (10.2 cm), body O.D. (25.4 mm), capacity (15 mL), pressure rating (150 PSI or 10.3 bar) and ACE pressure tubes, order code (CAS: 8648167), length (10.2 cm), body O.D. (38.1 mm), capacity (38 mL), pressure rating (150 PSI or 10.3 bar). The pressure tube was closed by a back seal PTFE plug 5845 with a 210 O-ring for #15 Ace-Thred in FETFETM or silicone, provided by Sigma Aldrich as well.

Silica gel (40–63 micron) was used for column chromatography. Thin layer chromatography was performed on precoated silica gel 60–F 254 plates. UV light, 2,4-dinitrophenylhydrzine was used for analysis of the TLC plates.

All compounds were characterized by spectroscopic data. The nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker ALS 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), a DRX 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or a Bruker DRX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer, in D_2O or DMSO-d_6 at 293K. Chemical shifts are reported in parts per million (ppm) and are calibrated on residual solvent peaks: D_2O 4.79 ppm in ^{1}H, or DMSO-d_6 2.50 ppm in ^{1}H and 39.52 ppm in ^{13}C.[1] Spin-spin coupling constants (*J*) are given in Hz. The peak patterns are indicated as follows: (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad).

GC-MS analyses were performed on a DSQ - Thermofinnigan spectrometer equipped with quadrupole analyzer and a DB-5MS capillary column (30.0 m × 0.25mm × 0.25µm). The carrier gas was helium, at a flow rate of 1 mL/min. Column temperature was initially 70 °C for 2 min, then gradually increased to 310 °C at 15 °C/min and finally kept at 310 °C for 10 min. The injector temperature was 220 °C and the transfer line temperature was 280 °C.

GC analyses were performed on a Shimadzu Gas Chromatograph GC-2025 equipped with a ZB-5-MS column (30.0 m × 0.25mm × 0.25µm). The carrier gas was N_2 at a flow rate of 1.27 mL/min. Column temperature was initially 70 °C for 2 min, then gradually increased to 280 °C at 15 °C/min and finally kept at 280 °C for 15 min. The injector temperature was 250 °C and for detection a FID was used at 280 °C.

4.2. Procedures

4.2.1. Typical procedure for the reduction of nitrile into aldehyde

In a sealed tube Ace-Thred #7 indicated above, Nickel(II)acetate tetrahydrate (49.7 mg, 0.2 mmol, 20 mol%) was introduced followed by water (1 mL, $[Ca(H_2PO_2)_2]$= 1M), the tube was stirred at room temperature. Calcium hypophosphite (170 mg, 1 mmol) was then added followed by calcium acetate monohydrate (70.4 mg, 0.4 mmol, 40 mol%). To this mixture was added the nitrile substrate (1 mmol) and ethanol absolute (1 mL, [nitrile] in ethanol= 1M), the tube was then sealed. The reaction mixture was stirred at 920 rpm and heated at 100°C. After the sufficient time for each substrate, the tube was cooled at room temperature, depressurized and an aliquot was taken and extracted with water and diethyl ether for GC analysis to check the conversion of the starting material. The reaction mixture was then diluted by excess of water to remove ethanol and extracted twice with diethylether. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure (800 mbar). After concentration, aldehydes were obtained as oils or solids. If needed a flash chromatography column was done on silica gel by using gradient of different solvents according to the final product. The products were then characterized by NMR spectroscopy and GC-MS.

4.2.2. Typical procedure for the reduction of nitrile into amine

In a sealed tube Ace-Thred #15 indicated above, calcium hypophosphite (425.15mg, 2.5 mmol) was introduced, followed by K_2CO_3 (55.12 mg, 0.4 mmol). 2,5 mL of H_2O was then added ($[Ca(H_2PO_2)_2]$= 1M), the tube was stirred at room temperature. To this

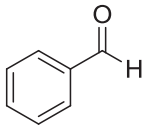
mixture was added benzonitrile (103.12mg, 1 mmol), followed by Pd/C 10 wt.% (26.5 mg, 2.5 mol%), the tube was then sealed. The reaction mixture was stirred at 800 rpm at 100°C. After 24 hours the tube was cooled in cold water and pressure was released carrefully. The reaction mixture was dilluted with HCl (2M in H_2O) and extracted with diethylether. To the acidic aqueous phase an alkaline solution of NaOH (2M in H_2O) was added until pH=14, an extraction was done twice with diethylether. The obtained organic phase was dried over Na_2SO_4. The crude was analyzed in GC and GC-MS.

4.2.3. Typical Procedure for isolation of amines as HCl salts

HCl (1M in diethylether, 1mL) was added to the extracted organic phase, stirring was maintained for 30 minutes at room temperature. The resulting precipitate was filtered and washed with diethyl ether then pumped under reduced pressure to dry.

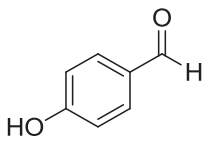
4.3. Characterization data

4.3.1. Caharacterization data of isolated aldehydes



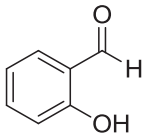
Benzaldehyde [100-52-7] (97)

Colorless oil. Eluent for isolation 5:5 pentane/DCM. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.92 (s, 1H, CHO), 7.79-7.77 (d, *J*=6 Hz, 2H, CH_{Ar}), 7.53-7.50 (m, 1H, CH_{Ar}), 7.45-7.40 (m, 2H, CH_{Ar}) ppm **^{13}C NMR (75 MHz, $CDCl_3$):** δ 192.51 (C_q, C-HC=O), 136.51 (C_q, C_{Ar}), 134.57 (C_q, C_{Ar}), 129.85 (2 CH, C_{Ar}), 129.1 (CH, C_{Ar}) ppm. **GC:** retention time: 4.3 min.



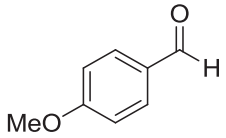
4-Hydroxy benzaldehyde [123-08-0] (105)

Offwhite powder. Eluent for isolation 9:1 DCM/diethylether. **^{1}H NMR (300 MHz, DMSO-d6):** δ 10.59 (s broad, 1 H, O*H*), 9.78 (s, 1H, CHO), 7.77-7.74 (d, *J*= 9 Hz, 2H, CH_{Ar}), 6.94-6.91 (d, *J*= 9 Hz, 2H, CH_{Ar}), ppm. **^{13}C NMR (75 MHz, DMSO-d6):** δ 190.96 (C_q, C-HC=O), 163.33 (C_q, C_{Ar}), 132.12 (CH, C_{Ar}), 128.45 (C_q, C_{Ar}), 115.85 (CH, C_{Ar}) ppm. **GC:** retention time: 8.7 min.



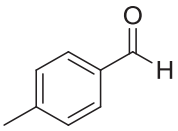
2-Hydroxy benzaldehyde [90-02-8] (107)

Colorless liquid. Eluent for isolation: 9:1 pentane/diethylether. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 10.92 (s, 1 H, O*H*), 9.80 (s, 1H, CHO), 7.48-7.40 (m, 2H, CH_{Ar}), 6.95-6.88 (m, 2H, CH_{Ar}), ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.75 (C_q, C-HC=O), 161.79 (C_q, C_{Ar}), 137.14 (CH, C_{Ar}), 133.87 (CH, C_{Ar}), 120.82 (C_q, C_{Ar}), 119.99 (CH, C_{Ar}), 117.77 (CH, C_{Ar}) ppm. **GC:** retention time: 5.3 min.



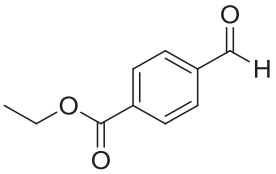
4-methoxybenzaldehyde [123-11-5] (109)

Colorless liquid. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.77 (s, 1 H, CHO), 7.74-7.71 (d, *J* = 9 Hz, 2 H, CH_{Ar}), 6.91-6.88 (d, *J* = 9 Hz, 2H, CH_{Ar}), 3.78 (s, 3H, OCH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 190.93 (C_q, C-HC=O), 164.72 (C_q, C_{Ar}), 132.09(2 CH, C_{Ar}), 130.06 (C_q, C_{Ar}), 114.42 (2 CH, C_{Ar}), 55.69 (CH_3) ppm. **GC:** retention time: 7.8 min.



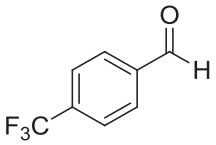
4-methyl benzaldehyde [104-87-0] (<u>111</u>)

Colorless liquid. Eluent for isolation 9:1 pentane/diethylether. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.82 (s, 1 H, C<u>H</u>O), 7.65-7.62 (dd, 2 H, CH_{Ar}), 7.2-7.17 (d, J = 9 Hz, 2H, CH_{Ar}), 2.29 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 190.96 (C_q, C-HC=O), 164.73 (C_q, C_{Ar}), 132.11 (2 CH, C_{Ar}), 130.07 (C_q, C_{Ar}), 114.43 (2 CH, C_{Ar}), 55.7 (CH_3) ppm. **GC:** retention time: 5.9 min.



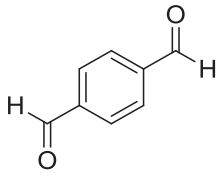
Ethyl 4- formyl benzoate [6287-86-1] (<u>113</u>)

Colorless liquid. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.97 (s, 1 H, C<u>H</u>O), 8.08-7.99 (m, 2 H, CH_{Ar}), 7.83-7.80 (d, J = 9 Hz, 1 H, CH_{Ar}), 7.63-7.60 (d, J = 9 Hz, 1 H, CH_{Ar}), 4.32-4.25 (q, 2H, CH_2), 1.31-1.26 (t, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 191.68 (C_q, C-HC=O), 165.5 (C_q, C-HC=O), 139.04 (C_q, C_{Ar}), 135.4 (C_q, C_{Ar}), 130.1 (2 CH, C_{Ar}), 129.4 (2 CH, C_{Ar}), 61.5 (CH_2), 14.2 (CH_3) ppm. **GC:** retention time: 9.7 min.



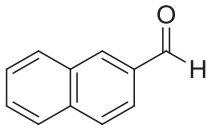
4-(Trifluoromethyl) benzaldehyde [455-19-6] (<u>115</u>)

Light yellow liquid. Eluent for isolation 9:1 pentane/diethylether. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.99 (s, 1 H, C<u>H</u>O), 7.92-7.89 (d, J = 9 Hz, 2 H, CH_{Ar}), 7.81-7.78 (d, J = 9 Hz, 2H, CH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 191.21 (C_q, C-HC=O), 138.78 (C_q, C_{Ar}), 130.03 (2 CH, C_{Ar}), 126.2 (2 CH, C_{Ar}), 125.36 (C_q, CF_3), 121.75 (C_q, C_{Ar}) ppm. **GC:** retention time: 4.2 min.



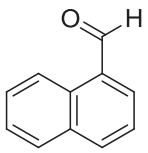
Terephthaldehyde [623-27-8] (117)

White crystals. Eluent for isolation 9:1 pentane/diethylether. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 10.03 (s, 2 H, CHO), 7.95 (s, 4H, CH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 191.62 (2 C_q, C-HC=O), 140.15 (2 C_q, C_{Ar}), 130.27 (4 CH, C_{Ar}) ppm. **GC:** retention time: 7.4 min.



2-Naphthalaldehyde [66-99-9] (119)

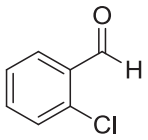
Slight yellow crystalline powder. Eluent for isolation 9:1 DCM/diethylether. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 10.05 (s, 1 H, CHO), 8.22 (s, 1H, CH_{Ar}), 7.91-7.78 (m, 4H, CH_{Ar}), 7.57-7.45 (m, 4H, CH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 192.36 (C_q, C-HC=O), 136.53 (C_q, C_{Ar}), 134.66 (CH, C_{Ar}), 134.19 (2 C_q, C_{Ar}), 132.72 (C_q, C_{Ar}), 129.62 (CH, C_{Ar}), 129.21 (CH, C_{Ar}), 128.17 (CH, C_{Ar}), 127.19 (CH, C_{Ar}), 122.84 (CH, C_{Ar}) ppm. **GC:** retention time: 10.2 min.



1-Naphthalaldehyde [66-77-3] (121)

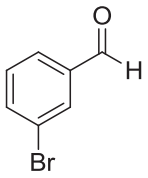
Colorless liquid. Eluent for isolation 9:1 DCM/diethylether. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 10.31 (s, 1 H, CHO), 9.17-9.14 (d, 1H, J = 9 Hz, CH_{Ar}), 8.02-7.99 (d, 1H, J =

9 Hz, CH_{Ar}), 7.91-7.89 (d, 1H, *J* = 6 Hz, CH_{Ar}), 7.84-7.82 (d, 1H, *J* = 6 Hz, CH_{Ar}), 7.63-7.47 (m, 3H, 3xCH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 193.58 (C_q, CHO), 136.71 (CH, C_{Ar}), 135.32 (CH, C_{Ar}), 133.76 (C_q, C_{Ar}), 131.42 (C_q, C_{Ar}), 130.56 (CH, C_{Ar}), 129.1 (CH, C_{Ar}), 128.53 (CH, C_{Ar}), 127 (CH, C_{Ar}), 124.91 (CH, C_{Ar}) ppm. **GC:** retention time: 10.1 min.



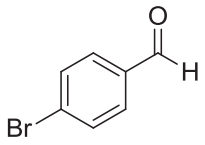
2-Chlorobenzaldehyde [89-98-5] (123)

Colorless Liquid. Eluent for isolation only pentane. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 10.38 (s, 1 H, C-CO-*H*), 7.83 (s, 1H, CH_{Ar}), 7.8-7.15 (m, 3H, CH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 189.94 (C_q, C-HC=O), 138.10 (C_q, C_{Ar}), 135.25 (CH, C_{Ar}), 132.64 (C_q, C_{Ar}), 130.76 (CH, C_{Ar}), 129.52 (CH, C_{Ar}), 127.43 (CH, C_{Ar}) ppm. **GC:** retention time: 6.2 min.



3-Bromobenzaldehyde [3132-99-8] (125)

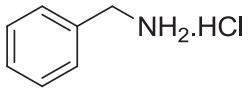
Yellow liquid. Eluent for isolation 6:4 pentane/DCM. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.86 (s, 1 H, CHO), 7.92 (s, 1H, CH_{Ar}), 7.91-7.63 (m, 2H, CH_{Ar}), 7.35-7.29 (m, 1H, CH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 190.88 (C_q, C-HC=O), 138.12 (C_q, C_{Ar}), 137.44 (CH, C_{Ar}), 132.49 (CH, C_{Ar}), 130.76 (CH, C_{Ar}), 128.51 (CH, C_{Ar}), 123.51 (C_q, C_{Ar}) ppm. **GC:** retention time: 7.3 min.



4-Bromobenzaldehyde [1122-91-4] (127)

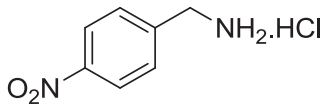
White crystals. Eluent for isolation 6:4 pentane/DCM. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.86 (s, 1 H, CHO), 7.65-7.62 (d, 2H, *J* = 9 Hz, CH_{Ar}), 7.58-7.55 (d, 2H, *J* = 9 Hz, CH_{Ar}) ppm. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 191.17 (C_q, C-HC=O), 135.18 (C_q, C_{Ar}), 132.54 (2CH, C_{Ar}), 131.07 (2 CH, C_{Ar}), 129.88 (C_q, C_{Ar}) ppm. **GC:** retention time: 7.4 min.

4.3.2. Characterization data of isolated hydrochloride salts



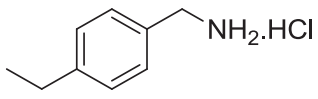
Phenyl methanammonium chloride (134)

^{1}H NMR (300 MHz, D_2O): δ 7.47 (s, 5H), 4.17 (s, 2H) ppm **^{13}C NMR (75 MHz, D_2O):** δ 132.54, 129.17, 128.78, 43.06 ppm.



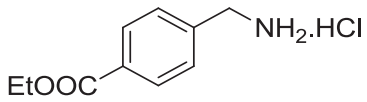
(4-nitrophenyl)methanammonium chloride (136)

^{1}H NMR (300 MHz, D_2O): δ 7.45-7.41 (m, 2H), 7.39-7.35 (m, 2H), 2.43 (s, 1H) ppm **^{13}C NMR (75 MHz, D_2O):** δ 139.65, 130.44, 126.89, 122.59, 20.03 ppm.



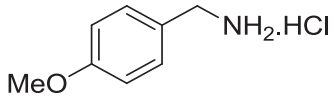
(4-ethylphenyl)methanammonium chloride (138)

^{1}H NMR (300 MHz, DMSO): δ 6.56-6.52 (m, 2H), 6.38-6.33 (m, 2H), 3.06 (s, 2H), 1.76-1.68 (q, 2H), 0.31-0.26 (t, 3H) ppm. **^{13}C NMR (75 MHz, DMSO):** δ 144.08, 131.39, 129.06, 127.91, 41.88, 27.91, 15.73 ppm.



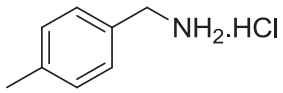
[(4-ethoxycarbonyl)phenyl]methanammonium chloride (<u>139</u>)

^{1}H NMR (300 MHz, D_2O): δ 8.05-8.03 (d, J=6 Hz), 7.55-7.53 (d, J=6 Hz), 4.40-4.33 (q, 2H), 4.25 (s, 2H), 1.39-1.34 (t, 3H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 168.31, 137.78, 130.33, 129.99, 128.80, 62.36, 42.58, 13.32 ppm.



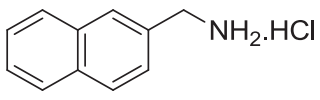
(4-methoxyphenyl)methanammonium chloride (<u>140</u>)

^{1}H NMR (300 MHz, D_2O): δ 7.53-7.50 (d, J= 9Hz, 2H), 7.16-7.13 (d, J= 9 Hz), 4.23 (s, 2H), 3.94 (s, 3H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 159.35, 130.54, 125.11, 114.52, 55.33, 42.54 ppm.



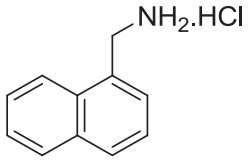
***p*-tolyl methanammonium chloride (<u>141</u>)**

^{1}H NMR (300 MHz, D_2O): δ 7.33 (m, 4H), 4.13 (s, 2H), 2.34 (s, 3H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 139.56, 129.7, 129.54, 128.82, 42.8, 20.19 ppm.



Naphthalene-2-ylmethanammonium chloride (<u>142</u>)

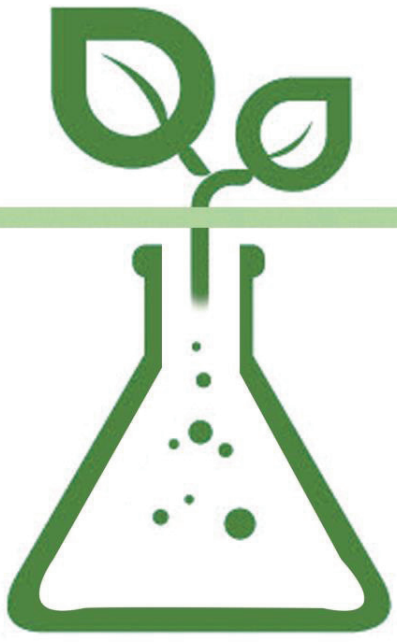
^{1}H NMR (300 MHz, D_2O): δ 7.95-7.92 (m, 4H), 7.61-7.55 (m, 2H), 7.52-7.49 (m, 1H), 4.3 (s, 2H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 132.89, 132.81, 130.10, 128.89, 128.13, 127.91, 127.67, 127.02, 126.86, 125.89, 43.14 ppm.



Naphthalene-1-ylmethanammonium chloride (<u>143</u>)

^{1}H NMR (300 MHz, D_2O): δ 8.02-7.94 (m, 3H), 7.68-7.5 (m, 4H), 4.6 (s, 2H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 133.44, 130.39, 129.89, 128.95, 128.25, 127.81, 127.24, 126.52, 125.58, 122.31, 40.13 ppm.

Part II: Direct Reductive Amination of Ketones Using Ammonium Hypophosphite

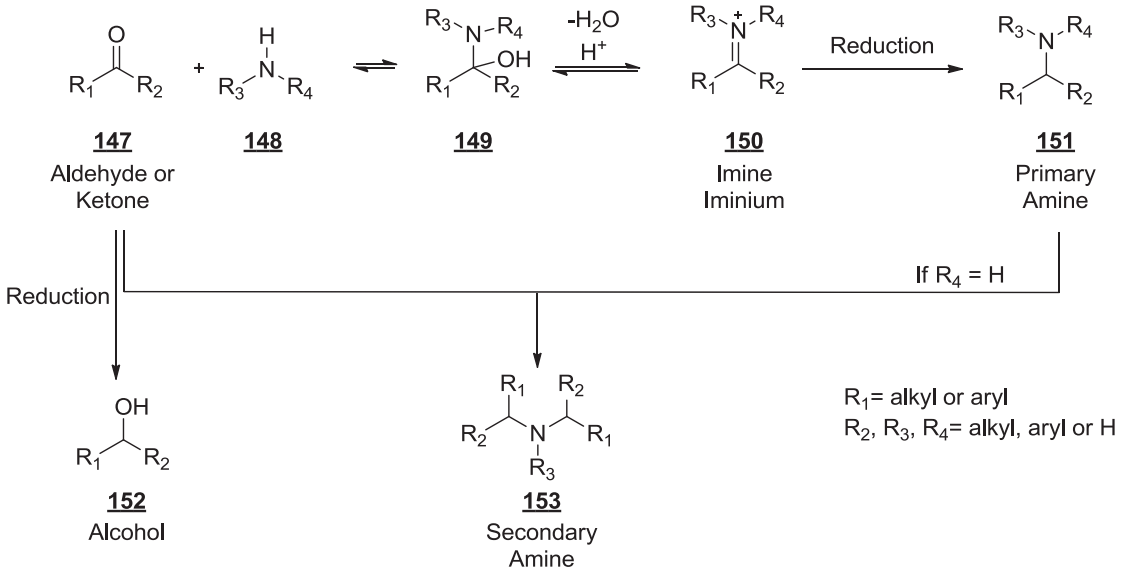


PART II. DIRECT REDUCTIVE AMINATION OF KETONES USING AMMONIUM HYPOPHOSPHITE

1. Introduction

Amines represent an important class of compounds in organic chemistry, especially for the pharmaceutical and agrochemical industries. Numerous methodologies have been reported for the synthesis of amines, including reductive amination (RA) of carbonyl compounds, which is the reaction of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines respectively.

The RA of aldehydes and ketones proceeds in several consecutive steps as shown in scheme 45. The reaction between **147** and **148** involves the initial formation of the intermediate carbinol amine **149**, which dehydrates to form an imine. Under the reaction conditions which are usually weekly acidic to neutral, the imine is protonated to form an iminium ion **150**.[109]



Scheme 45. Reductive amination pathway.

Subsequent reduction of this iminium ion produces the amine **151** as the final product. However, there are some reports that provide evidence suggesting a direct reduction of the carbinol amine **149** as a possible pathway leading to **151**.[110] The choice of the reducing agent is very critical to the success of the reaction, since it must reduce selectively the intermediate imine to amine, and not to produce the corresponding alcohol **152** or secondary amine **153** according to scheme 45.

The reductive amination reaction is described as a *direct* reaction when the carbonyl compound and the amine are mixed with the proper reducing agent without prior formation of the intermediate imine or iminium salt. A *stepwise* or *indirect* reaction involves the preformation of the intermediate imine followed by the reduction in a separate step.

In literature, there exist many methods for this type of reaction. However, there is a big demand for new environmentally friendly methods which are more practical and less expensive.

In this part, different methods from literature for the RA of aldehydes and ketones to form amines will be discussed. Then, we will explain our new investigated method, finishing with a conclusion, perspectives and experimental section.

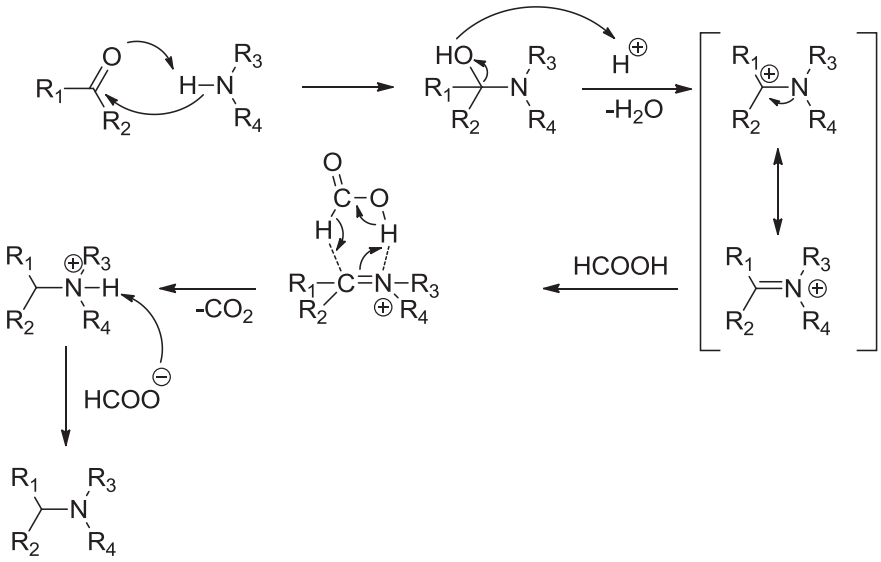
2. Bibliographic data

A powerful route to synthesize amines is the RA of carbonyl groups using ammonia or amine to form the imine intermediate, which is then reduced to amine. This reaction is attractive in organic synthesis because ketones and aldehydes can be transformed, in one reaction vessel, directly to the corresponding secondary or primary amine, without isolation of the intermediary imine or hydroxyl amine. Herein, we reported the literature data concerning this type of reaction.

2.1. Catalytic Leuckart-Wallach-Type reductive amination of ketones

In 1885, Leuckart first described the conversion of certain aldehydes and ketones to the corresponding amines by heating with excess ammonium formate.[111] In 1892, Wallach applied the method to a number of alicyclic and terpenoid ketones, as well as certain aldehydes, and showed it's general application.[112] After this, the reaction was known as Leuckart-Wallach (LW) reaction.

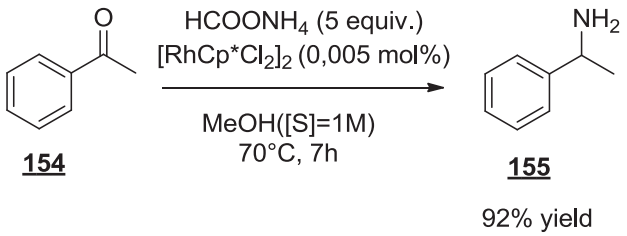
The LW reaction takes place via several steps. At the beginning, ammonium formate dissociates into ammonia and formic acid upon heating, and the produced ammonia condenses on the carbonyl carbon forming carbenium ion which was rearranged into iminium ion. Subsequently, a cyclic transition state was formed with the aid of formic acid, followed by decarboxylation and finally deprotonation to form the corresponding amine (Scheme 46).[111, 112, 113]



Scheme 46. Mechanism of LW reaction.[111, 112, 113]

In 2002, M. Kitamura et al. produces a novel catalytic system facilitating the Leuckart-Wallach-type reaction at lower temperature with chemoselectivity and generality.[114] The reaction is catalysed by Cp*Rh(III) complex (0,005 mol%), in the presence of 5 equiv. $HCOONH_4$ in methanol at 50-70°C, to give the amines with yields up to 99% (Scheme

47). This method has been applied also to the synthesis of α-amino acids directly from α-keto acids.

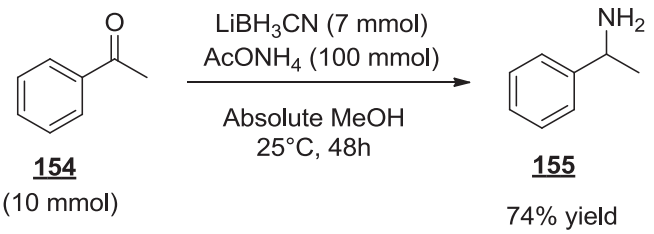


Scheme 47. DRA of acetophenone **154** using Cp*Rh(III) and $HCOONH_4$.[114]

2.2. DRA of ketones using cyanohydridoborate anion

Considerable attention has been devoted to the study of modified boron hydrides as selective reducing agents for organic functional groups.[115, 116] In 1970, R. F. Borch et al. has established that the reduction of the iminium moiety with BH_3CN^- was rapid at pH 6-7, and that the reduction of aldehydes and ketones was negligible in this pH range. Thus, it was conceivable that an aldehyde or ketone could be reductively aminated by simply reacting the carbonyl compound with amine or ammonia at pH~6 in the presence of BH_3CN^- to get the amine, where the pre-equilibrium step that generates the iminium moiety is the rate determining step.[117]

For example, when acetophenone **154** was treated with fivefold excess of ammonia in methanol at pH=6 in the presence of $LiBH_3CN$, α-phenylethylamine **155** was obtained after 48h in 74% yield (scheme 48).



Scheme 48. DRA of **154** in the presence of ammonium acetate and $LiBH_3CN$.[117]

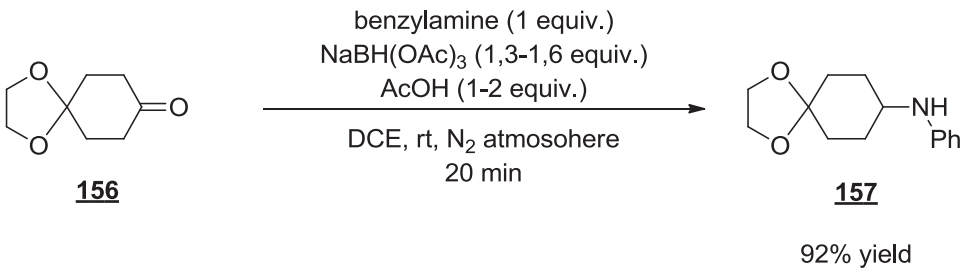
The literature is replete with publications that document the use of $NaBH_3CN$ in reductive amination reactions. [118]

This reaction can be carried out under mild conditions, and is compatible, in some cases, with many functional groups. However, the processes based on such reducing agents have many limitations, it may require up to fivefold excess of the amine,[117] it is usually slow and sluggish with aromatic ketones and with weakly basic amines, [119] and may result in the contamination of the product with cyanide.[120] The reagent is highly toxic, since it leads to the production of toxic byproducts such as HCN and NaCN.

2.3. DRA of ketones using sodium triacetoxyborohydride

Sodium triacetoxy borohydride $NaBH(OAc)_3$ was presented by Abdel-Magid et al. in 1996, as a general reducing agent for the RA of aldehydes and ketones. This reagent is considered to be mild in comparison to other boron hydride reagents.[121] The effectiveness of this reaction includes aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, with primary and secondary amines including a variety of weakly basic and non-basic amines. Reaction times vary from 20 min to 10 d depending on the structure of the reactants.

Taking an example, 1,4-dioxaspiro[4.5]decan-8-one **156** was reacted with 1 equiv. of benzylamine in the presence of acetic acid and 1,2-dichloroethane (DCE) as a solvent, using 1,3-1,6 equiv. of $NaBH(OAc)_3$ at rt and under N_2 atmosphere. The corresponding amine **157** was obtained after 20 min and isolated as an oxalate salt in 92% yield (Scheme 49).[121]



156 **157**

92% yield

Scheme 49. DRA of **156** in the presence of $NaBH(OAc)_3$.[121]

For the same ketone, the reaction was dependent on the steric and electronic factors associated with the amines. For example, the reaction of **156** with piperidine requires 75 min to give the amine in 66% isolated yield. This method suffers from several drawbacks since $NaBH(OAc)_3$ is flammable, water-reactive and poorly soluble in the most common organic solvents and has limitations with aromatic and unsaturated ketones. In addition, this reagent has only one available hydride and usually excess (1.5 equiv.) of the reagent are necessary for reaction.

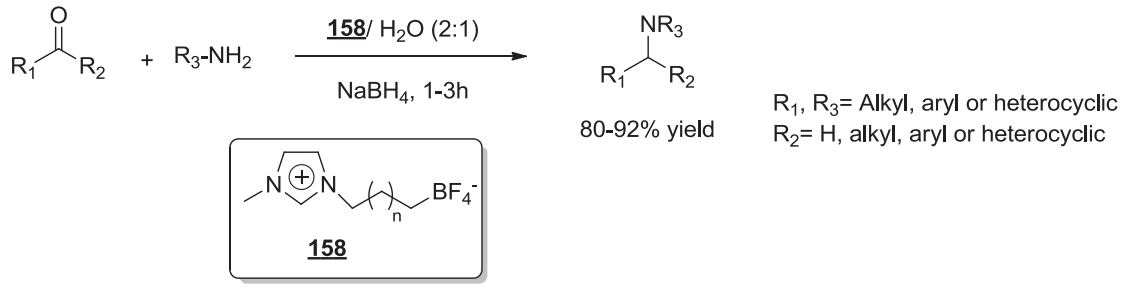
2.4. DRA of ketones using sodium borohydride

Sodium borohydride $NaBH_4$ is an inexpensive reducing agent known to reduce imines and other functionalities, thus limiting its application in broader sense. Moreover, it is understood that the poor electrophilic carbonyls, poor nucleophilic amines, and sterically crowded reactive centers do not favor the completion of imine formation. Thus, it is quite apparent that $NaBH_4$ alone may not afford excellent yields. For that reason $NaBH_4$ should be associated with metal catalysts and additives. Literature is full with these examples.

2.4.1. With Brønsted acids

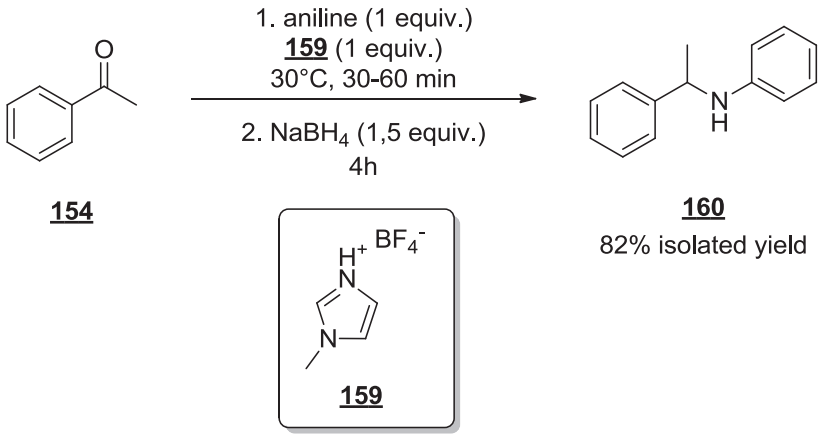
$NaBH_4$ has been employed with various Brønsted acids (H_2SO_4, *p*-toluenesulfonic acid) in order to facilitate the initial formation of the imine leading to a successful RA without byproducts.[122] However, these are corrosive, toxic and difficult to separate from the reaction solution, so they were substituted by more environmentally friendly solid acids such as heteropolyacids (HIPAs).[123]

Other researchers focused on ionic liquids (IL), which have potential as green solvents for several chemical and biochemical transformations.[124] In 2006, Nagaiah et al. described a combination of IL ([Bmim]BF_4) **158** and H_2O as solvent and $NaBH_4$ as the reducing agent for the one pot RA of aldehydes and ketones (Scheme 50).[125] The requirement of a large excess of IL was a disadvantage of this reaction.



Scheme 50. RA of aldehydes and ketones using $NaBH_4$/ **158**. [125]

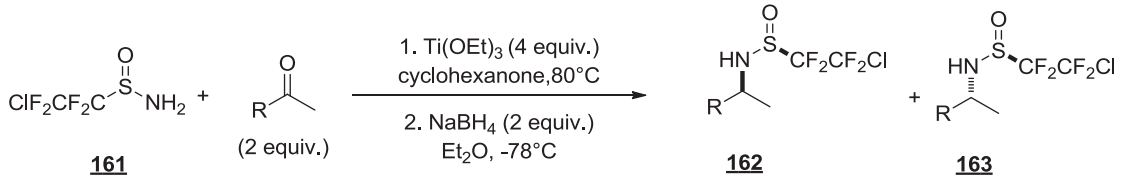
Prasad and co-workers made a combination of all these concepts, and reported for the first time the RA of carbonyl compounds using $NaBH_4$ in the presence of Brønsted acidic IL, in which the Brønsted acidic nature of the IL is responsible for imine formation.[126] Reaction was conducted by adding the amine and carbonyl compound in 1-methyl imidazium tetrafluoroborate ([Hmim][BF_4]) **159**, which is efficient in various organic transformations,[127] then stirred at 30°C for 30-60 min in order to monitor the conversion of **154** for example to imine, at the end $NaBH_4$ was added to achieve 82% yield of **160** within 4h (Scheme 51).[126] Using this methodology a series of aldehydes and ketones were reductively aminated in excellent yields. An advantage of the process is the recovery of the IL at the end of the reaction, which is recycled for four consecutive reactions during the RA of benzaldehyde. Another advantage is the selectivity towards imines in the first step of the reaction without the formation of any side product.



Scheme 51. RA of aldehydes and ketones using $NaBH_4$/ **159**. [126]

2.4.2. With fluorinated chiral auxiliary

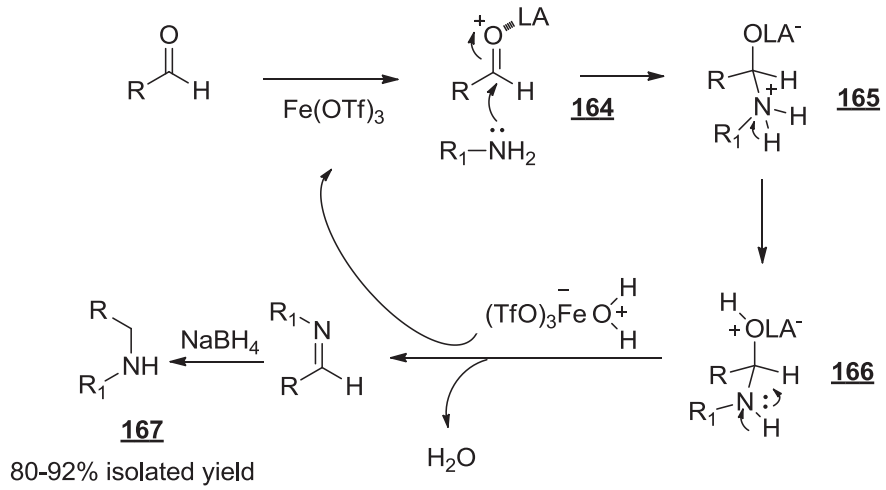
Recently, the reduction of *N-tert*-butylsulfinyl ketimines has attracted much attention and has been applied in the synthesis of many drug candidate.[128,129] The reduction of *N*-sulfinyl imines was firstly reported by Cozzi[130] and later studied by Ellman.[131, 132] Encouragingly, K. Yang and J.-T. Liu developed a novel fluorinated chiral auxiliary 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide (CTFSA) **161**, which was used for the asymmetric RA of ketones in the presence of $NaBH_4$ (Scheme 52).[133] Both aromatic and aliphatic ketones reacted well under the indicated reaction conditions, giving the corresponding amination products **162** and **163** in good yields with excellent diastereoselectivities.



Scheme 52. One pot RA of ketone using **161** and $NaBH_4$. [133]

2.4.3. With Lewis acid

Metal triflate catalyzed reductive amination procedures are well documented. R. Bandichlor and co-workers employed the combination of 1 mol% $Fe(OTf)_3$ along with stoichiometric amount of $NaBH_4$ (1 equiv.) for the DRA of a variety of aldehydes bearing alkyl, aryl or heterocyclic groups.[134] Mechanistically, $Fe(OTf)_3$ as a Lewis acid activates the carbobyl functionality of the aldehyde, and provides very reactive electrophile source **164**. Amine that was used as a substrate reacts with the activated **164** to afford the hemiaminol **165**. A dehydration event regenerates the catalyst. The *in situ* generated imine **166** can further be reduced with $NaBH_4$ affording the product **167** as shown in Scheme 53.

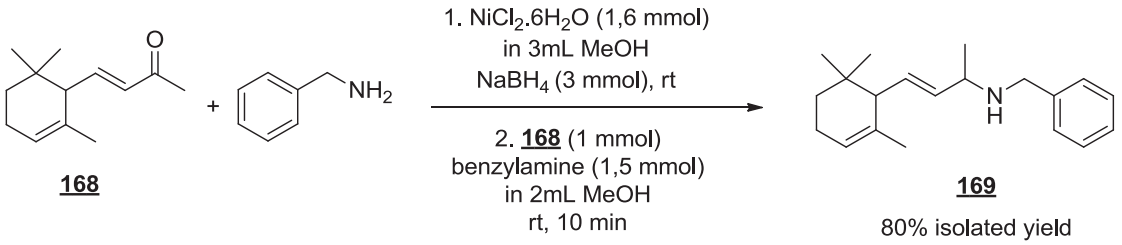


Scheme 53. Possible mechanism of DRA of aldehydes using $Fe(OTf)_3$/ $NaBH_4$.[134]

2.4.4. With Nickel chloride

Since its discovery in Brown's laboratory in the early sixties,[135] nickel boride (BNi_2) has been developed by different research groups as an important catalyst for various transformations.[136] The moistened reagent is non-pyrophoric in nature relative to many metal hydrogenation catalysts. J. C. Sarma and coworkers studied the *in situ* generation of BNi_2 from $NaBH_4$ and nickel chloride ($NiCl_2$).[137] During the course of the reaction it was observed that a carbonyl group remains unaffected under appropriate reaction conditions. So it was argued that the system could be suitable for RA of aldehydes and

ketones. This was confirmed in 2000, when the group generated BNi_2 and used it for the RA of ketones and aldehydes in the presence of amine.[138] For example, α-ionone **168** was reacted with benzylamine to give **169** in 80% yield (Scheme 54).



Scheme 54. RA of **168** in the presence of $NaBH_4/NiCl_2$.[138]

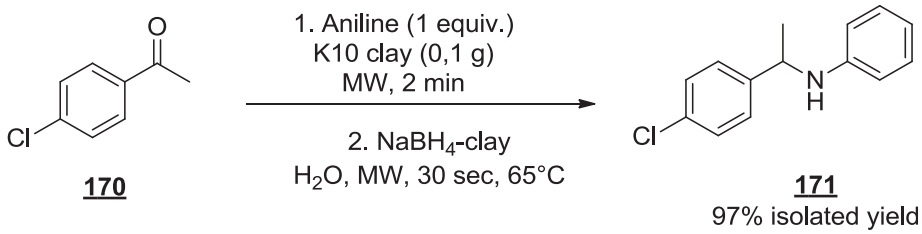
2.4.5. With wet clay

Heterogeneous reactions facilitated by supported reagents on various solid inorganic surfaces have received attention in recent years because of the greater selectivity and simple reaction work-up.[139] Microwave (MW) heating has been used for the rapid synthesis of a variety of organic compounds both in solution phase as well as under solvent-free conditions.[140] Further, the solvent-less microwave-assisted reactions are now gaining popularity as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development.

R. S. Varma and co-workers reported the RA of carbonyl compounds under solvent-free conditions using $NaBH_4$-wet clay coupled with MW activation.[141] Clay not only behaves as an acid, but also provides water from its interlayers that is responsible for the acceleration of the reducing ability of $NaBH_4$.[142]

The synthesis of N-phenyl-*p*-chlorobenzylamine **171** is representative of the general procedure employed (Scheme 55). A mixture of *p*-chlorobenzaldehyde **170**, aniline and montmorillonite K10 clay were placed in MW oven and irradiated for 2 min, followed by the addition of freshly prepared $NaBH_4$-clay and water. The reaction mixture was again

irradiated for 30 sec at 65°C to give the corresponding amine **171** in 97% yield. Without this support a poor yield was obtained (~10%).[141]

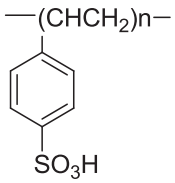


170 **171**
97% isolated yield

Scheme 55. Reduction of **170** using $NaBH_4$-clay under microwave irradiation.[141]

2.4.6. With Amberlyst-15

In the past decade, the chemistry of Amberlyst-15 **172** (Figure 13) has experienced a rapid development.[143e] This growing interest in Amberlyst-15 is mainly due to its mild and highly selective properties, combined with its environmentally benign character and commercial availability. Amberlyst-15 is now routinely used in organic synthesis as other heterogeneous reusable acid catalysts for various selective transformations of simple and complex molecules.[143]

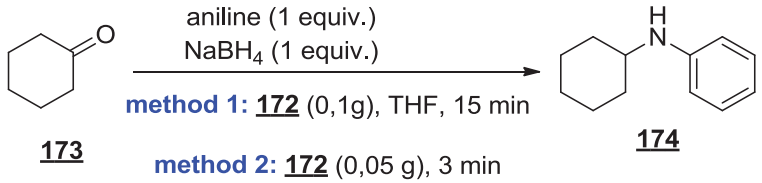


172

Figure 13. Structure of Amberlyst-15.[143e]

In 2010, N. Mahdavi and co-workers reported the DRA of aldehydes and ketones with primary or secondary amines in the presence of $NaBH_4$ and **172** in THF (method 1), and under solvent-free conditions (method 2). In both methods, the reaction was carried out using an equimolar ratio between carbonyl compound, amine and the reducing agent.[144]

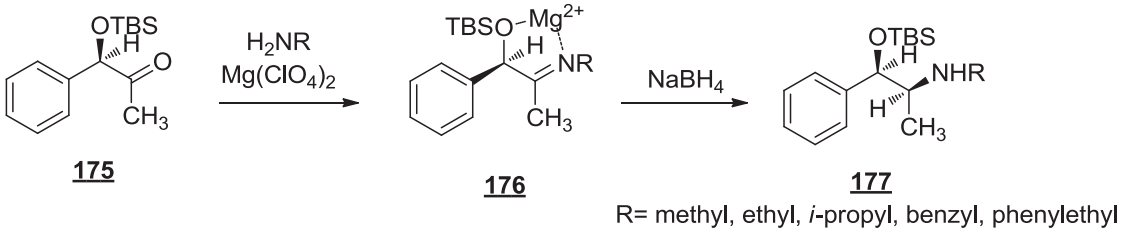
For example, the DRA of cyclohexanone **173** using method 1 requires 15 min, whereas it requires 3 min using method 2 to obtain the N-cyclohexylamine **174** in excellent yields (91-94%) as shown in Scheme 56.[144]



Scheme 56. Reduction of **173** using $NaBH_4$- **172**.[144]

2.4.7. With Magnesium Perchlorate

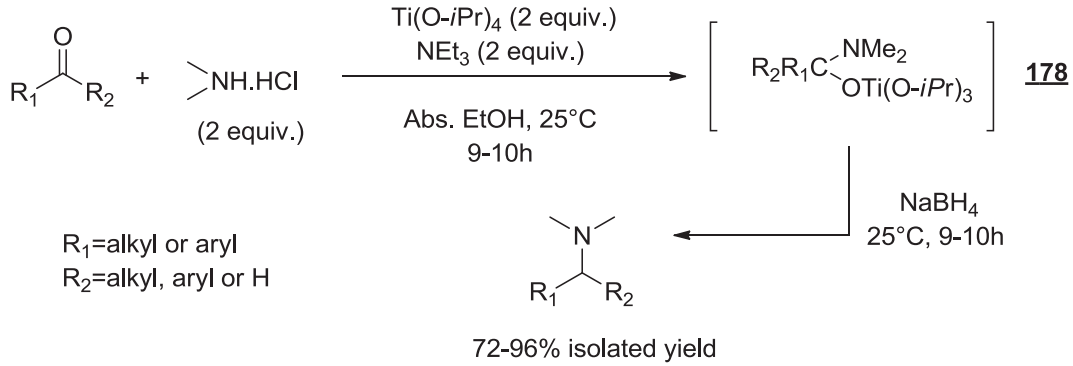
In 1990, J. Brussee et al. reported the DRA of *(R)*-O-protected-α-hydroxyketone **175** with primary amines by $NaBH_4$ in the presence of $Mg(ClO_4)_2$ to form erythro (*1R, 2S*)-O-protected-N-substituted ethanol amine **177** (scheme 57).[145]



Scheme 57. DRA of **175** using $NaBH_4/Mg(ClO_4)_2$.[145]

2.4.8. With Titanium (IV) Isopropoxide

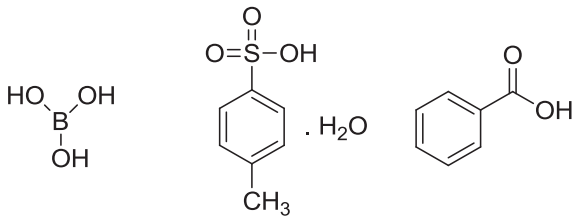
S. Bhattacharyya reported an efficient method for the DRA of carbonyl compounds using a combination of titanium isopropoxide $Ti(O\text{-}iPr)_4$ and $NaBH_4$ for the preparation of *N,N*-dimethylalkylamines.[146] The reaction possibly proceeded through the formation of (dimethylamino)carbinolatotitanium(IV) complex **178**[147] as an intermediate which is reduced either directly or via transient iminium species (Scheme 58).



Scheme 58. DRA if aldehydes and ketones using $NaBH_4$/ Ti(O-*i*Pr)$_4$.[146]

2.4.9. With solid acids

In 2005, B. T. Cho and S. K. Kang examined the RA of aldehydes and ketones using $NaBH_4$ activated by boric acid **179**, *p*-toluene sulfonic acid monohydrate **180** or benzoic acid **181** under solvent-free conditions (Figure 14).[148]

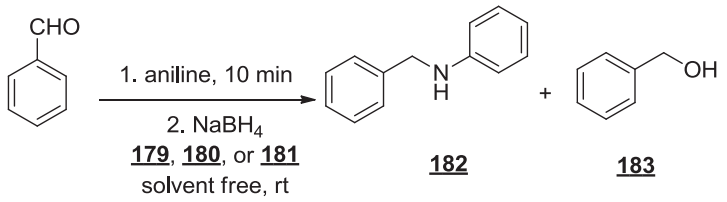


179 **180** **181**

Figure 14. Structure of different acids **179**, **180** and **181** used by Cho and kang for RA of aldehydes and ketones.[148]

Initially, the group studied the RA of benzaldehyde with aniline using **179** and $NaBH_4$, they showed that the yield of the desired amine is dependent on time and mixing order, so that when benzaldehyde was mixed firstly with aniline for 10 min, and the resulting mixture was then grounded with $NaBH_4$ and **179**, the reaction afforded 94% of **182** and only 6% of **183**. *P*-toluene sulfonic acid monohydrate **180** and benzoic acid **181** showed the same result (Scheme 59).

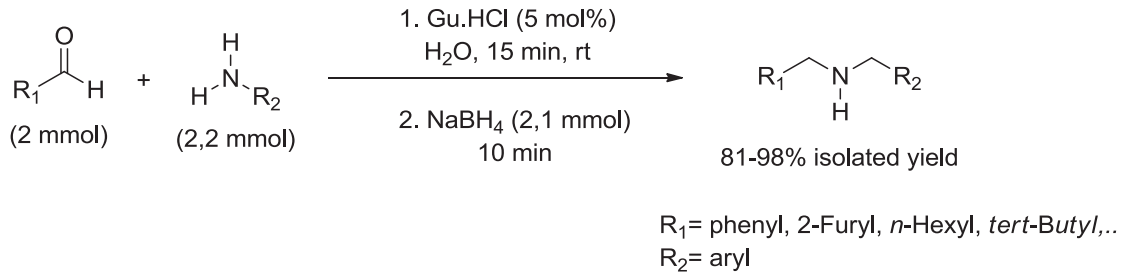
Using this methodology, aromatic, aliphatic, cyclic and heterocyclic aldehydes and ketones were reductively aminated with other aromatic and aliphatic primary amines. Limitations include the reduction with secondary amines and morphine, where reactions led to the formation of alcohols. Moreover acetophenone and β-ionone were not reduced using this method.



Scheme 59. RA of benzaldehdye with aniline using boric acid-activated $NaBH_4$.[148]

2.4.10. With Guanidine hydrochloride

The group of Heydari found an interest in the application of guanidine hydrochloride (Gu.HCl) in water for different organic transformations.[149,150,151] Gu.HCl found applications in the DRA of aldehydes with a variety of primary amines to give the desired products in high isolated yields (81-98%) as shown in Scheme 60.[152] However, using this system α-β-unsaturated ketones were reduced into allyl alcohols and not into amines.

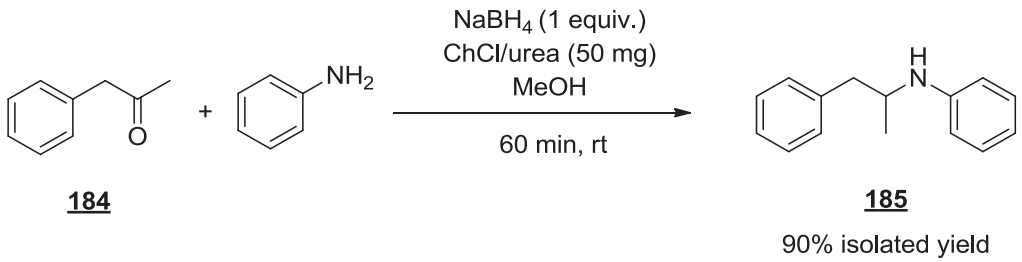


Scheme 60. DRA of aldehydes with primary amine using Gu.HCl/$NaBH_4$.[152]

2.4.11. With Deep eutectic solvent

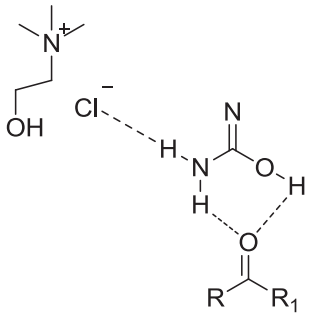
Recently, deep eutectic solvents (DESs) have emerged. DESs are peers of the conventional ionic liquids (ILs). They have low vapor pressure and flammability.[153] The main difference between these two families of compounds is that ILs are neither biodegradable nor cost-effective, however, DESs are biodegradable, non-toxic, and inexpensive. DESs are easily prepared by combining two components, a hydrogen acceptor (mainly choline chloride) and a hydrogen donor. The easiest component of this family is the combination of choline chloride and urea (ChCl/Urea) which are very cheap and non-toxic compounds. The occurrence of these compounds and their ability to serve as catalysts dates back to 2003.[154]

In 2016, the group of Heydari reported the synthesis of secondary amines by the DRA of aldehydes and ketones using the following conditions: aldehyde/ketone (1mmol), MeOH (2 mL), ChCl/urea (50 mg), at rt for 30-60 min. Different derivatives of benzaldehyde, furfural, cinnamaldehyde, acetophenone and phenyl acetophenone were well reduced to the corresponding amines with high isolated yields ranging between 89-98%.[155] For example phenylacetone **184** was reduced with aniline in 60 min to give *N*-(1-phenylpropan-2-yl)aniline **185** in 90% isolated yield (Scheme 61).



Scheme 61. DRA of **184** ito **185** using ChCl/urea and $NaBH_4$.[155]

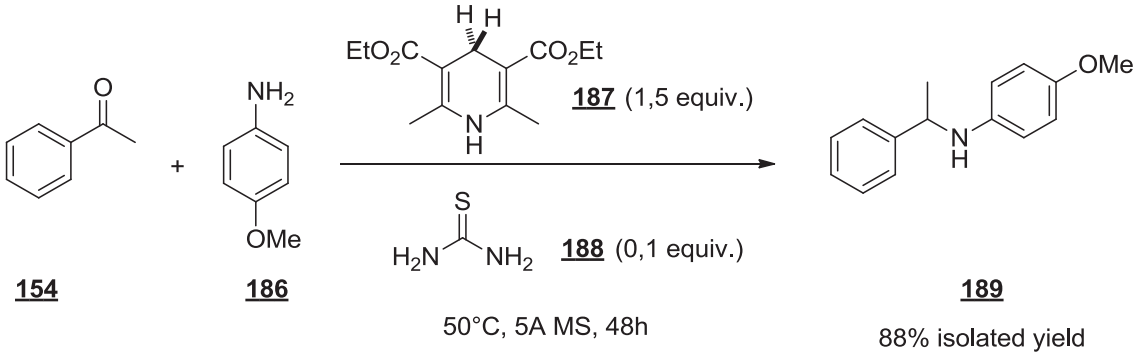
According to the previously reported ChCl/urea catalyzed reactions,[156] it seems that this reagent catalyze the reaction through the formation of hydrogen bonds with carbonyl compound (Scheme 62).



Scheme 62. Formation of hydrogen bond between carbonyl and ChCl/urea.[155]

2.4.12. With thiourea and Hantzsch ester

Another DRA process that relies on hydrogen bonding for imine activation was reported by D. Menche and co-workers.[157] The complete acid-free reaction is mediated by catalytic amounts of thiourea as a simple and readily modifiable organocatalyst, and uses the Hantzsch ester for transfer hydrogenation. As an example, the DRA of acetophenone **154** with equimolar amounts of *p*-anisidine **186** and the Hantzsch ester **187** was carried out in the presence of 0,1 equiv of thiourea **188** and 5Å MS at 50°C for 48h. Under these conditions 4-methoxy-*N*-*(*1-phenylethyl)aniline **189** was obtained in 88% isolated yield (Scheme 63).



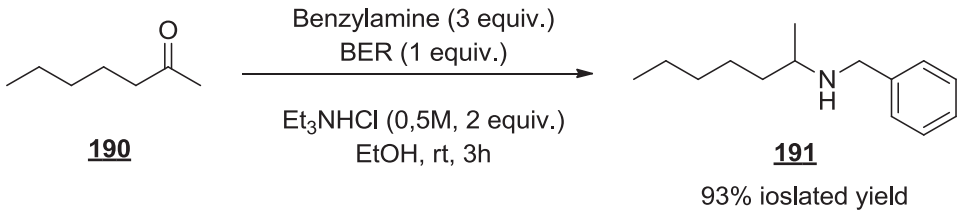
Scheme 63. The Hydrogen Bond Catalyzed DRA of **154** in the presence of thiourea/ Hantzsch ester.[157]

Notably, the amount of thiourea **188** added have no significant influence on the reaction rate where similar results were obtained using 1, 0.5 or 0.1 equivalents. However, in its absence the amine **189** was not observed, proving its crucial influence as an organocatalyst.[157] Finally, $NaBH_4$ was associated with many other reagents such as $ZnCl_2$,[158] $ZrCl_4$,[159] and carbon-based solid acid (CBSA).[160]

2.5. DRA of ketones using Borohydride Exchange Resin

In 1977, Borohydride Exchange Resin (BER) was introduced by Gibson and Baily.[161] Later N. M. Yoon and co-workers reported that BER is an interesting chemoselective reducing agent for carbonyl compounds in alcoholic solvents.[162,163] Several other significant applications were also presented.[164] The group have shown that BER is a good alternative to cyanoborohydrides and $NaBH(OAc)_3$ since it is non-toxic and less expensive in comparison to these reagents.

In 1993, N. M. Yoon et al. reported the DRA of aldehydes and ketones using BER in a medium of EtOH.[165] For ketone series, aliphatic ketones such a 2-heptanone **190** reacted readily with less hindered benzylamine to give 93% isolated yield of the secondary amine **191** as shown in Scheme 64. Lower yields were obtained with cyclohexylamine, piperidine and aniline. Acetophenone proceeded the DRA sluggishly. On the other hand, aldehydes were reduced rapidly with only few exceptions.[165]



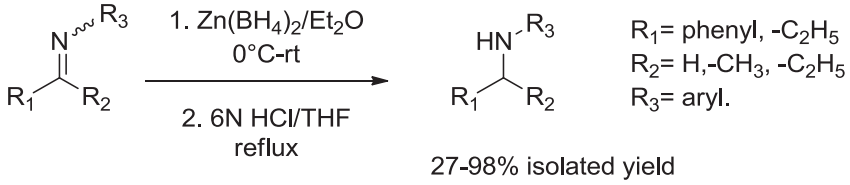
Scheme 64. DRA of 2-heptanone **191** using BER.[165]

2.6. DRA of ketones using zinc borohydride

To overcome the elevated pressures and the expensive toxic reagents that are accompanied with borohydrides and the LW reaction, reactions with zinc were introduced. The use of zinc borohydride,[166] prepared from sodium borohydride and zinc chloride, as a unique mild reducing agent for the reduction of aldehydes and ketones into the corresponding alcohols has been amply demonstrated in the 1iterature.[167] It has shown a great reactivity in RA reactions as well.

2.6.1. With Zinc borohydride in diethylether

In 1990, H. Kotsuki and co-workers described the reduction of Schiff's bases using 1 equiv. of zinc borohydride in Et_2O at room temperature to give the corresponding amines in 27-98% isolated yields (Scheme 65).[168] Schiff's bases were prepared by conventional condensation of amines with aldehydes or ketones.



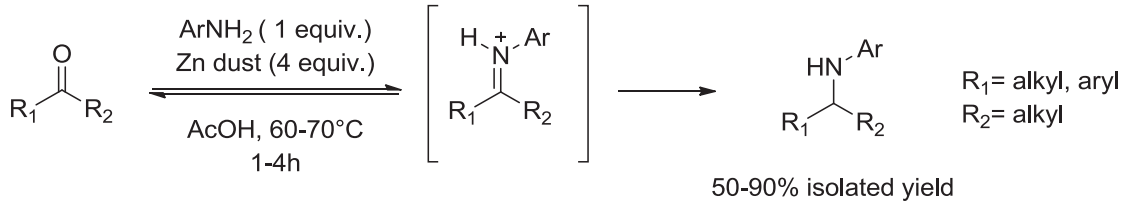
Scheme 65. RA of Schiff's bases using $Zn(BH_4)_2/Et_2O$.[168]

2.6.2. With activated Zinc/acetic acid

Few aldehydes and ketones have been reductively aminated albeit in low yields with the simpler and inexpensive zinc amalgam and hydrochloric acid,[169, 170] but it has not been generally applied to carbonyl compounds. Moreover, it affects the hydrolysis of various functional groups.[171]

In 1991, Miccovic et al. found a simple and efficient method for the preparation of secondary *N*-alkylarylamines via RA of ketones with primary aromatic amines using zinc dust and AcOH.[172] The reaction proceeded rapidly in the presence of stoichiometric

amounts of the reagents being complete in 1-4h, at 60-70°C, where the corresponding secondary amines were afforded in good isolated yields 50-90% (Scheme 66).[172]

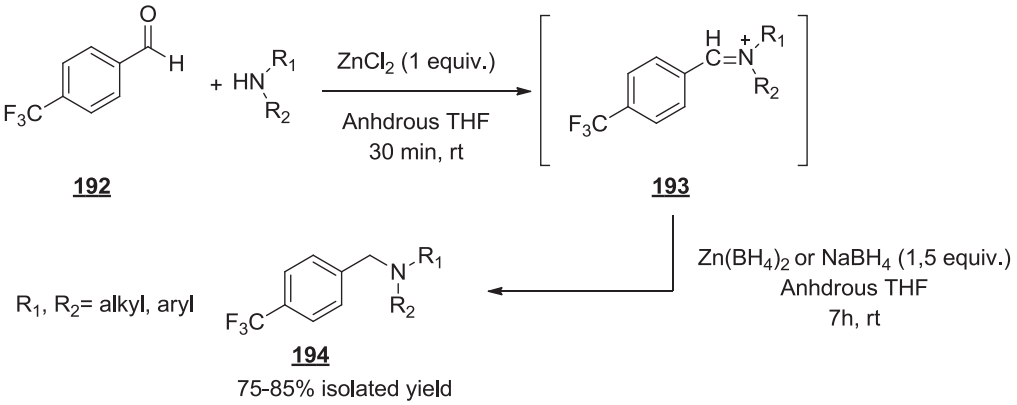


Scheme 66. DRA of ketones using activated Zn/AcOH.[172]

2.6.3. With activated Zinc borohydride/ Zinc chloride

In the same context of developing borohydride-based reagent systems for selective transformations, S. Bhattacharyya and co-workers utilized a combination of zinc chloride $ZnCl_2$ and zinc borohydride $Zn(BH_4)_2$ for the reductive methylation of amines.[173] As a sequel of this work, they presented the DRA of available fluorobenzaldehydes with a number of secondary amines.[174] They demonstrated that one-pot reagent system comprising of $ZnCl_2$ and $NaBH_4$ generated $Zn(BH_4)_2$ *in situ*, which is also an effective alternative making the reaction more simple by avoiding the preparation of $Zn(BH_4)_2$.

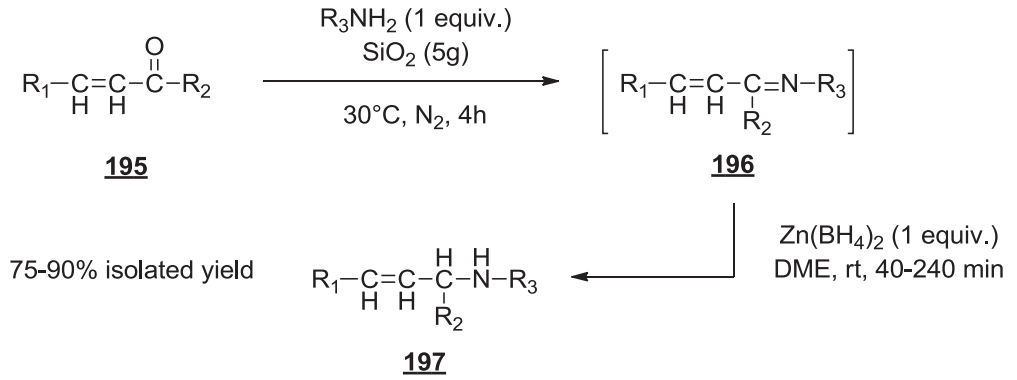
Typically, $ZnCl_2$ was added to a mixture of secondary amine and fluorobenzaldehyde **192** for example, in anhydrous THF, and the reaction was stirred for 30 min at rt to ensure the formation of the intermediate imine **193**. This step was followed by the addition of 1,5 equiv. of either $Zn(BH_4)_2$ or $NaBH_4$ in anhydrous THF, resulting in tertiary amines **194** as shown in Scheme 67.[174] It is important to mention that this transformation did not take place in the absence of $ZnCl_2$, which is functioning as a Lewis-acid to produce iminium ions that are then reduced by zinc borohydride.



Scheme 67. DRA of **192** using $Zn(BH_4)_2$.[174]

2.6.4. With Zinc borohydride and silica gel

In 1998, B. C. Ranu[175] and co-workers discovered that the RA of conjugated aldehydes and ketones is achieved by treatment of the corresponding carbonyl compound **195** with an appropriate amine on the surface of silica gel in a surface-mediated solid-phase reaction[176] to favor the formation of imine intermediate **196**. A solution of $Zn(BH_4)_2$ in DME was then added, and the corresponding amine **197** was obtained in 75-90% isolated yield (Scheme 68).[175] A variety of α-β-unsaturated aldehydes and ketones were reduced successfully.

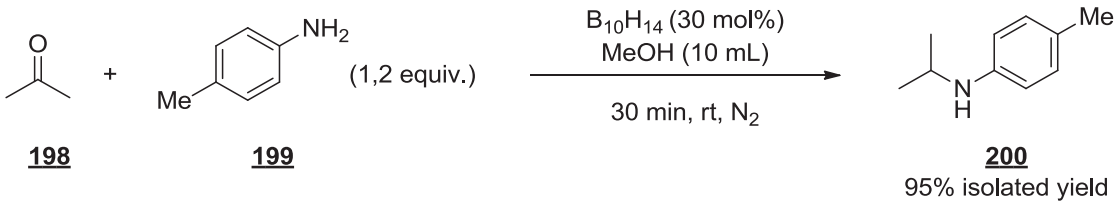


Scheme 68. RA of unsaturated carbonyl compounds **195** using $Zn(BH_4)_2/SiO_2$.[175]

2.7. DRA of ketones using Decaborane

In 1986, T. Kudo and A. Nose described the selective reduction of imines to the corresponding secondary amines using diborane (B_2H_6)-MeOH system.[177]

Later in 2000, C. M. Yoon and his group studied the DRA using decaborane ($B_{10}H_{14}$) as a mild reducing agent. For example, acetone **198** was reductively aminated using 1,2 equiv. of *p*-toluidine **199**, 30 mol% of $B_{10}H_{14}$ in MeOH. The reaction was stirred for 30 min at room temperature under N_2 atmosphere to produce the corresponding amine *N*-isopropyl-4-methylaniline **200** in 95% isolated yield (Scheme 69).[178] The effectiveness and fast rate of the reaction is resulting from the catalytic activity of decaborane for imine formation, which is known to be the rate determining step. Several examples of aldehydes and ketones were reduced using this method in the presence of variety of aromatic and aliphatic amines.



198 **199** **200**
95% isolated yield

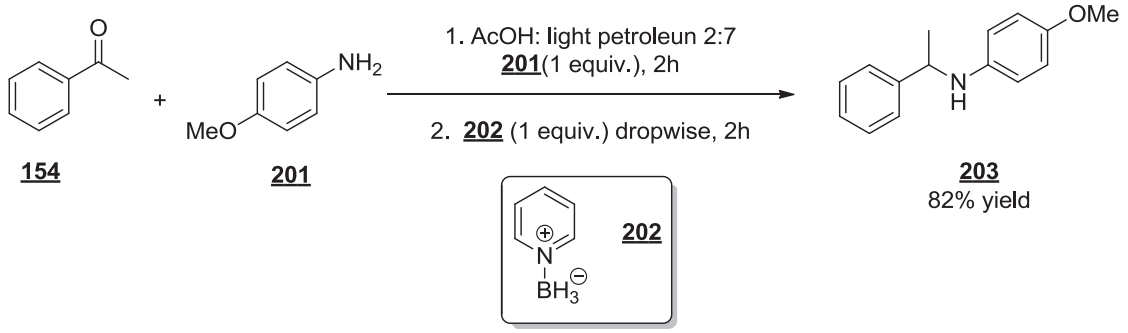
Scheme 69. DRA of acetone **198** using $B_{10}H_{14}$.[178]

2.8. DRA of ketones using amine boranes

Amine boranes are effective reagents to carry out RAs due to their acid stability and functional group compatibility.[179] Amine boranes derived from primary or secondary amines suffer from incorporation of the amine, therefore, are only appropriate for reduction of pre-formed imines. Amine boranes derived from tertiary amines or aromatic amines do not incorporate into the imine intermediate.

2.8.1. With Pyridine-Borane

In 1984, A. Pelter and R. M. Rosser introduced pyridine borane (pyr-BH_3), as a cheap and readily available alternative to cyanohydroborate.[180] In this work, acetophenone **154** was mixed with a solvent system consisting of glacial acetic acid and light petroleum (2:7), with an equimolar quantity of *p*-methoxyaniline **201**. The mixture was stirred at room temperature for 2h, after which an equimolar quantity of neat pyr-BH_3 **202** was added dropwise. The reaction was stirred for further 2h to get 4-methoxy-N-(1-phenylethyl)aniline **203** in 82% isolated yield (Scheme 70). Few examples of ketones and aldehydes were reductively aminated using this method.



Scheme 70. DRA of **154** in the presence of **203** and pyr-BH_3.[180]

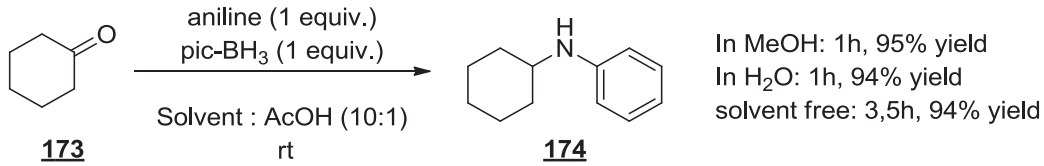
Another reaction was developed in 1995 by DiMare et al., where *in situ* RA of aldehydes and ketones were done using methanolic pyr-BH_3 in the presence of 4Å MS.[181] However, this reagent is quite unstable to heat and attempted distillation of the liquid residue at reduced pressures sometimes resulted in violent decompositions.[182] Thus, extreme care is necessary if this reagent is handled in large quantities. Moreover, industrial applications seem problematic, despite the availability of a patented method for purification.[183]

2.8.2. With α-picoline-borane

α-Picoline-borane (Pic-BH_3) is a thermally stable transparent solid that can be stored on a shelf for months without any appreciable loss of the reducing ability in comparison to pyr-BH_3, as well as cheap and commercially available. Y. Kikugawa and his group

showed that the use of this reagent eliminated the problems encountered with the use of previously mentioned reducing agents. The reaction was carried out in MeOH, in H_2O and in neat conditions in the presence of small amounts of AcOH.[184]

For example the DRA of cyclohexanone **173** with aniline was carried out using equimolar amounts of aniline, **173** and pic-BH_3 at room temperature in the presence of traces of AcOH. The results were the similar in three different solvent systems where N-cyclohexylaniline **174** was obtained with 94-95% yield (Scheme 71).



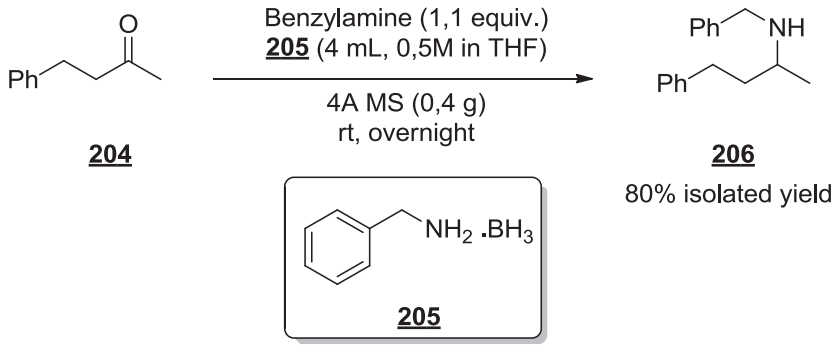
173 **174**

Scheme 71. DRA of cyclohexanone **173**with pic-BH_3 in three different solvent media.[184]

2.8.3. With benzylamine-borane

Between 1960-1980, dimethylamine-borane was used as a reducing agent for two-step RA in glacial AcOH. However, its use has been limited to aryl aldimines derived from substituted anilines.[185] In 2002, M. A. Peterson group discovered that benzylamine-borane is an effective reductant for *in situ* RA of carbonyl compounds.[186]

For example, the reduction of 4-phenyl-2-butanone **204** using benzylamine-borane **205** in the presence of stoichiometric amounts of benzylamine (1,1 equiv.) and 4Å MS gave the corresponding *N*-Benzyl-(1-methyl-3-phenyl)propylamine **206** in 80% isolated yield (scheme 72).



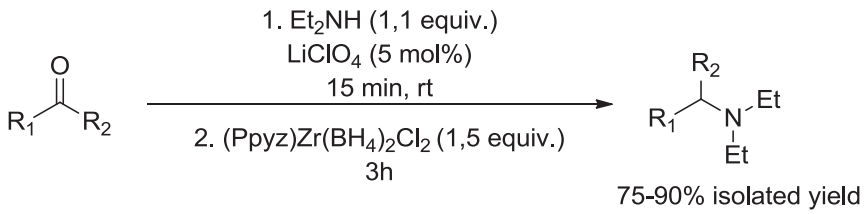
Scheme 72. DRA of **204** using benzylamine-borane **205** in THF.[186]

The reaction was employed under neutral conditions, and was effective in both protic and aprotic solvents including THF, DCM and MeOH. Moreover, it did not involve production of any toxic byproduct. Aliphatic and aromatic ketones were successfully reduced with this method, as well as aromatic aldehydes. However, the reaction was less effective with hindered ketones.[187]

Finally, E. R. Burkhardt and B. M. Coleridge designed a liquid aromatic amine borane 5-ethyl-2-methylpyridine borane (PEMB).[188] The advantageous properties of PEMB including liquid physical state, the thermal stability at ambient temperatures, and the slow reaction with protic solvents made it an attractive replacement for other amine boranes in reduction reactions.[189]

2.9. DRA of ketones using zirconium borohydride–piperazine

Heydari group used zirconium borohydride-piperazine complex (Ppyz)$Zr(BH_4)_2Cl_2$, which is air and thermally stable, in the selective reduction of various important functionalities.[190] These results promoted the group to study the RA of aldehydes and ketones using this reagent in the presence of 5 mol% lithiumperchlorate ($LiClO_4$) as a Lewis acid (Scheme 73).[191]



Scheme 73. DRA of aldehydes ane ketones with $LiClO_4$ and $(Ppyz)Zr(BH_4)_2Cl_2$.[191]

Acyclic and conjugated carbonyl compounds underwent successfully the RA with diethylamine and with a series of different amines. It should be noted that without $LiClO_4$, the process did not lead to any reduction, but was generally accompanied by products resulting from the reduction of carbonyl group. In some cases, stoichiometric amount of trimethylsilyl chloride (TMSCl) was added as an activator in order to obtain good yields, such as in the case of 4-chlorobenzaldehyde with aniline.[191]

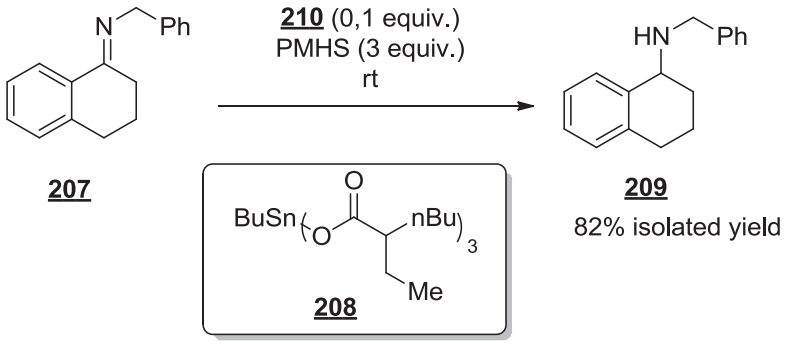
2.10. DRA of ketones with silanes and siloxanes

2.10.1. With polymethylhydrosiloxane (PMHS)

PMHS has been reported as an air and moisture stable, inexpensive, non-toxic, versatile, and widely used reducing agent in organic synthesis.[192] This reagent has minimal or no reducing ability in the absence of an activator, usually a transition metal catalyst such as Zn(II),[193] Ru(0),[194] and Cu(I-II),[195] or fluoride.[196] Once activated, PMHS becomes a powerful reagent that can effectively perform a wide range of reactions.

2.10.1.1. PMHS-Tin Catalyst

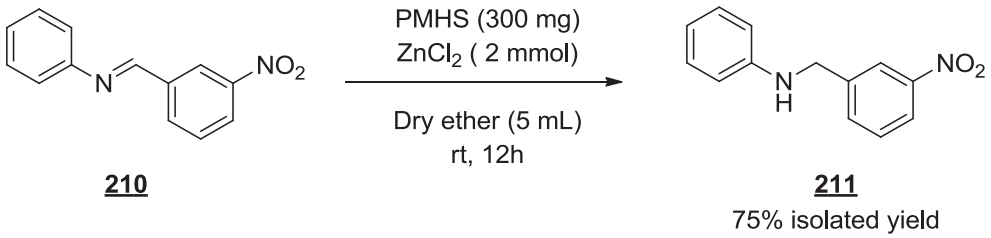
Because organotin compounds mediate an array of important transformations, they are widely used in synthetic organic chemistry, usually as stoichiometric reagents.[197] In 1997, G. C. Fu and R. M. Lopez developed a mild and convenient method for converting imines **207** derived from aldehydes and ketones to secondary amines **209** with *n*-Butyltris(2-ethylhexanoate)tin **208** as the catalyst and PMHS as the reductant.[198]



Scheme 74. Reduction of imine **207** using PMHS-Tin Catalyst **208**.[198]

2.10.1.2. PMHS-Zinc chloride

In 1999, S. Chaodrasekhar and co-workers prepared amines by reduction of imine using inexpensive PMHS as a hydride source activated by $ZnCl_2$.[199] Imines were prepared by the condensation of amine over carbonyl compound at ambient temperature for 20 h. For example imine **210** was reduced in the presence of PMHS and $ZnCl_2$ in dry ether at rt. The corresponding amine N-anilinomethyl-3-nitrobenzene **211** was obtained in 75% isolated yield after 12h (Scheme 75).

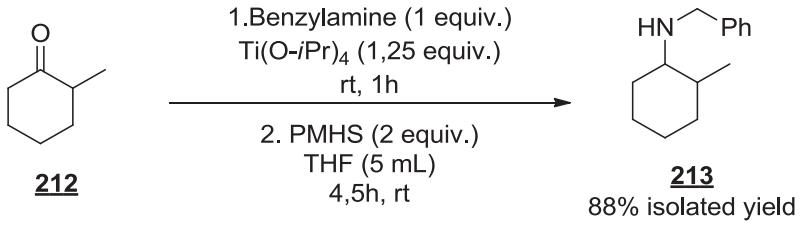


Scheme 75. Reduction of imine **210** using PMHS/$ZnCl_2$ system.[199]

2.10.1.3. PMHS-Titanium isopropoxide

In 2000 S. Chaodrasekhar group identified the important role of $Ti(O\text{-}iPr)_4$ in the DRA of carbonyl compounds, where it acts as a catalyst and as an efficient activator of PMHS.[200] For example, the DRA of 2-methylcyclohexanone **212** with benzylamine took place in 4.5 h affording the corresponding *N*-benzyl-2-methylcyclohexanamine **213** in

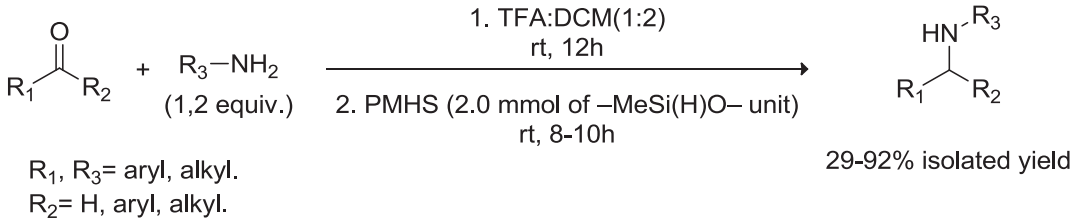
88% isolated yield (Scheme 76). A variety of aliphatic and aromatic aldehydes and ketones were reduced with a variety of amines successfully.



Scheme 76. DRA of **212** using PMHS/ Ti(O-*i*Pr)$_4$ system.[200]

2.10.1.4. PMHS-Trifluoroacetic acid

In 2009, A.-H. Li and co-workers invented the DRA of carbonyl compounds and acetals with a variety of anilines via a novel metal-free system using PMHS being activated with Brønsted acid.[201] Thus in a typical operation, a carbonyl compound and an amine were stirred in a mixture of TFA and DCM (1:2) at rt for 12h, to form an imine intermediate, which was reduced *in situ* by the addition of PMHS with continuous stirring for another 8–10 h at the same temperature (scheme 77).

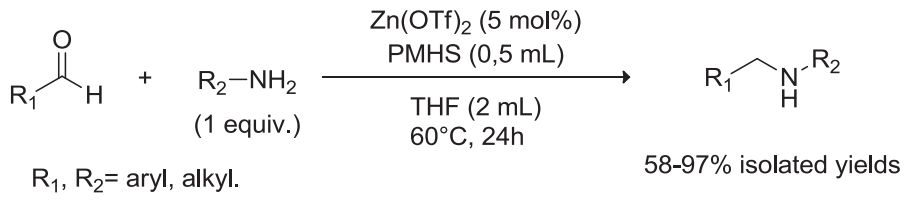


Scheme 77. RA of carbonyl compounds using PMHS/ TFA system.[201]

Aliphatic, heteroaromatic, and aromatic aldehydes and ketones with EWG and EDG react smoothly to generate the desired products. The group hypothesized that TFA plays a dual role in facilitating the intermediate imine formation and activating PMHS through hypervalent silicon intermediates for the reduction of *in situ* formed imine.[202]

2.10.1.5. PMHS-Zinc(II)triflate

In 2010, S. Enthaler investigated the DRA of aldehydes in the presence of variety of amines, using PMHS being activated with Lewis acid.[203,204] Simple zinc(II) triflate [$Zn(OTf)_2$] (5 mol%) was applied as the hydrosilylation catalyst for the reduction of the *in situ* formed imine by condensation of an aldehyde with an amine (1 equiv.), in the presence of PMHS in THF at 60°C for 24h (scheme 78). Broad functional group tolerance was achieved, giving the corresponding amines in 58-97% isolated yield. Under these conditions acetophenone was not reduced.



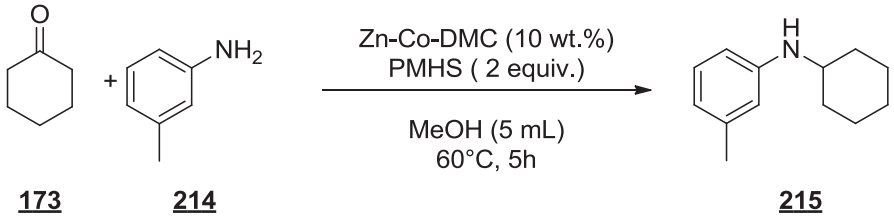
Scheme 78. DRA of aldehydes using PMHS/ $Zn(OTf)_2$ system.[203]

2.10.1.6. PMHS-Double metal cyanide

Double metal cyanide (DMC) catalyst represents a category of molecular salts constructed by the metal cyanide crystalline frame work with two different metal centers. The easy synthetic procedure, high thermal stability and specific surface area gave DMC high importance as a catalyst in organic synthesis.[205] Since Lewis-acid catalysts have been demonstrated to be one of the best catalysts for RA as mentioned before, DMC would be ideal catalysts in this transformation, since they are considered to be heterogeneous water tolerant Lewis acids.[206]

In 2016, H. Kim et al. proved the effectiveness of DMC in DRA of aldehydes and ketones. The group tested several metal combination of double metal cyanide, among which zinc and cobalt metal combination was found to be highly active in comparison with other metal combinations. Thus, Zn-Co-DMC catalyst was synthesized and used in the DRA of carbonyl groups.[207] For example, the DRA of cyclohexanone **173** with *m*-

toluidine **214** was carried out in the presence of 2 equiv. PMHS and 10 wt.% of Zn-Co-DMC catalyst in MeOH at 60°C under reflux for 5h, to yield the corresponding *N*-cyclohexyl-3-methylaniline **215** in 92% isolated yield (scheme 79).



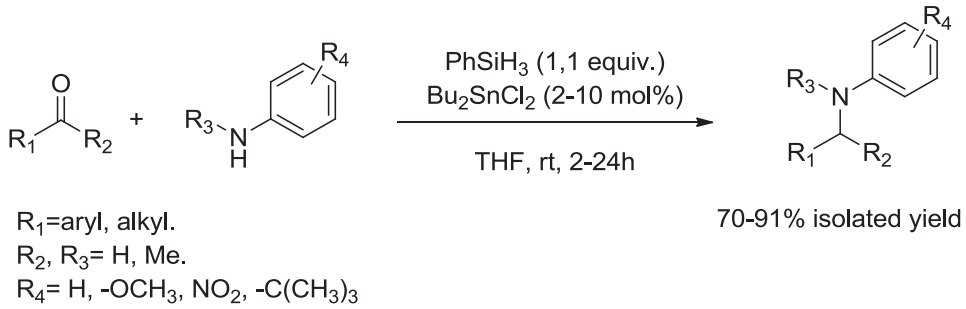
Scheme 79. DRA of cyclohexanone with **214** using PMHS/Zn-Co-DMC system.[207]

Acetophenone was less reactive in this method where it reacted with benzylamine, aniline, *m*-toluidine and *p*-anisidine to give the corresponding secondary amines in 52-68% isolated yield. Moreover, the results showed that Zn–Co-DMC is reusable for at least four times with little loss in catalytic activity.

2.10.2. With phenylsilane

Recent literature reports suggested the possibility that diorganotin dihalides could catalyze DRA in the presence of organosilane reductants.[208] In particular, catalysis of both imine formation,[209] and imine reduction with organosilanes,[210] have been separately described.

In 2001, R. Apodaca and W. Xiao, investigated a procedure for the DRA of aldehydes and ketones in the presence of phenylsilane ($PhSiH_3$) as a stoichiometric reductant, and dibutyltin dichloride (Bu_2SnCl_2) as a catalyst (Scheme 80).[211] Reactions with substrates bearing potentially reducible functional groups including aryl iodide, cinnamyl, nitro and benzyloxy gave the anticipated products, without detectable reduction side products. Moreover, acetophenone was reduced using 10 mol% of Bu_2SnCl_2 with good yield.

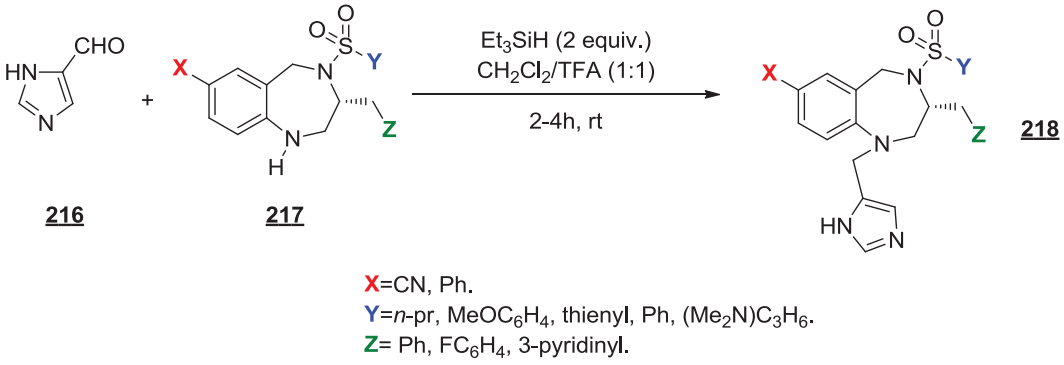


Scheme 80. DRA of carbonyl compounds using $PhSiH_3/Bu_2SnCl_2$ system.[211]

In 2005, the group of J. J. Kangasmetsa investigated a similar improved procedure using $PhSiH_3$ (2 equiv.)/ Bu_2SnCl_2 (0,1 equiv.) in THF, promoted by MW at 100°C for 7 min.[212]

2.10.3. With Triethylsilane

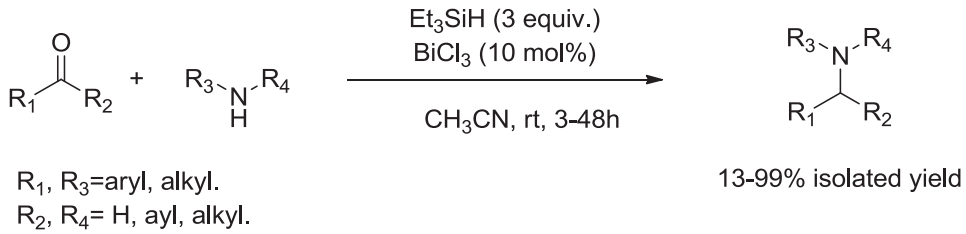
In 2001, B.-C. Chen and co-workers reported the synthesis of 1-(4-Imidazolyl)methyl-4-sulfonylbenzodiazepines **218**, which are a novel class of farnesyltransferase inhibitors,[213] by the DRA of 4-formylimidazole **216** with the secondary amine **217**, using triethylsilane Et_3SiH in DCM/TFA (1:1). In a time range between 2-4h at rt, reactions were complete and the corresponding tertiary amines **218** were isolated in 90-95% yield (Scheme 81).[214]



Scheme 81. DRA of **216** using **217** and Et_3SiH.[214]

Later in 2014, T. Matsumura and M. Nakada discussed the DRA of different carbonyl compounds using Et_3SiH and catalytic bismuth(III)chloride ($BiCl_3$). The DRA of various

aldehydes and ketones including cyclic and acyclic aryl and alkyl as well as heterocyclic, were examined using 3 equiv. Et_3SiH, 10 mol% $BiCl_3$ in acetonitrile at rt.[215] Depending on the structures of reacted carbonyl compound and amine, reaction time ranged from 3-48h to give the corresponding products in 13-99% isolated yields (Scheme 82).

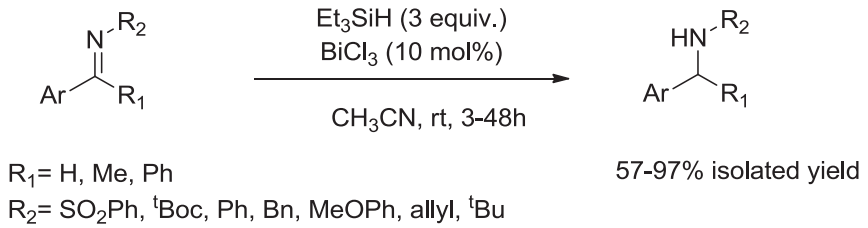


Scheme 82. DRA of carbonyl compounds using $Et_3SiH/BiCl_3$ system.[215]

For the mechanism, the group suggested that Bi(0) would be formed by the reaction of Et_3SiH and $BiCl_3$, which has been already suggested by other researchers.[216]

2.10.4. With Dimethylphenylsilane

In 2002, W. E. Piers and his group reported the reduction of imines to amines, using Tris(pentafluorophenyl)borane $B(C_6F_5)_3$ as a catalyst in conjunction with simethylphenylsilane ($PhMe_2SiH$). The rate of the reaction varried considerably, ranging from 30 min at rt to 26h at 70°C depending on the nature of R_2 (scheme 83).[217]

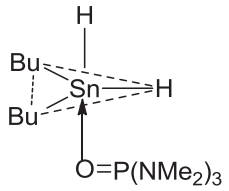


Scheme 83. Reduction of imines into amines using $Et_3SiH/ BiCl_3$ system.[217]

2.11. Organotin Hydrides

2.11.1. Bu_2SnClH-HMPA

A. Baba group have provided a set of organotin hydrides by the introduction of a halogen substituent or a ligand on the tin atom to achieve highly chemoselective reductions of multifunctionalized substrates.[218] The five coordinate tin hydride, Bu_2SnClH-HMPA **219** (Figure 15),[219] easily formed *in situ* from dibutylchlorostannane (Bu_2SnClH) and hexamethylphosphoramide (HMPA), successfully reduced imines in the presence of carbonyls.

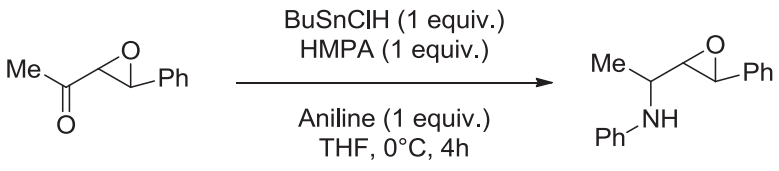


Bu_2SnClH-HMPA
219

Figure 15. Structure of Bu_2SnClH-HMPA.[220]

This high imine-selectivity indicated that **219** would be a good candidate for DRA. In 1998, the same group presented the use of tin hydrides in the DRA of aldehydes and ketones under mild conditions.[220] Highly chemoselective reactions were achieved for ketone and aldehydes even with co-existence of aryl halides, vinyl halides, hydroxyl group, double bonds and epoxide functionalities.

For example, 1-(3-phenyloxiran-2-yl)ethanone **220** was reductively aminated using equimolar amounts of BuSnClH, HMPA and aniline in THF at 0°C. The corresponding amine *N*-(1-(3-phenyloxiran-2-yl)ethyl)aniline **221** was obtained after 4h in 99% yield of the mixture of diastereomers (Scheme 84).



220 **221**

99% isolated yield

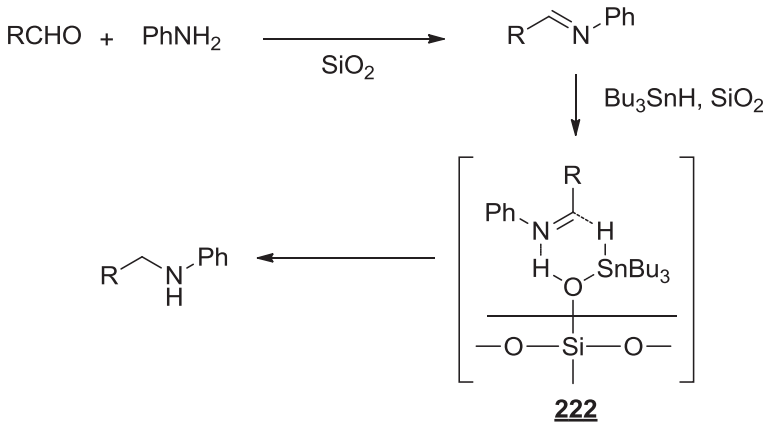
Scheme 84. DRA of **225** to amine **226** using Bu_2SnClH-HMPA system.[220]

2.11.2. Tributyltin Hydride on Silica Gel

In 2002, M. Wada and co-workers described the reduction of imines generated *in situ* from aldehyde and aniline using tributyltin hydride Bu_3SnH on SiO_2 under solvent-free conditions. The reaction proceeded well with aliphatic and aromatic aldehydes, giving the expected products in good yields ranging between 45-90% (Scheme 85).[221]

Scheme 85. Reduction of aldehydes using Bu_3SnH on SiO_2.[221]

For the mechanism, the group proposed that hydrogen bonding between the imino group and the acidic silanol group exerts the predominant activating effect. A six-membered transition state **222** involving the silanol coordination to tin and hydrogen bonding to the imino group can be invoked, allowing the selective reduction of the imine to proceed smoothly (Scheme 86).[221] Using this method acetophenone was reductively aminated to give the corresponding amine in 45% isolated yield.



Scheme 86. Proposed mechanism for the RA of aldehydes using Bu_3SnH/SiO_2 via the intermediate **227**.[221]

2.12. DRA of ketones using catalytic hydrogenation

Hitherto several chemical reducing agents, have been shown to be valuable for DRA and giving rise to the alkylated amines in good yields. However, from the ecological point of view and taking into account the demand for atom economy, a more promising approach involves the use of molecular hydrogen as a reducing agent.

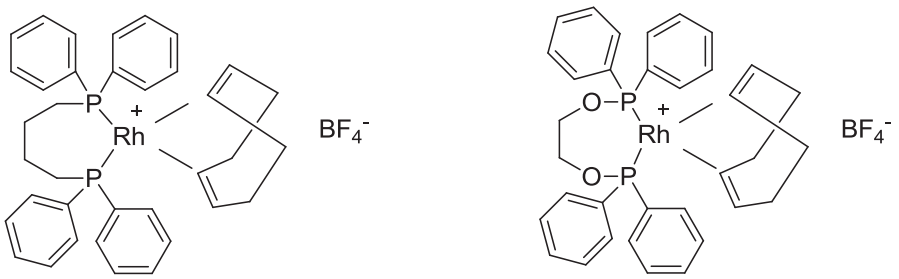
2.12.1. Homogeneous Catalysis

Only a few preliminary studies on the homogeneous version of this reaction can be found in the literature in spite of the tremendous progress that homogeneous catalysis has seen over the last decades.[222]

2.12.1.1. Rhodium Catalysts

2.12.1.1.1. Rh(I) catalysts based on Chelating diphosphines and diphosphinites

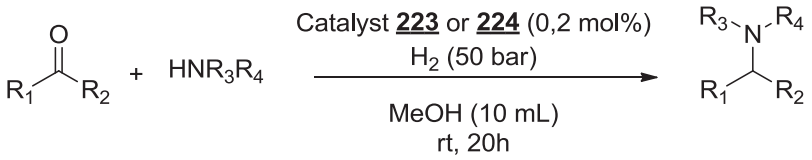
In 1999, A. Börner and co-workers reported that cationic rhodium(I) complexes [Rh(dppb)(cod)]BF_4 **223** and [Rh(dpoe)(cod)]BF_4 **224** are highly efficient pre-catalysts in the hydrogenation of imines and enamines under mild conditions (Figure 16).[223, 224]



223 **224**

Figure 16. Rhodium(I) complexes **223** and **224** developed by Börner. [223, 224]

Advantageously in 2002, the same group reported the DRA of aldehydes and ketones using these Rh(I) catalysts **223** and **224**. It was the first example of a homogeneously catalyzed reductive amination using primary and secondary amines. The reaction took place under mild conditions: amine (1 equiv.), H_2 (50 bar), Catalyst (0,2 mol%) in MeOH at rt for 20h (Scheme 87). [225] Limitations of the reaction include steric effects that leads to the formation of only traces of desired amine. In addition some functional groups including -CN and-NO_2 did not survive under these reaction conditions.

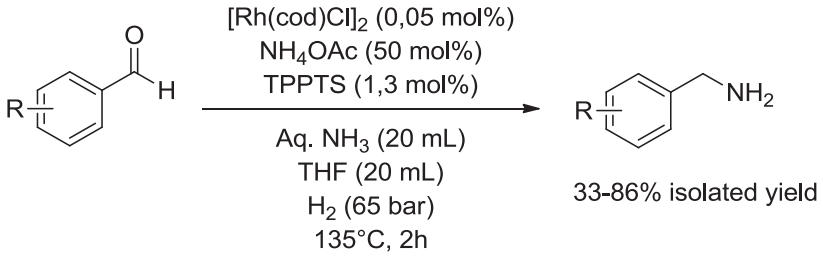


Scheme 87. DRA of carbonyl group using Catalysts **223** and **224** in the presence of H_2.[225]

In 2003, the same group developed the first highly enantioselective DRA of α-keto acids using a cationic Rh-Deguphos catalyst, where several α-amino acids were produced in good yields and by up to 98% *ee*.[226]

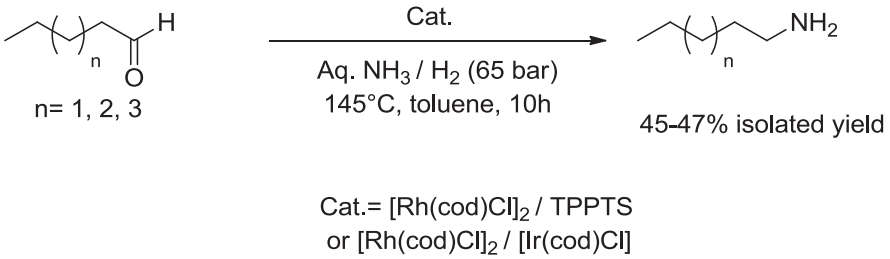
2.12.1.1.2. Chloro(1,5-cyclooctadiene)rhodium(I) dimer

In 2002, Beller group presented the first procedure for the selective DRA of aromatic and aliphatic carbonyl compounds to primary amines using NH_3 in the presence of water-soluble transition metal complexes. [227] The DRA or aromatic aldehydes was carried out using: Chloro(1,5-cyclooctadiene)rhodium(I) dimer $[Rh(cod)Cl]_2$ as the catalyst, NH_4OAc (50 mol%) as a co-catalyst, TPPTS (tris sodium salt of meta trisulfonated triphenylphosphine) as a ligand, 25% aqueous NH_3 solution (20 mL), H_2 (65 bar) at 135°C in THF for 2h. Using this methodology the corresponding amines were reduced with 33-86% isolated yields (Scheme 88).



Scheme 88. DRA of aromatic aldehydes using $[Rh(cod)Cl]_2$/TPPTS in the presence of NH_3 and H_2.[227]

Aliphatic aldehydes were also reductively aminated in similar conditions either with $[Rh(cod)Cl]_2$/TPPTS or by using the bimetallic $[Rh(cod)Cl]_2$/$[Ir(cod)Cl]_2$ catalyst at 145°C in toluene for 10h. In this case the corresponding amines were obtained in lower yields (45-47%), this is due to the formation of secondary amines as well as aldol condensation products in considerable amounts (Scheme 89).



Scheme 89. DRA of aliphatic aldehydes using different catalytic systems in the presence of NH_3 and H_2.[227]

Although high selectivity and yields toward aromatic primary amines were achieved, high pressures and temperatures is one of the disadvantages of this reaction. On the other hand, the yields of aliphatic primary amines from aliphatic aldehydes were still poor.

2.12.1.2. Iridium Catalysts

In 2001, the group of X. Zhang developed a chiral ligand, f-Binaphane **225** (Figure 17), that has shown excellent reactivities and enantioselectivities for Ir-catalyzed asymmetric hydrogenation of acyclic imines (up to 99% ee).[228]

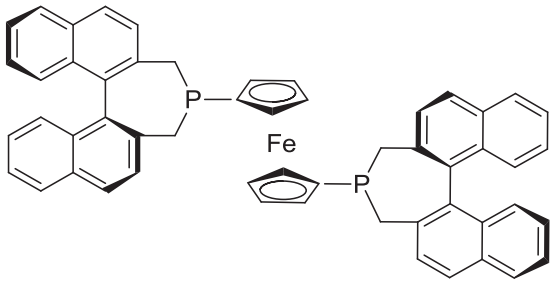
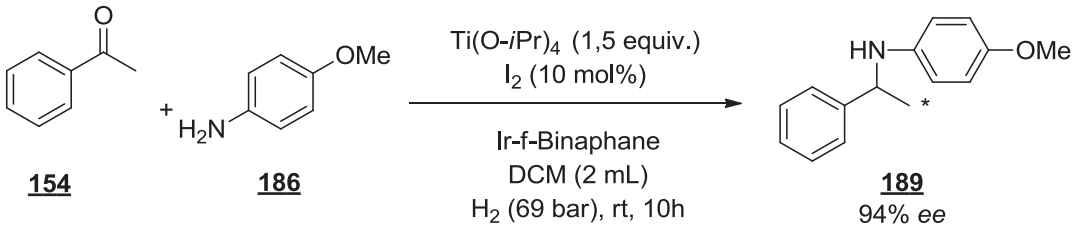


Figure 17. (S,S)-f-Binaphane **225**.[228]

In 2003, the same group investigated the RA or aryl ketones using Ir-f-Binaphane complex as the catalyst. For example, acetophenone **154** was reduced with *p*-anisidine **186** (1,2 equiv.), in the presence of I_2 (10 mol%) and Ti(O-*i*Pr)$_4$ (1,5 equiv.) as additives under H_2 pressure of 69 bar in DCM at rt for 12h (Scheme 90).[229]



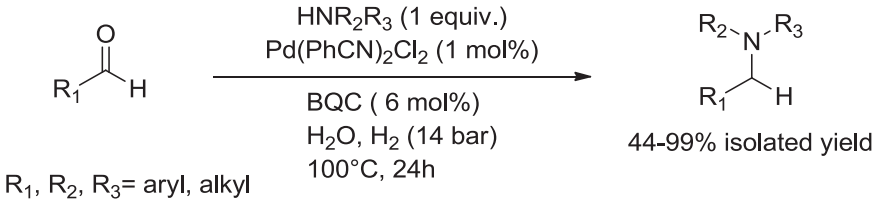
Scheme 90. Assymetric RA of **154** using Ir-f-Binaphane complex.[229]

In 2005, T. Ohta and co-workers have found that [Ir(cod)$_2$]BF$_4$ is sufficiently effective for the DRA of carbonyl compounds with amines in the presence of H_2. Yields up to 99% with an aldehyde, and up to 92% with a ketone were obtained in benzene and toluene solvents, respectively. On the other hand ketones were also reductively aminated using a combination of ionic liquid [Bmim]BF$_4$ **158** as a solvent and [Ir(cod)$_2$]BF$_4$ as the catalyst.[230]

2.12.1.3. Palladium Catalysts

In 2006, A. N. Ajjou and co-workers described the DRA of aliphatic and aromatic aldehydes with primary and secondary amines, catalyzed by water-soluble transition

metal complexes under H_2 pressure.[231] The reaction was performed using 1 equiv. of amine, 1 mol% of $Pd(PhCN)_2Cl_2$, 6 mol% of BQC (2,2'-biquinoline-4,4'-dicarboxylic acid dipotassium salt), in aqueous medium at 100°C. After 24h the corresponding amines were isolated in 44-99% isolated yields (Scheme 91).

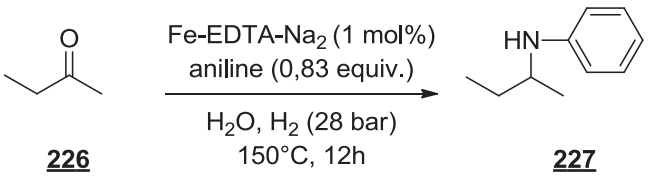


Scheme 91. DRA of aldehydes using $Pd(PhCN)_2Cl_2$/ BQC system.[231]

For ketones, taking acetophenone as an example, the DRA was sluggish with incomplete conversion and only 50% selectivity of the amine. An important note, is that the catalytic system was recycled by simple decantation and reused three times without loss of activity.

2.12.1.4. Iron Catalysts

In 2008, M. D. Bohr et al. Developed the DRA of aliphatic, aromatic and heterocyclic carbonyl compounds with primary and secondary amines. The catalytic system is a combination of Fe(II) salt and EDTA-$Na_2.2H_2O$ (ethylenediaminetetraaceticacid disodium salt dehydrate) as a ligand. For example, 2-butanone **226** was reductively aminated with aniline using 1 mol% of Fe-EDTA-Na_2 catalyst with 28 bar of H_2 pressure at 150°C in aqueous medium, to afford the *N*-(*sec*-butyl)aniline **227** in 70% isolated yield (Scheme 92).[232]



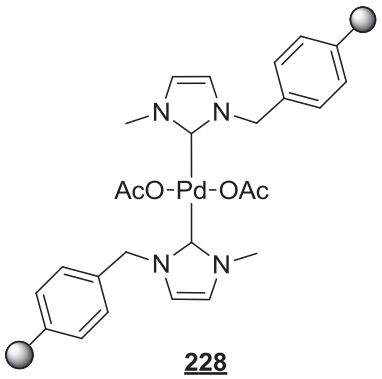
Scheme 92. DRA of **226** using Fe-EDTA-Na_2 in the presence of H_2.[232]

2.12.2. Heterogenous Catalysis

For practical applications, homogeneous catalytic systems have problems in the catalyst recovery and reuse in most of the cases. Unlikely, heterogeneous catalysts could be separated easily at the end of the reaction by simple filtration, thus, they are more ideal for large scale applications.

2.12.2.1. Polymer supported palladium-N-heterocyclic carbene

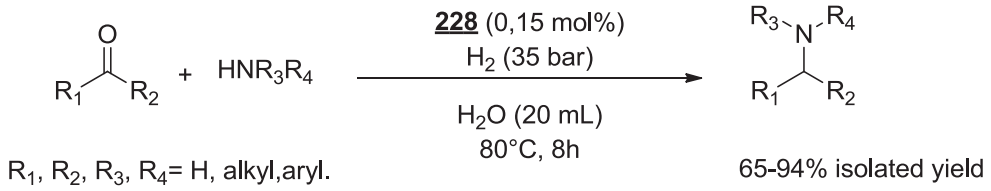
Recently, N-heterocyclic carbenes (NHCs) have been found to become valuable ligands in organometallic chemistry and catalysis,[233] because of their effective binding ability to any transition metal irrespective of their oxidation states. Palladium-*N*-heterocyclic carbene (Pd-NHC) systems have been successfully employed in various reactions,[234] including hydrogenation reactions.[235] The polymer supported palladium-N-heterocyclic carbene (PS-Pd-NHC) **228** offers several advantages like reuse of expensive transition metals and ligand with a possibility to prevent the contamination of ligand residue in synthesized products (Figure 17).



228

Figure 17. Structure of palladium-N-heterocyclic carbene (PS-Pd-NHC) **234**.

In 2012, B. M. Bhanage and co-workers, described the DRA of Substituted benzaldehydes, 2-furaldehyde, and cyclohexanone in the presence of various primary and secondary aromatic, cyclic and acyclic amines, using 0,15 mol% of **228** with 35 bars of H_2 at 80°C for 8h in H_2O, to afford the corresponding secondary and tertiary amines in good to excellent isolated yields (65-94%) as shown in Scheme 93.[236]



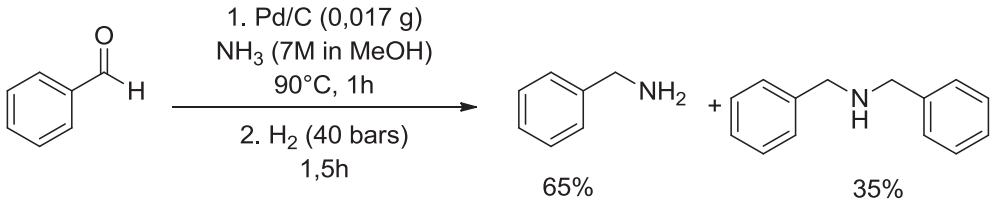
Scheme 93. DRA of carbonyl compounds using PS-Pd-NHC in the presence of H_2.[236]

It is important to mention that the catalyst complex **228** was effectively recycled up to six consecutive cycles with maintenance of appreciable catalytic activity.

2.12.2.2. Palladium on Carbon

The DRA of carbonyl compounds with NH_3 and H_2 is an alternative route to produce primary amines in practical production. However, one-pot amination of carbonyl compounds with NH_3 generally suffers from a main issue that the chemoselectivity is relatively poor, as the initially-generated amines are more nucleophilic than ammonia itself, thus often resulting in a mixture of products of primary, secondary, and tertiary amines.[237] The first catalyzed amination of aldehydes or ketones using NH_3 and H_2 with Ni catalyst was reported by Mignonac in 1919.[238] Later in 1964, F. S. Dovell and H. Greenfield investigated the use of base-metal sulfides,[239] as a catalysts in the RA of ketones in the presence of NH_3 and H_2.[240]

In 2000, A. W. Heinen and co-workers described the DRA of benzaldehyde on Pd/C catalyst, where Pd/C is the most often used and commercially available palladium-based catalyst featured with cheap price and easy preparation. The reaction took place in the presence of high concentration of NH_3 in MeOH and 40 bars of H_2 pressure, giving a mixture of products with benzylamine as the major one (Scheme 94).[241]

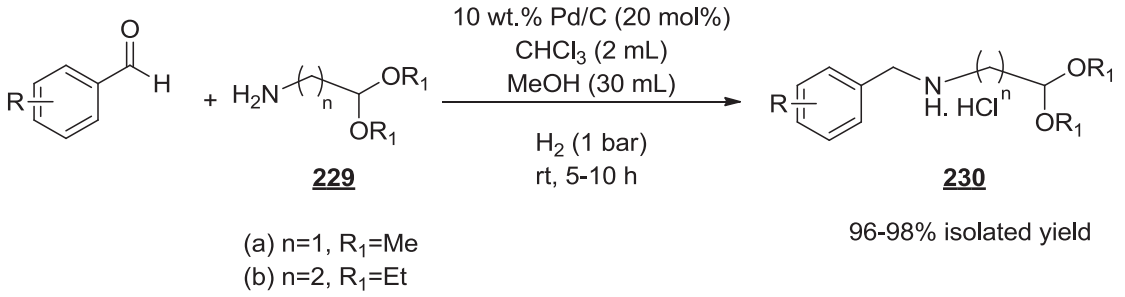


Scheme 94. DRA of benzaldehyde using Pd/C, NH_3 and H_2.[241]

This year, L. Prati and co-workers used Pd/C treated at different temperatures for the DRA of halogen substituted benzaldehydes with dimethylamine to obtain halogenated benzylamines, an important pharmacophores and agrochemical interemdiates. The results show that the increase of calcination temperatures from 100°C to 400°C has a positive effect on the selectivity towards hydrogenated benzylamines, avoiding the undesired dehalogenation. So that, bigger Pd particles obtained at the highest calcination temperature showed the best selectivity of the desired products (92-98%).[242]

2.12.2.3. Palladium on Carbon Chloroform system

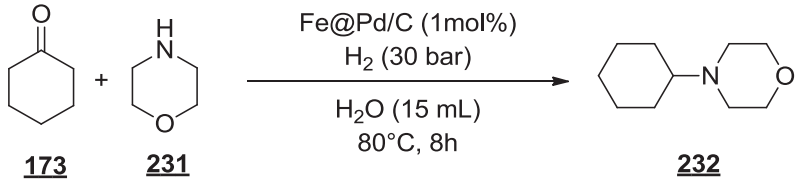
Since the hydrogenation of benzaldehyde into the corresponding alcohol proceeds under very mild conditions, so the Pd/C catalytic hydrogentation was not used often in the DRA of benzaldehyde. Recently, Wand and Hu group modulated the reactivity of Pd/C in the presence of choloform $CHCl_3$ to achieve a chemoselective hydrogenation.[243] This result from the fact that Pd/C catalyst was partially poisoned,[244] by HCl moelcules released *in situ* from the Pd/C catalyzed hydrodechlorenation of $CHCl_3$.[245] Interested by these results they prformed the Pd/C catalytic hydrogenation DRA of benzaldehydes and aminoaldehyde acetals **229** in the presence of $CHCl_3$ to yield the corresponding *N*-benzyl amino-aldehydeacetal hydrochlorides **230** in excellent yields (Scheme 95).[246]



Scheme 95. DRA od benzaldehydes with **229** in the presence of Pd/C-$CHCl_3$ and H_2.[246]

2.12.2.4. Core-shell Fe@Pd/C catalyst

In the effort to develop heterogeneous recyclable catalyst system for DRA using environmental-friendly molecular hydrogen, N. M. Patil and B. M. Bhanage reported core-shell Fe@Pd/C as a versatile catalyst for the DRA of carbonyl compounds with primary and secondary amines in aqueous reaction media. For example, cyclohexanone **173** was reductively aminated with morpholine **231** using 1 mol% of Fe@Pd/C catalyst, 30 bar of H_2 pressure at 80°C for 8h in 15 mL of water. The corresponding amine **232** was obtained in 92% isolated yield (Scheme 96).[247]

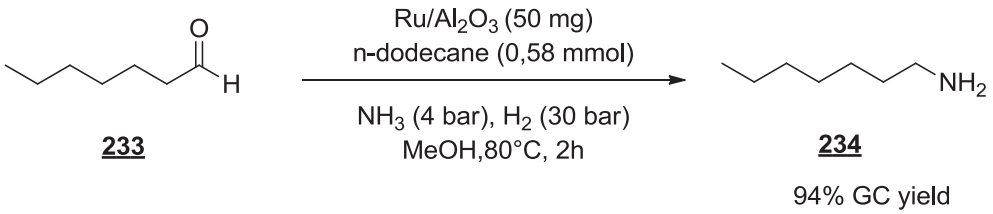


Scheme 96. DRA of cyclohexanone with **239** using Fe@Pd/C in the presence of H_2.[247]

2.12.2.5. Supported Ru Catalyst

In 2005, Bodis and co-workers used carbon supported group VIII noble metals (Pt, Pd, Rh and Ru) as catalysts for the DRA of butyraldehyde with NH_3. It was found that Rh and Ru catalysts were active and selective in the production of primary amine under 50 bar of H_2 pressure, while Pt and Pd catalysts favored the secondary amine formation.[248]

In 2015, X. Chen, S. Han and co-workers presented the DRA of aldehydes with NH_3 over Ru based catalysts. For example, n-heptaldehyde **233** was reductively aminated to 94% GC yield of 1-heptylamine **234** over Ru/γ-Al_2O_3 in the presence of gaseous NH_3 and H_2 pressure (Scheme 97).[249]A variety of aliphatic and aromatic aldehydes were reduced using this method.

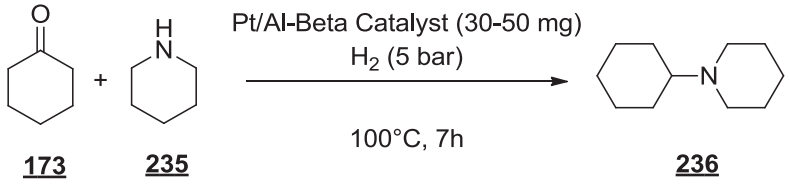


Scheme 97. DRA of **233** using Ru/γ-Al_2O_3 in the presence of H_2 and NH_3.[249]

Ru supported on θ-Al_2O_3 gave similar results. Other purely basic and relative acids supports were tested, however, only amphoteric supports showed good results.

2.12.2.6. Platinum Catalyst

In 2011, M. E. Domine and co-workers designed metal catalysts based on Pt and Pd nanoparticles supported on structured microporous Beta Zeolites and mesoporous MCM-41 materials, as well as specially designed γ-Al_2O_3 samples.[250] These metal/solid acid composites were applied as efficient catalysts under mild reaction conditions in the selective DRA of ketones to produce substituted amines and *N*-heterocycles. Pt/Al-Beta catalyst possess the best catalytic activity, with amine selectivity up to 95%. For example, cyclohexanone **173** was mixed with 1equiv. of piperidine **235** in the presence of 30-50 mg of solid catalyst under H_2 pressure of 5 bars at 100°C (Scheme 98).

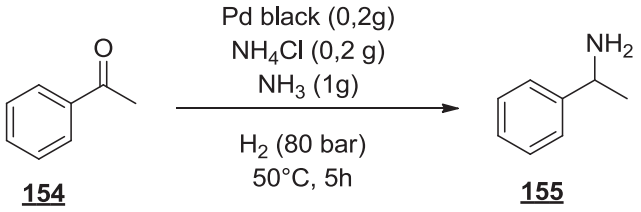


Scheme 98. DRA of **173** using Pt/Al-Beta catalyst in the presence of H_2.[250]

2.12.2.7. Palladium and Ruthenium black catalysts

Another work was done using palladium and ruthenium by S. Yada and co-workers for the RA of acetophenone, (+)-camphor, and 5α-cholestan-3-one over Ru and Pd metals as well as their carbon supported catalysts.[251] Alcohols were obtained as by-products, but this was effectively depressed by adding ammonium chloride NH_4Cl as an additive.[252]

For example, when acetophenone **154** was reductively aminated with Pd black without any addtitive, the alcohol was the sole product. However, upon adding NH_4Cl the corresponding amine α-phenylethylamine **155** was obtained with82% selectivity (Scheme 99).[251]



Scheme 99. DRA of **154** using Pd black/NH_4Cl system in the presence of H_2 and NH_3.[251]

Although of all these interesting results using molecular hydrogen, this reaction still has the limitation of requirement of high pressures and in some cases high temperatures.

2.13.Conclusion

Indeed, during the last decades several reductive amination protocols to synthesize amines from carbonyl compounds are present in literature.

The DRA using cyanoborohydrides and sodium triacetoxyborohydride, offers the advantages of simplicity, wide availability of substrates, mild reaction conditions, and tolerance to other functional groups. However, the former is highly toxic and generates

toxic byproducts such as, HCN and NaCN, moreover, it requires large quantities of excess amine.

Examples for the DRA using sodium borohydride are many, but this reagent needs to be associated with metal catalysts and additives for the reaction to go smoothly and successfully. The major problem in these reactions is the formation of alcohols as byproducts.

Several reagents other than those mentioned above have been utilized in DRA, including borohydride exchange resin, zinc borohydrides, zirconium borohydrides, decaborane, and amine boranes. In these cases, the reactions require filtration, aqueous workup, evaporation orcombination of these techniques prior to purification.

Organic-soluble reducing reagents such as organosilanes and siloxanes have been reported as good alternatives to classical hydrides. However, there exist several drawbacks, where hydrosilanes are expensive, toxic and flammable, and siloxanes such as PMHS are also expensive, they require the association with toxic me.tals and expensive ligands. Tin hydrides were also used, but it is well known that these reagents are harmful to health and environment.

Finally, the most convenient way with a good atom economy is the use of molecular hydrogen involving homogeneous or heterogeneous catalysis, however, high pressures and temperatures are the main disadvantages.

3. Results and discussion

3.1.Objective

Although literature is full of examples discussing the DRA of aldehydes and ketones, the development of newly improved protocols for performing DRA by using greener and milder reaction conditions is still desirable. As we mentioned in the previous part that hypophosphites are cheap, harmless and non-toxic reagents that have been employed in

several organic transformations. However, their use in DRA of carbonyl compounds have not been reported yet. Among the commercially available hypophosphites we focused on ammonium hypophosphite $NH_4PO_2H_2$, which could play two roles: (1) a direct source of NH_3, so there is no need to add an extra amine in the reaction mixture; (2) as a reducing agent.

This part will summarize all methodologies found in literature for the RA of aldehydes and ketones. Followed by our investigated method for the DRA of ketones using ammonium hypophosphite in the presence of heterogeneous catalyst, where different reaction parameters were studied, including: ammonium source, time, temperature, type of catalyst, concentration and additives. Heterogeneous catalysis has an advantage since the catalyst can be easily removed at the end of the reaction, so there is possibility for recycling. Moreover, the used supports, for example charcoal and alumina, present a large specific area for hydrogen adsorption.

3.2. Feasibility and optimization of reaction conditions

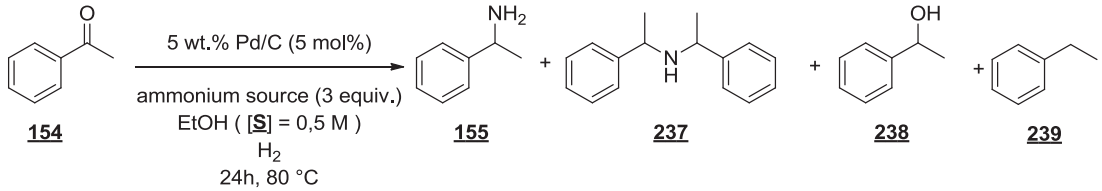
Our investigations started by choosing acetophenone, the challenging aromatic substrate, as a model substrate for DRA, and reactions were followed by GC.

a. Type of ammonium source

In the first part of this manuscript aromatic nitriles were reduced into amines in the presence of Pd/C. Encouraged by these results, the first array of experiments were done using 5wt.% Pd/C, 3 equiv. of ammonium source, in the presence of EtOH at 80 °C for 24h in the presence of a ballon of hydrogen pressure. Three different ammonium sources were tested in order to compare their efficiency as shown in Table 12. Using ammonium hypophsophite ($NH_4PO_2H_2$), the conversion of **154** was complete, however only 12% of the desired α-phenylethylamine **155** was obtained, and bis(1-phenylethyl)amine **237** was the major product with 73% GC ratio (Table 12, entry 1). In case of ammonium acetate (NH_4OAc) the conversion of **154** was lower with 15% of **155** and 75% of ethylbenzene

239 (Table 12, entry 2). In contrast, only 39% conversion was attained in the presence of ammonia, however 25% of **155** were obtained (Table 12, entry 3).

Table 12. DRA of **154** using different ammonium sources.



Entry	Ammonium source	Conv. [%][a]	GC ratio [%][a]				
			155	**237**	**238**	**239**	**by-products**
1	$NH_4PO_2H_2$	100	12	73	1	2	12
2	NH_4OAc	91	15	7	-	75	3
3	NH_3	39	25	35	40	-	-

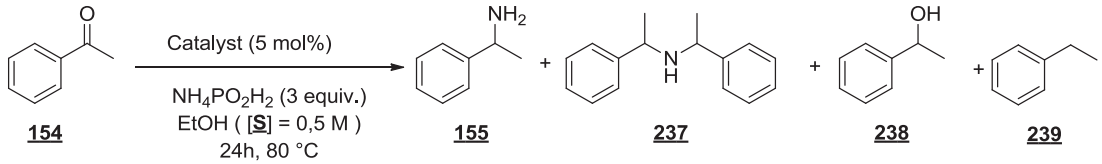
[a] Conv. and GC ratio were determined by gas chromatography.

According to these results, $NH_4PO_2H_2$ was the best in terms of conversion, so we went forward with this reagent to study other reaction parameters.

b. Screening of different heterogeneous catalysts

In the second array of experiments, the activity of different heterogeneous catalysts was studied in the presence of 5 mol% of the heterogeneous catalyst, 3 equiv. of $NH_4PO_2H_2$, in a medium of EtOH at 80°C for 24h. Only 5wt.% Pd/C showed acitivity as mentioned before (Table 13, entry 1). In case of Pt/C, Rh/C and Ru/Al_2O_3 the conversion of **154** was almost negligible (1-5%) (Table 13, entries 2-4). On the other hand, Ru/C did not show any reactivity (Table 13, entry 5).

Table 13. DRA of **154** using $NH_4PO_2H_2$ and different heterogeneous catalysts.



Entry	Catalyst	Conv. [%][a]	GC ratio [%][a]				
			155	**237**	**238**	**239**	**By-products**
1	Pd/C	100	12	73	1	2	12
2	Pt/C	1	-	-	100	-	-
3	Rh/C	1	-	-	100	-	-
4	Ru/Al_2O_3	5	-	6	-	-	94
5	Ru/C	-	-	-	-	-	-

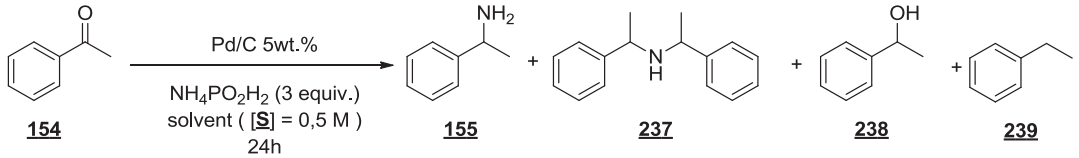
[a] Conv. and GC ratio were determined by gas chromatography.

c. Effect of different solvents

The solubility of $NH_4PO_2H_2$ was the major problem while running the above reactions. By performing solubility tests, it was noticed that $NH_4PO_2H_2$ is more soluble in oxygenated solvents upon heating. Thus we increased the temperature of the reaction to 100°C, and the efficiency of other solvents was investigated according to Table 14. Using n-BuOH (Table 14, entry 2), the conversion of **154** was complete, and the yield of **155** was improved to 35%, with 60% of diamine **237** and only 5% of alcohol **238**. Trying to be in milder reaction conditions and to have better stirring in the reaction mixture, the amount of Pd/C was decreased to 2.5mol%, in this case with n-BuOH, the result was promising with total conversion giving a mixture of primary amine **155** (45%) and secondary amine **237** (55%) (Table 14, entry 3). This could be explained with better stirring in the reaction mixture. With other solvents such as, CPME, 1,2,3-TMP,[84] and 2-MeTHF, the reactions were less efficient, with a drop in the conversion as well as in the yield of the desired product **155** (Table 14, entries 4-6).

Therefore, 5 wt.% Pd/C (2,5mol%), n-BuOH and 100°C were chosen to be the best conditions for further studies.

Table 14. DRA of acetophenone **154** using $NH_4PO_2H_2$ in different reaction conditions.



154 155 237 238 239

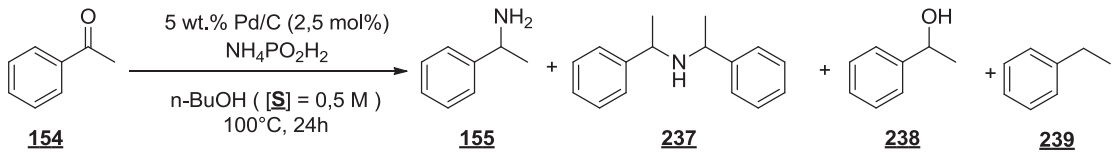
Entry	Pd/C [mol%]	Solvent	T [°C]	Conv. [%][a]	GC Ratio [%][a]				
					155	**237**	**238**	**239**	**byproducts**
1	5	EtOH	80	100	12	73	1	2	12
2	5	n-BuOH	100	100	35	60	5	-	-
3	2,5	n-BuOH	100	100	45	55	-	-	-
4	2,5	CPME	100	55	-	40	25	35	-
5	2,5	1,2,3-TMP	100	36	-	86	14	-	-
6	2,5	2-MeTHF	100	32	-	68	19	13	-

[a] Conv. and GC ratio were determined by gas chromatography.

d. Effect of amount of $NH_4PO_2H_2$

In the next step, we studied the effect of the amount of hypophosphite $NH_4PO_2H_2$ on the DRA of **154**, according to Table 15. Decreasing the amount of $NH_4PO_2H_2$ to 1 and 2 equivalents favoured the formation of secondary amine **237**, with lower conversions (Table 15, entries 1 & 2). This was expected, due to the fact that when the primary amine is formed, there is still starting material to react with. Less reducing agent can also explain the low conversion. However, increasing the amount of $NH_4PO_2H_2$ led to a complete conversion, promoting the formation of primary amine **155** as the major product (Table 15, entries 3 & 4).

Table 15. Effect of the amount of $NH_4PO_2H_2$ on the DRA of acetophenone **154**.



154 155 237 238 239

Entry	$NH_4PO_2H_2$ equiv.	Conv. [%][a]	GC Ratio [%][a]			
			155	**237**	**238**	**239**
1	1	66	-	52	34	14
2	2	65	12	73	15	-
3	3	100	45	55	-	-
4	4	100	88	12	-	-
5	5	100	100	-	-	-
6	6	-	-	-	-	-

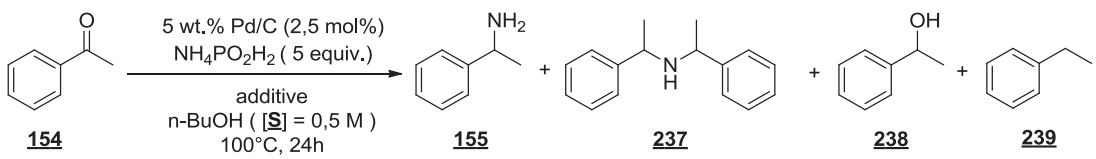
[a] Conv. and GC ratio were determined by gas chromatography.

The best result was obtained in the presence of 5 equiv. of the ammonium hypophosphite, in which the conversion of **154** was complete, and α-phenylethylamine **155** was obtained as the sole product assisted by GC (Table 15, entry 5). Moving up to 6 equiv. the mixture starts to turn thick with no conversion (Table 15, entry 6).

e. The effect of additives

Although optimal conditions were in hand, but we also investigated the effect of adding an additive in the reaction mixture according to Table 16. During the condensation step between NH_3 and ketone, H_2O is released which can hinder the reaction by limiting the equilibrium between the starting material and the imine group. Therefore calcium hydride (CaH_2), a well-known desiccant, was added to react with water to form hydrogen thus increasing the reduction rate. However, results showed a decrease in the yield of **155** (70%) after 24h (Table 16, entry 1). MS were also tried as drying additives, however, only 56% of **155** was obtained (Table 16, entry 2).

Table 16. DRA of acetophenone **154** with $NH_4PO_2H_2$ in the presence of different additives.



Entry	Additive [mol%]	Conv. [%][a]	GC ratio [%][a]				
			155	**237**	**238**	**239**	**byproduct**
1	CaH_2/ 0.6 mol%	100	70	1	-	-	29
2	MS[b]/ 20 mol%	100	56	13	2	27	2
3	NaOH/ 250 mol%	100	34	55	2	8	1

[a] Conv. and GC ratio were determined by gas chromatography.[b] molecular sieves 3 Å.

We hypothesized that adding NaOH to the reaction mixture will facilitate the ammonia releasing and promote the formation of primary amine. However, results showed a drop in the yield of **155** to 34% (Table 16, entry 3). Actually, NaOH helped to produce more water in the system which decreased the rate of the reaction. According to these results, we can conclude that the small quantity of water generated during the condensation step does not have a big impact on conversion or on the yield of the desired product. However, excess water affects the selectivity of the reaction.

f. Effect of temperature

In order to evaluate the effect of the temperature of the reaction, the reduction of acetophenone **154** was performed using the optimized conditions: $NH_4PO_2H_2$ (5 equiv.), 5 wt.% Pd/C (2,5 mol%) in n-BuOH where [acetophenone]= 0.5M, while varying the temperature as presented in Figure 18. It is clear that upon increasing the temperature, the conversion of the starting material increases, where it reach 100% at 100°C.

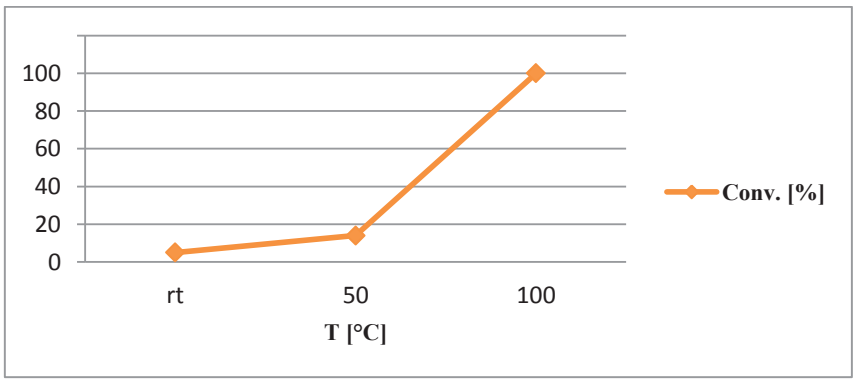


Figure 18. The variation in the conversion of **154** as a function of temperature.

g. Effect of concentration of acetophenone in butanol

The effect of concentration of acetophenone **154** in n-BuOH was also studied as shown in Figure 19. It was obvious that the concentration of **154** in n-BuOH had an effect on the yield of α-phenylethylamine **155**.

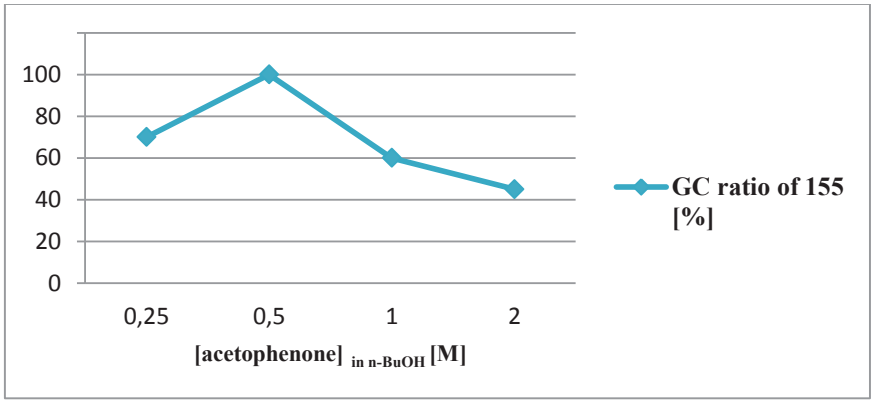


Figure 19. The variation in the conversion of **154** as a function of [**acetophenone**] in n-BuOH.

The ideal concentration was 0.5M in which **155** was obtained as the sole product. As the reaction mixture is more diluted, the yield of **155** dropped to 70% at [acetophenone]= 0.25M. When the reaction mixture is more concentrated, the yield of **155** droped to 45% at [acetophenone]= 2M. It is possible that at higher concentrations, reactants, reagents and catalysts are less soluble.

3.3. Application of the methodology on different substrates

In order to evaluate the generality of our methodology, we investigated the DRA of a series of ketones under the optimized reaction conditions: $NH_4PO_2H_2$ (5 equiv.) as a reducing agent and as a source of ammonia, 5 wt.% Pd/C (2,5 mol%) as the catalyst, n-BuOH ([S]=0,5M) as a solvent at 100°C. Generally very good to excellent yields of

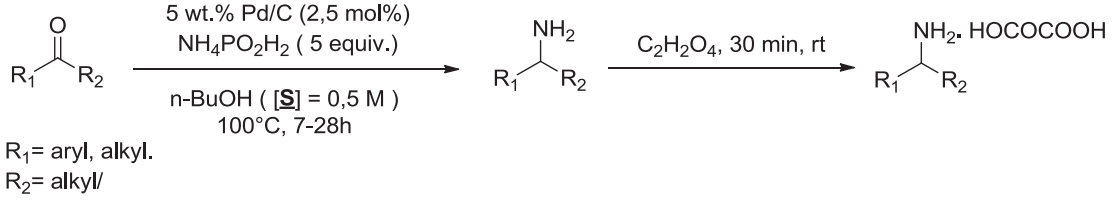
primary amines were isolated as oxalic acid salts after treatment of the filtrated reaction mixture with oxalic acid (Table 17).

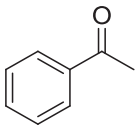
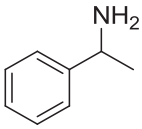
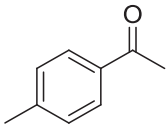
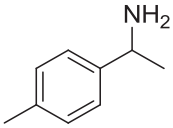
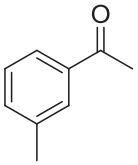
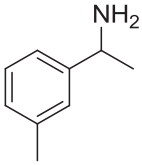
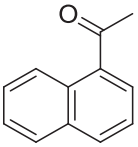
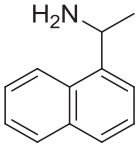
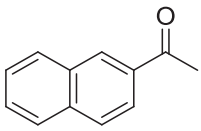
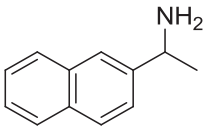
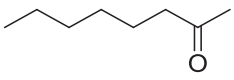
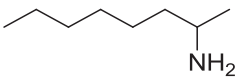
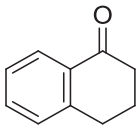
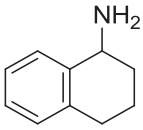
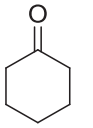
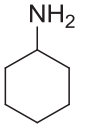
It is important to mention that the time required for the complete conversion of each substrate is not the same, thus the kinetics of each subtstrate was studied by running more that one reaction at different time intervals.

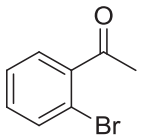
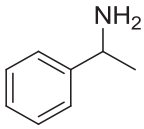
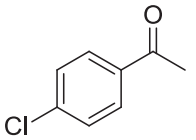
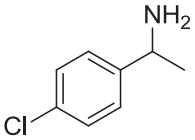
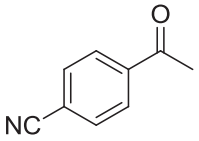
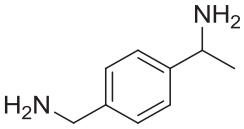
With respect to acetophenone, the corresponding amine oxalic acid salt was isolated in a high yield of 95% (Table 17, entry 1). The reduction of acetophenone derivatives containg $–CH_3$, an electron donating group, at para and meta positions was done successfully (Table 17, entries 2 & 3), the corresponding amines **241** and **243** were obtained with 99 and 90% isolated yields respectively, however, the reaction was faster in case of meta positions (Table17, entry 3). 1-Acetylnaphthalene **244** and 2-acetylnaphthalene **246** were also reduced under the optimized reaction conditions in very good to excellent yields after 21-22h (Table 17, entries 4 & 5). However, the reduction of 2-octanone **248** needed 28h for complete conversion, where 2-aminooctane **249** was obtained in 96% isolated yield (Table 17, entry 6). The reduction of alpha-tetralone **250** was also performed within 26h, resulting in a good isolated yield of the corresponding amine salt (Table 17, entry 7).

The substrate versatility of this method was further demonstrated by the reduction of cyclohexanone **173** so that cyclohexylamine **252** was obtained in an excellent isolated yield after 28h (Table 17, entry 8).

Table 17. Direct reductive amination of ketones using ammonium hypophosphite and Pd/C.



Entry	ketone	amine	Time [h]	Conv. [%][a]	GC ratio [%][a]	Isolated yield [%][b]
1	 **154**	 **155**	24	100	100	95
2	 **240**	 **241**	24	100	100	99
3	 **242**	 **243**	7	100	100	90
4	 **244**	 **245**	22	100	98	80
5	 **246**	 **247**	21	100	100	99
6	 **248**	 **249**	28	100	100	96
7	 **250**	 **251**	26	90	90	85
8	 **173**	 **252**	28	100	100	99

9	 **253**	 **155**	7	100	100	99
10	 **170**	 **254**	15	100	100	98
11	 **255**	 **256**	7	100	100	99

[a] Conversion and GC Ratio were determined by GC; [b] yield of products isolated as oxalic acid salt.

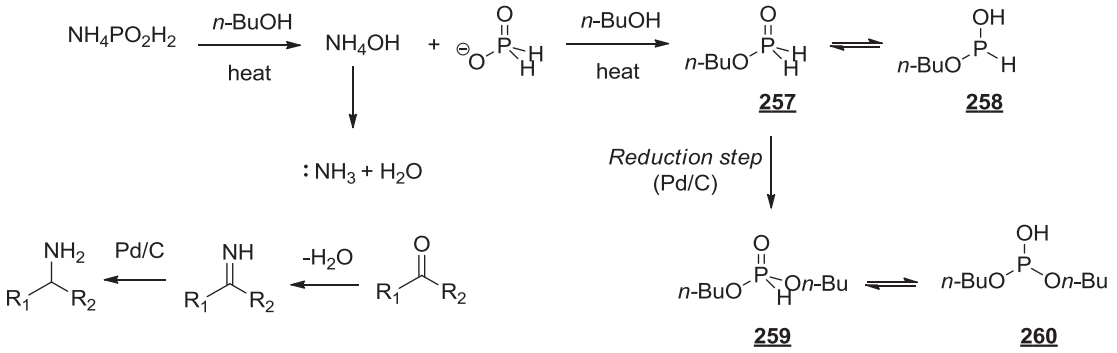
Halogenated acetophenone derivatives were also reduced. In case of 2'-bromoacetophenone **253** the reduction was fast within 7h accompanied by dehalogenation reaction, so that α-phenylethylamine **155** was obtained in almost complete isolated yield (Table 17, entry 9). 4'-cholorbenzonitrile **170** was also reduced after 15h, with chlorine group remaining at the end of the reaction (Table 17, entry 10). Finally, the challenging 4-acetylbenzonitrile **255** was reduced, the system was able to reduce the cyano and keto group at the same time resulting in 1-(4-(aminomethyl)phenyl)ethanamine **256** after 7h with excellent isolated yield (Table 17, entry 11).

3.4.Mechanism

Moving to the mechanistic part, during the analysis of the reaction we observed in GC chromatogram a product formed in significant quantities other than the corresponding amine. By mass spectroscopic analysis, the structure of di-*n*-butylphosphonate **259** was confirmed. To be sure, a ^{31}P NMR was done for the crude reaction, two peaks were observed, which means that there are two phosphorous species at the end of the reaction. By going back to literature it is known that hypophosphite salts can react with alcoholic

solvents to form hypophosphite esters.[246] According to these data, we assumed that $NH_4PO_2H_2$ react with *n*-BuOH, as a result ammonium hydroxide NH_4OH and hypophosphite anion were formed. The former dissociates to give ammonia and water, however, the later undergoes alkylation reactions leading to the formation of *n*-butylphosphinate **257** and di-*n*-butylphosphonate **259**. In the next step, ammonium formed adds to the carbonyl group, leads to the formation of imine intermediate, which was reduced in the presence of Pd/C and reducing agent to the corresponding amine (Scheme 100).

With respect to the reducing agent, there is two possibilities, the first one is that ammonium hypophosphite acts as a reducing reagent and the formation of **259** is in competition with the reduction. The second one is that ammonium hypophosphite firstly reacts with butanol to form the alkyl phosphonate **259** which can be the real reducing agent. Further experiments should be done to confirm the exact pathway of the reaction.



Scheme 100. Proposed mechanism for the DRA of ketones using $NH_4PO_2H_2$ in *n*-BuOH.

3.5. Conclusion and perspectives

In this part, we have investigated for the first time, the DRA of ketones into amines using ammonium hypophosphite in the presence of Pd/C. After studying the reaction parameters, best results were obtained using 5 equiv. of $NH_4PO_2H_2$ and 2,5 mol% equiv. of 5 wt.% Pd/C in the presence of n-BuOH as a solvent. In these conditions a variety of cyclic, acyclic aliphatic and aromatic ketones were reduced to give the corresponding amines in excellent isolated yields. In this reaction ammonium hypophosphite plays two

crucial roles, so that it acts as a source of ammonia in the medium as well as a reducing agent.

For future perspectives, it is important to study the DRA of more challenging substrates, including aliphatic and sterically hindered ketones and aldehydes, and to study the chemoselectivity of this method in the presence of other competitive functional groups. On the other hand, it is interesting to synthesize hypophosphite esters and to evaluate their reductive ability in different organic transformations.

4. Experimental Part

4.1. General information

All reagents were obtained from commercial sources and used as recieved without any furthur purification. Ammonium hypophosphite 97%, NaOH, Molecular sieves 3Å and oxalic acid were purchased from Sigma Aldrich. Pd/C 5wt.%, Ru/C 5wt.%, Ru/Al_2O_3 5%, Rh/C 5% and Pt/C 5% were purchased from Strem Chemicals. Calcium hydride 90-95% was purchased from Alfa Aesar.

The complete references of the pressure tubes are: ACE pressure tubes, #15 Ace-Thred, order code (CAS: 8648-03), length (10.2 cm), body O.D. (25.4 mm), capacity (15 mL), pressure rating (150 PSI or 10.3 bar) and ACE pressure tubes, order code (CAS: 8648167), length (10.2 cm), body O.D. (38.1 mm), capacity (38 mL), pressure rating (150 PSI or 10.3 bar). The pressure tube was closed by a back seal PTFE plug 5845 with a 210 O-ring for #15 Ace-Thred in FETFETM or silicone.

All compounds were characterized by spectroscopic data. The nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker ALS 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), a DRX 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or a Bruker DRX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer, in D_2O at 293K or DMSO-d_6 at 343 K . Chemical shifts are reported in parts per million (ppm) and are calibrated on residual solvent peaks: D_2O 4.79

ppm in ^{1}H, or DMSO-d_6 2.50 ppm in ^{1}H and 39.52 ppm in ^{13}C.[2] Spin-spin coupling constants (*J)* are given in Hz. The peak patterns are indicated as follows: (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad).

GC-MS analyses were performed on a DSQ - Thermofinnigan spectrometer equipped with quadrupole analyzer and a DB-5MS capillary column (30.0 m × 0.25mm × 0.25µm). The carrier gas was helium, at a flow rate of 1 mL/min. Column temperature was initially 70 °C for 2 min, then gradually increased to 310 °C at 15 °C/min and finally kept at 310 °C for 10 min. The injector temperature was 220 °C and the transfer line temperature was 280 °C.

GC analyses were performed on a Shimadzu Gas Chromatograph GC-2025 equipped with a ZB-5-MS column (30.0 m × 0.25mm × 0.25µm). The carrier gas was N_2 at a flow rate of 1.27 mL/min. Column temperature was initially 70 °C for 2 min, then gradually increased to 280 °C at 15 °C/min and finally kept at 280 °C for 15 min. The injector temperature was 250 °C and for detection a FID was used at 280 °C.

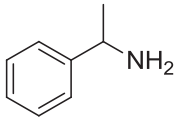
4.2.Typical procedure for the DRA of ketones

In a sealed tube ammonium hypophosphite (415.15mg, 5 mmol) was added, followed by acetophenone (120 mg, 1 mmol) in n-butanol (2 mL, [acetophenone] in n-butanol= 0.5M). pd/C 5wt.% (53 mg, 2.5 mol%) was then added. The tube was sealed and the reaction was stirred at 800 rpm at 100°C. After 24 hours the tube was cooled in cold water and depressurized carrefully. The reaction mixture was dilluted with HCl (2M in H_2O) and extracted with diethylether. To the acidic aqeous phase an alkaline solution of NaOH (2M in H_2O) was added until pH=14, an extraction was done twice with diethylether. The obtained organic phase was dried over Na_2SO_4. The crude was analyzed in GC and GC-MS.

4.3.Typical procedure for the isolation of amines as oxalic acid salts

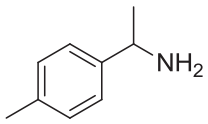
Oxalic acid $C_2H_2O_4$ (1mL) was added to the extracted organic phase, constant stirring was maintained for 30 minutes at room temperature. The resulting precipitate was filtered and washed with diethyl ether and dried under reduced pressure.

4.4.Characterization data



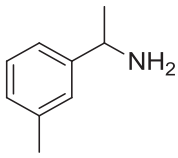
1-phenylethylamine [618-36-0] (155)

Oxalate salt: white solid, **^{1}H NMR (300 MHz, D_2O):** δ 7.56-7.51 (m, 5H), 4.63-4.57 (q, 1H), 1.72-1.7 (d, J= 6Hz , 3H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 164.11, 137.68, 129.19, 126.45, 50.95, 19.22 ppm.



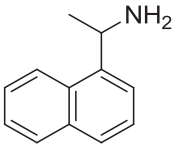
1-(4-Methylphenyl)ethylamine [586-70-9] (241)

Oxalate salt: white solid, **^{1}H NMR (300 MHz, D_2O):** δ 7.35-7.28 (m, 4H), 4.45-4.44 (q, 1H), 2.32 (s, 3H), 1.62-1.59 (d, J= 9 Hz, 3H) ppm.**^{13}C NMR (75 MHz, D_2O):** δ 139.46, 134.70, 129.69, 126.45, 50.70, 20.11, 19.19 ppm.



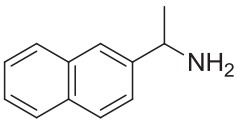
1-(3-Methylphenyl)ethylamine [70138-19-1] (243)

Oxalate salt: white solid, **^{1}H NMR (300 MHz, D_2O):** δ.7.39-7.34 (m, 1H), 7.28-7.22 (m, 3H), 4.51-4.44 (q, 1H), 2.34 (s, 3H), 1.62-1.59 (d, J= 9 Hz, 3H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 139.46, 137.8, 129.68, 129.14, 127, 123.32, 50.92, 20.33, 19.29 ppm.



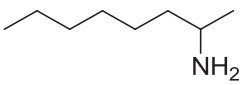
1-(1-Naphthyl)ethylamine [42882-31-5] (245)

Oxalate salt: white solid, **^{1}H NMR (400 MHz, DMSO, 70°C):** δ 8.19-8.17 (d, J= 8 Hz, 1H), 7.99-7.97 (d, J= 8 Hz, 1H), 7.92-7.9 (d, J= 8 Hz, 1H), 7.77-7.75 (d, J= 8 Hz, 1H), 7.64-7.54 (m, 3H), 5.2-5.15 (q, 1H), 1.61-1.59 (d, J= 8 Hz, 3H) ppm. **^{13}C NMR (100 MHz, DMSO, 70°C):** δ 163.90, 137.58, 133.12, 129.67, 128.44, 127.72, 126.13, 125.48, 125.08, 122.44, 122.40, 45.50, 21.81 ppm.



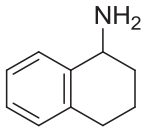
1-(2-naphthyl)ethanamine (247)

Oxalate salt: white solid, **^{1}H NMR (400 MHz, DMSO, 70°C):** δ 8.00-7.90 (m, 4H), 7.66-7.63 (m, 1H), 7.58-7.51 (m, 2H), 4.55-4.54 (q, 1H), 1.61-1.59 (d, J= 8 Hz, 2H) ppm. **^{13}C NMR (100 MHz, DMSO, 70°C):** δ 163.95, 132.43, 132.35, 127.95, 127.48, 127.19, 126.12, 126.01, 125.20, 124.19, 49.94, 20.53 ppm.



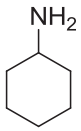
2-aminooctane [693-16-3] (249)

Oxalate salt: white solid, **^{1}H NMR (300 MHz, D_2O):** δ 3.35-3.28 (q, 1H), 1.69-1.47 (m, 2H), 1.33-1.24 (m, 11H), 0.86-0.81 (t, 3H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 47.84, 33.92, 30.74, 27.98, 24.45, 21.81, 17.57, 13.26 ppm.



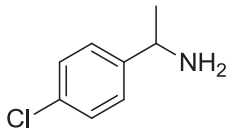
1,2,3,4-Tetrahydro-1-naphthylamine [2217-40-5] (251)

Oxalate salt: white solid, **^{1}H NMR (300 MHz, D_2O):** δ 4.36-7.23 (m, 4H), 4.58-4.54 (t, 1H), 2.90-2.73 (m, 2H), 2.21-1.94 (m, 2H), 1.91-1.82 (m, 2H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 138.15, 131.04, 129.77, 128.90, 128.24, 126.44, 48.95, 27.90, 27.14, 17.71 ppm.



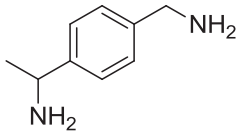
Cyclohexyl amine [108-91-8] (<u>252</u>)

Oxalate salt: white solid, **^{1}H NMR (300 MHz, D_2O):** δ 3.12 (m, 1H), 1.97-1.94 (m, 2H), 1.79-1.76 (m, 2H), 1.64-1.12 (m, 6H) ppm. **^{13}C NMR (75 MHz, D_2O):** δ 50.31, 30.27, 24.23, 23.75 ppm.



1-(4-chlorophenyl)ethylamine [6299-02-1] (<u>254</u>)

Oxalate salt: white solid, **^{1}H NMR (400 MHz, DMSO):** δ 7.54-7.50 (m, 2H), 7.47-7.44 (m, 2H), 4.43-4.38 (q, 1H), 1.52-1.50 (d, J= 6 Hz, 3H) ppm. **^{13}C NMR (75 MHz, DMSO):** δ 163.90, 138.27, 132.69, 128.42, 128.24, 49.13, 20.24 ppm.



1-(4-(aminomethyl)phenyl)ethylamine (<u>256</u>)

Oxalate salt: white solid, **^{1}H NMR (400 MHz, DMSO, 70°C):** δ 6.92-6.90 (d, J= 8 Hz, 2H), 6.76-6.74 (d, J= 8 Hz, 2H), 3.45-3.40 (q, 1H), 1.63 (s, 2H), 0.55-0.53 (d, J= 8 Hz, 3H) ppm. **^{13}C NMR (100 MHz, DMSO, 70°C):** δ 164.04, 148.51, 132.18, 127.32, 118.45, 110.27, 49.75, 22.24 ppm.

General Conclusion and Perspectives

GENERAL CONCLUSION AND PERSPECTIVES

The purpose of this work was to replace boron and aluminum hydrides by air-stable, easy-to-handle, less expensive and less toxic reducing agents, that are selective and compatible with other functional groups.

In the laboratory, hydrosiloxanes associated with different metals have been used for the reduction of a wide variety of organic functions.

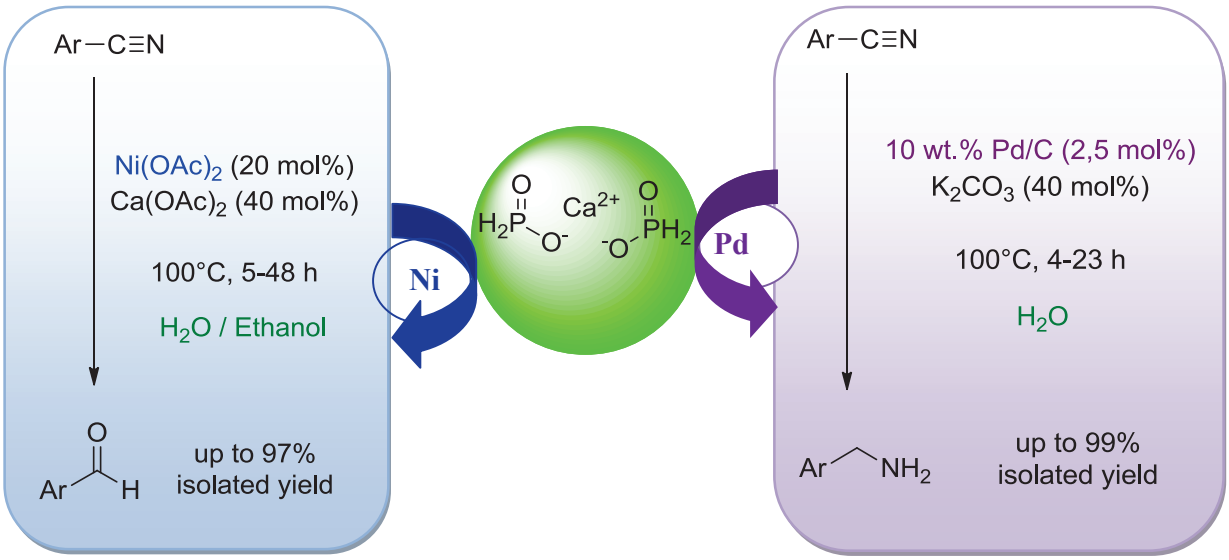
Among the available reagents meeting these criteria, sodium hypophosphite, calcium and magnesium hydrides, which have been used in our laboratory for the reduction of ketones to alcohols and alkanes, as well as in reductive amination and reductive alkylation reactions.

Based on these results, respecting the principles of green chemistry, such as the minimization of waste, the use of renewable materials and catalysts, my thesis project focuses on the study of new reducing systems based on hypophosphites in order to reduce new organic functions.

Taking the advantage of solubility of hypophosphites in water, the reduction of nitriles to aldehydes using calcium hypophosphite was carried out in two-phase water/ethanol medium, in the presence of $Ca(OAc)_2$ and $Ni(OAc)_2$ at 100°C (Scheme 105). The reaction allowed the reduction of aromatic nitriles to the corresponding aldehydes with good yields and good selectivities.

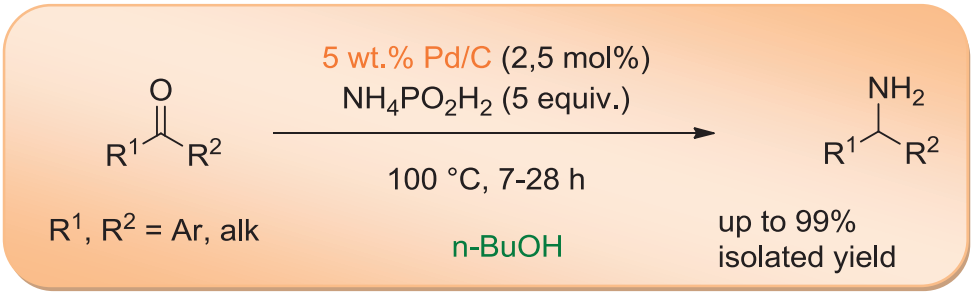
The reduction of aromatic nitriles catalyzed by different catalysts led to different products at the end of the reaction in each case. In the presence of 10 wt.% Pd/C, primary amine was the sole product. Thus, the determining factor for the selectivity towards aldehyde or amine is the type of catalyst. Variety of aromatic nitriles were reduced with the following optimized conditions: calcium hypophosphite (2,5 equiv.), 10 wt.% Pd/C (2,5 mol%), K_2CO_3 (40 mol%) at 100°C in aqueous medium (Scheme 105). The reaction is generally

better in the presence of K_2CO_3. Moreover, decreasing the catalyst load to 1 mol%, changes the selectivity towards the diamine.



Scheme 105. Reduction of aromatic nitriles using calcium hypophosphite.

In the second part, the potential of ammonium hypophosphite in reductive amination was studied. In this reaction ammonium hypophosphite plays to roles: as a source of ammonia and as a reducing agent. A variety of aliphatic and aromatic ketones were reductively aminated in the following conditions: ammonium hypophosphite (5 equiv.), 5 wt.% Pd/C (2,5 mol%), in butanol at 100 °C (Scheme 106).



Scheme 106. Reductive amination of ketones in the presence of $NH_4PO_2H_2$ and Pd/C.

As a result, it has been shown for the first time that calcium and ammonium hypophosphites are potential alternatives for conventional reducing agents.

For future perspectives, it is very important to find the optimized conditions to reduce aliphatic nitriles into aliphatic aldehydes. Moreover, cyclization of dinitriles should be studied in details. On the other hand, reductive amination methodology should be applied on aliphatic and aromatic aldehydes, and it is interesting to study the indirect reductive amination reaction. Finally, the synthesis of hypophosphite esters and studying their reductive ability could be also interesting.

References

1. R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.
2. R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854-862.
3. Y. Xu, J.-Q. Jiang, *Ind. Eng. Chem. Res*. **2008**, *47*, 16-24.
4. T. Sakamoto, H. Saito, K. Ishii, H. Takahashi, S. Tanabe, Y. Ogasawara, *FEBS Letters* **2006**, *580*, 6543-6549.
5. D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411-420.
6. (a) S. C. Berk, S. L. Buchwald, *J. Org. Chem*. **1992**, *57*, 3751-3753; (b) A. S. Wells, *Org. Process Res. Dev*. **2010**, *14*, 484.
7. a) Y.-J. Zhang, W. Dayoub, G.-R. Chen, M. Lemaire, *Green Chem.* **2011**, *13*, 2737-2742; b) Y.-J. Zhang, W. Dayoub, G.-R. Chen, M. Lemaire, *Eur. J. Org. Chem.* **2012**, 1960-1966; c) L. Pehlivan, E. Métay, S. Laval, W. Dayoub, D. Delbrayelle, G. Mignani, M. Lemaire, *Eur. J. Org. Chem.* **2011**, 7400-7406; d) Y. Shi, W. Dayoub, G.-R. Chen, M. Lemaire, *Tetrahedron Lett.* **2011**, *52*, 1281-1283; e) L. Pehlivan, E. Métay, O. Boyron, P. Demonchaux, G. Mignani, M. Lemaire, *Eur. J. Org. Chem.* **2011**, 4687-4692; f) L. Pehlivan, E. Métay, S. Laval, W. Dayoub, P. Demonchaux, G. Mignani, M. Lemaire, *Tetrahedron Lett.* **2010**, *51*, 1939-1941; g) L. Pehlivan, E. Métay, S. Laval, W. Dayoub, P. Demonchaux, G. Mignani, M. Lemaire, *Tetrahedron* **2011**, *67*, 1971-1976; h) L. Pehlivan, E. Métay, D. Delbrayelle, G. Mignani, M. Lemaire, *Eur. J. Org. Chem.* **2012**, 4689-4693; i) L. Pehlivan, E. Métay, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron* **2012**, *68*, 3151-3155. j) S. Laval, W. Dayoub, L. Pehlivan, E. Métay, A. Favre-Réguillon, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron Lett.* **2011**, *52*, 4072-4075; k) S. Laval, W. Dayoub, A. Favre Réguillon, P. Demonchaux, G. Mignani, M. Lemaire, *Tetrahedron Lett.* **2010**, *51*, 2092-2094; l) M. Berthod, A. Favre-Réguillon, J. Mohamad, G. Mignani, G. Docherty, M. Lemaire, *Synlett* **2007**, 1545-1548; m) C. Petit, A. Favre Réguillon, B. Albela, L. Bonneviot, G. Mignani, M. Lemaire, *Organometallics* **2009**, *28*, 6379-6382; n) C. Petit, E. Poli, A. Favre-Réguillon, L. Khrouz, S. Denis-Quanquin, L. Bonneviot, G. Mignani, M. Lemaire, *ACS Catal.* **2013**, *3*, 1431-1438; o) S. Laval, W. Dayoub, L. Pehlivan, E. Métay, A. Favre-Reguillon, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron* **2014**, *70*, 975-983; p) S. Laval, W. Dayoub, L. Pehlivan, E. Métay, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron Lett.* **2014**, *55*, 23-26.
8. M. Baron, E. Metay, M. Lemaire, F. Popowycz, *Green Chem.* **2013**, *15*, 1006-1015.
9. C. Guyon, E. Métay, F. Popowycz, and M. Lemaire, Org. Biomol. Chem. **2015**, *13*, 7879-7906.
10. (a) C. Guyon, E. Metay, N. Duguet, M. Lemaire, *Eur. J. Org. Chem.* **2013**, 5439-5444; (b) C. Guyon, M. Baron, M. Lemaire, F. Popowycz, E. Metay, *Tetrahedron* **2014**, *70*, 2088-2095.
11. M. B. Smith, J. March, *March's Advanced Organic Chemistry 5 th Edition*; Wiley – Interscience; 2001; pp 1506-1604.
12. (a) D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis Using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, 2009; (b) H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351-10372; (c) D. J. Edmonds, D. Johnston, D. Procter, *Chem. Rev.*

2004, *104,* 3371-3404; (d) K. C. Nicolaou, S. P. Ellery, J.S. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 7140-7165; (e) M. Szostak, D. J. Procter, *Angew. Chem.* **2011**, *123*, 7881-7883; *Angew. Chem. Int. Ed.* **2011**, *50*, 7737-7739; (f) M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev*. **2013**, *42*, 9155-9183.

13. (a) H. J. Stephen, *Chem. Soc***. 1925**, *127*, 1874-1877; (b) L. Kürti, B. Czako, *Strategic Applications of Named Reaction in Organic Synthesis*; Elsevier Academic Press, 2005; pp 430-431.
14. P. R. Carlier, K. M. Lo, M. M.-C. Lo, I. D. Williams, *J. Org. Chem.* **1995***, 60,* 7511-7517.
15. (a) H. C. Brown, C. J. Schoaf, C. P. Garg, *Tetrahedron Lett*. **1959**, *1*, 9-10; (b) H. C. Brown, C. P. Garg, *J. Am. Chem. Soc.* **1964**, *86*, 1085-1089.
16. Yoon, N. M.; Kim, S. K.; Kyong, Y. S. Bull. Korean, Chem. Soc. 1986, 7, 323-325.
17. J. S. Cha, S. H. Jang, S. Y. Kwon, *Bull. Korean Chem. Soc.* **2002**, *23*, 1697-1698.
18. J. S. Cha, *Bull. Korean Chem. Soc.* **1992**, *13*, 670-676.
19. G. J. Wells, T.-H. Yan, L. A. Paquette, *J. Org. Chem.* **1984**, *49*, 3604-3609.
20. (a) A. E. G. Miller, J. W. Biss, L. H. Schwartzman, *J. Org. Chem.* **1959**, *24*, 627-630; (b) N. M. Yoon, S. G. Young, *J. Org. Chem.* **1985**, *50*, 2343-2350; (c) T. Katoh, Y. Nagata, Y. Kobayashi, K. Arai, J. Minami, S. Terashima, *Tetrahedron Lett.* **1993**, *34*, 5743-5746.
21. (a) J. H. Ha, J. H. Ahn, D. K. An, *Bull. Korean Chem. Soc*. **2006**, *27*, 121-122; (b) Y. M. Choi, S. J. Choi, K. Y. Eom, H. Hwang, D. K. An, *Bull. Korean Chem. Soc.* **2008**, *29*, 2303-2304; (c) Y. M. Choi, M. Yoo, D. K. An, *Bull. Korean Chem. Soc*. **2010**, *31*, 473-474.
22. (a) J. S. Cha, S. Y. Oh, J. E. Kim, *Bull. Korean Chem. Soc.* **1987**, *8*, 301-304; (b) J. S. Cha, M. S. Yoon, *Tetrahedron Lett.* **1989**, *30*, 3677-3680.
23. (a) J. P. Ferris, F. R. Antonucci, *Chem. Commun.* **1971**, 1294-1295; (b) J. P. Ferris, F. R. Antonucci, *J. Am. Chem. Soc.* **1972**, *94*, 8091-8095.
24. F. Xi, F. Kamal, M. A. Schenerman, *Tetrahedron Lett.* **2002**, *43*, 1395-1396.
25. K. Z. Schwabe, *Elektrochem.* **1957**, *61*, 744-752.
26. H. Matloubi, A. Shafiee, N. Saemian, G. Shirvani, F. J. Daha, *J Label Compd Radiopharm* **2004**, *47*, 31-36.
27. W.W Zajac Jr., J. F. Siuda, M. J. Nolan, T. M. Santosusso, *J. Org. Chem.* **1971**, *36*, 3539-3541 and cited references.
28. A. Chatterjee, R. A. Shaikh, A. Raj, A. P. Singh, *Catalysis Letters* **1995**, *31*, 301-305.
29. (a) R. Calas, E. Frainnet, A. Bazouin, *Compt. Rend. Acad. Sci.* **1961**, *252*, 240; (b) R. Calas, *Sur Quelques Aspects de la Réactivité des Hydrogénosilanes en Chimie Organique* **1966**, 61-79; (c) J. P. Llonch, E. Frainnet, *Compt. Rend. Acad. Sci.* **1972**, *274*, 70.
30. A. J. Chalk, *J. Organometal. Chem*. **1970**, *21*, 207-213.
31. (a) R. J. P. Corriu, J. J. E. Moreau, *J. Chem. Soc. Chem. Commun*. **1980**, 278-279; (b) R. J. P. Corriu, J. J. E. Moreau, M. Pataud-Sat, *J. Org. Chem.* **1981**, *46*, 3374-3376; (c) R. J. P. Corriu, J. J. E. Moreau, M. Pataud-Sat, *Organometallics* **1985**, *4*, 623-629.
32. (a) J. Kim, Y. Kang, J. Lee, Y. K. Kong, M. S. Gong, S. O. Kang, J. Ko, *Organometallics* **2001**, 20, 937-944; (b) N. P. Reddy, Y. Uchimaru, H. –J. Lautenschlager, M. Tanaka, *Chem. Lett.* **1992**, 45-48; (c) R. J. P. Corriu, J. J. E. Moreau, M. Patuad-Sat, *J. Organometal. Chem.* **1982**, *228*, 301-308.
33. (a) M. Ochiai, H. Hashimoto, H. Tobita, *Angew. Chem. Int. Ed.* **2007**, *46*, 8192-8194; (b) H. Hashimoto, I. Aratani, C. Kabuto, M. Kira, *Organometallics* **2003**, *22*, 2199-2201; (c) T.

Watanabe, H. Hashimoto, H. Tobita, *J. Am. Chem. Soc.* **2006**, *128*, 2176-2177; (d) T. Komuro, R. Begum, R. Ono, H. Tobita, *Dalton Trans.* **2011**, *40*, 2348-2357; (e) A. Y. Khalimon, R. Simionescu, L. G. Kuzmina, J. A. K. Howard, G. I. Nikonov, *Angew. Chem. Int. Ed.* **2008**, *47*, 7701-7704.

34. (a) E. Peterson, A. Y. Khalimon, R. Simionescu, L. G. Kuzmina, J. A. K. Howard, G. I. Nikonov, *J. Am. Chem. Soc.* **2009**, *131*, 908-909; (b) D. V. Gutsulyak, G. I. Nikonov, *Angew. Chem. Int. Ed.* **2010**, *49*, 7553-7556.
35. S. Laval, W. Dayoub, L. Pehlivan, E. Métay, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron Letters* **2014**, *55*, 23-26.
36. O. G. Backeberg, B. Staskun, *J. Chem. Soc.* **1962**, 3961-3963.
37. (a) M. E. Salvati, J. A. Balog, D. A. Pickering, S. Giese, A. Fura, W. Li, R. N. Patel, R. L. Hanson, T. Mitt, J. Roberge, J. R. Corte, S. H. Spergel, R. A. Rampulla, R. Misra, H.-Y. Xiao, WO 2003/062241, 2003; (b) C. Kuhn, L. Skaltsounis, C. Monneret, J.-C. Florent, *Eur. J. Org. Chem.* **2003**, 2585–2595; (c) M. Amat, O. Bassas, M. Cantó, N. Llor, M. M. M. Santos. J. Bosch, *Tetrahedron* **2005**, *61*, 7693–7702; (d) J. Shirai, T. Yoshikawa, H. Sugiyama, WO 2007/089031, 2007; (e) A. Robinson, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 6673–6675; (f) K. Zhu, J. S. Panek, *Org. Lett.* **2011**, *13*, 4652–4655; (g) L. Alcaraz, A. Bailey, N. Kindon, WO 2011/012896, 2011; (h) P. H. Cui, T. Rawling, K. Bourget, T. Kim, C. C. Duke, M. R. Doddareddy, D. E. Hibbs, F. Zhou, B. N. Tattam, N. Petrovic, M. Murray, *J. Med. Chem.* **2012**, *55*, 7163– 7172.
38. (a) G. Billek, H. Kindl, A. Schimpl, F. P. Schmook, *J. Labelled Compd.* **1969**, *5*, 3–7; (b) J. Rokach, EP Patent, 0 138 532, 1985; (c) S. P. East, M. M. Joullié, *Tetrahedron Lett.* **1998**, *39*, 7211–7214; (d) S. P. East, F. Shao, L. Williams, M. M. Joullié, *Tetrahedron* **1998**, *54*, 13371–13390; (e) H.-H. Chen, J. A. May, B. S. Severns, U.S. Patent, 6 696 476, 2004; (f) W. A. Metz Jr., F.-X. Ding, WO 2006/023467, 2006; (g) A. S. Judd, A. J. Souers, D. Wodka, G. Zhao, M. M. Mulhern, R. R. Iyengar, J. Gao, J. K. Lynch, J. C. Freeman, H. D. Falls, S. Brodjian, B. D. Dayton, R. M. Reilly, G. Gintant, J. T. Limberis, A. Mikhail, S. T. Leitza, K. A. Houseman, G. Diaz, E. N. Bush, R. Shapiro, V. Knourek-Segel, L. E. Hernandez, K. C. Marsh, H. L. Sham, C. A. Collins, P. R. Kym, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2365–2371; (h) T. Mcinally, T. Mochel, F. Hasegawa, S. Hori, WO 2012/066336, 2012.
39. (a) F. Troxler, A. Harnisch, G. Bormann, F. Seemann, L. Szabo, *Helv. Chim. Acta* **1968**, *51*, 1616–1628; (b) S. Passannanti, M. P. Paternostro, F. Piozzi, G. Savona, *J. Heterocyclic Chem.* **1977**, *14*, 103–106; (c) F. M. Kaspersen, F. A. M. van Rooij, E. G. M. Sperling, J. H. Wieringa, *J. Labelled Compd. Radiopharm.* **1989**, *27*, 1055–1068; (d) C. A. Veale, J. R. Damewood Jr., G. B. Steelman, C. Bryant, B. Gomes, J. Williams, *J. Med. Chem.* **1995**, *38*, 86–97; (e) R. Mannhold, G. Cruciani, H. Weber, H. Lemoine, A. Derix, C. Weichel, M. Clementi, *J. Med. Chem.* **1999**, *42*, 981–991; (f) M. M. Cudahy, M. E. Shnute, S. P. Tanis, W. R. Perrault, P. M. Herrinton, S. K. Nair, WO 2003/ 059911, 2003; (g) M. Gerspacher, S. Weiler, WO 2005/ 068433, 2005; (h) M. Van Eis, P. Von Matt, J. Wagner, J.-P. Evenou, WO 2005/068454, 2005 and WO 2005/068455 and WO 2007/006533; (i) M. Shimizu, A. Takahashi, S. Kawai, *Org. Lett.* **2006**, *8*, 3585–3587; (j) J. S. Lazo, R. Nunes, J. J. Skoko, P. E. Queiroz de Oliveira, A. Vogt, P. Wipf, *Bioorg. Med. Chem.* **2006**, *14*, 5643–5650; (k) Y. Muneaux, S. Jegham, B. Bourrie, P. Casellas, P. Ciapetti, J.-M. Derocq, C.-G. Wermuth, WO 2007/ 045758, 2007; (l) M. Van Eis, P. Von Matt, J. Wagner, WO 2008/074752, 2008; (m) D.

Allen, M. K. Ameriks, F. U. Axe, M. Burdett, H. Cai, I. Choong, J. P. Edwards, W. Lew, S. P. Meduna, WO 2008/100620, 2008 and WO 2008/100635; (n) W. M. Kazmierski, P. Y. Chong, WO 2009/075960, 2009; (o) P. B. Sampson, S.-W. Li, Y. Liu, H. W. Pauls, L. G. Edwards, B. T. Forrest, M. Feher, N. K. B. Patel, G. Pan, WO 2010/115279, 2010; (p) D. Robaa, C. Enzensperger, S. S. El Din, Abul Azm, E. S. El Khawass, O. El Sayed, J. Lehmann, *J. Med. Chem.* **2010**, *53,* 2646–2650; (q) M. Gerspacher, E. Altmann, R. Beerli, T. Buhl, R. Endres, R. Gamse, J. Kameni-Tcheudji, M. Kneissel, K. H. Krawinkler, M. Missbach, A. Schmidt, K. Seuwen, S. Weiler, L. Widler, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5161–5164; (r) P. B. Sampson, Y. Liu, S.-W. Li, B. T. Forrest, H. W. Pauls, L. G. Edwards, M. Feher, N. K. B. Patel, R. Laufer, G. Pan, WO 2011/123946, 2011; (s) S. Sipos, I. Jablonkai, O. Egyed, M. Czugler, *Carb. Res.* **2011**, *346*, 2862–2871; (t) Y.-K. Zhang, J. J. Plattner, E. E. Easom, L. Liu, D. M. Retz, M. Ge, H.-H. Zhou, *J. Labelled Compd. Radiopharm.* **2012**, *55*, 201–205.

40. A. K. Ghosh, D. K. Moon, *Org. Lett.* **2007**, *9*, 2425– 2427.
41. B. Cao, H. Park, M. M. Joullié, *J. Am. Chem. Soc.* **2002**, *124*, 520–521.
42. H. W. Pauls, B. T. Forrest, R. Laufer, M. Feher, P. B. Sampson, G. Pan, WO 2009/079767, 2009.
43. (a) S. A. Lawrence, *Amines: Synthesis Properties and Application,* Cambridge University Press, Cambridge, **2006**; (b) K. Eller, E. Henkes, R. Rossbacher, H. Hoke, *Amines, Aliphatic in Ullman's Encyclopedia of Industrial Chemistry,* Wiley-VCH, Weinheim, **2000**.
44. (a) P. Camurlu, E. Eren, C. Gultekin, *J. Polym. Sci. Part A* **2012**, *50*, 4847-4853; (b) K. S. Hayes, *Appl. Catal. A* **2001**, *221*, 187-195.
45. (a) D. B. Bagal, B. M. Bhanage, *Adv. Synth. Catal.* **2015**, *537*, 883-900; (b) S. Takemoto, H. Kawamura, Y. Yamada, T. Okada, A. Ono, E. Yoshikawa, Y. Mizobe, M. Hidai, *Organometallics* **2002**, *21*, 3897-3904; (c) P. Kukula, M. Studer, H.-U. Blaser, *Adv. Synth. Catal.* **2004**, *346*, 1487-1493.
46. (a) B. M. Trost, I. Fleming, Comprehensive Organic Synthesis; Pergamon; Oxford, 1991; Vol.8., pp 251-254; (b) J. Seyden-Penne, Reduction by Alumino- and Borohydrides in Organic Synthesis 2nd Edition; Wiley – VCH; 1997; pp 149-154; (c) V. Bazant, M. Capka, M. Cerny, V. Chvalovsky, K. Kochloefl, M. Kraus, J. Malek, *Tetrahedron Lett.* **1968**, *29*, 3303-3306.
47. P. R. Carlier, K. M. Lo, M. M.-C Lo, I. D. Williams, *J. Org. Chem.* **1995***, 60,* 7511-7517.
48. T. Kudo, A. Nose, *Chem. Pharm. Bull.* **1986**, *34*, 3905-3909.
49. (a) N. Kunesch, Y. Lu, C. Miet, J. Poisson, *Tetrahedron Asymmetry* **1990**, *1*, 707-710; (b) S. Caddick, A. K. Haynes, D. B. Judd, M. R. V. Williams, *Tetrahedron Lett.* **2000**, *41*, 3513-3516; (c) S. Caddick, D. B. Judd, A. K. Lewis, M. T. Reich, M. R. V. Williams, *Tetrahedron* **2003**, *59*, 5417-5423.
50. (a) S. W. Heinzman, B. Ganem, *J. Am. Chem. Soc.* **1982**, *104*, 6801-6802; (b) J. O. Osby, S. W. Heinzman, B. Ganem, *J. Am. Chem. Soc.* **1986**, *108*, 67-72; (c) P. L. Beaulieu, P. W. Schiller, *Tetrahedron Lett.* **1988**, *29*, 2019-2021; (d) J. G. Buchanan, K. W. Lumbard, R. J. Sturgeon, D. K. Thompson, R. H. Wightman, *J. Chem. Soc. Perkin Trans. 1* **1990**, 699-706.
51. C. J. Collins, G. B. Fisher, A. Reem, C. T. Goralski, B. Singaram, *Tetrahedron Lett.* **1997**, *38*, 529- 532.
52. (a) P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis;* Academic Press: New York, 1979; (b) P. G. Andersson, I. J. Munslo, *Modern Reduction Methods*; Wiley: New York, 2008.

53. J. Pritchard, G. A. Filonenko, R. van Putten, E. J. Hensen, E. A. Pidko, *Chem. Soc. Rev.* **2015**, *44*, 3808-3833.
54. (a) M. L. Clarke, *Catal. Sci. Technol.* **2012**, *2*, 2418-2423; (b) S. Werkmeister, K. Junge, M. Beller, *Org. Process Res. Dev.* **2014**, *18*, 289-302.
55. S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley, New York, **2001**.
56. W. Reeve, W. M. Eareckson III, *J. Am. Chem. Soc.* **1950**, *72*, 3299.
57. F. Chen, C. Topf, J. Radnik, C. Kreyenschulte, H. Lund, M. Schneider, A.-E. Surkus, L. He, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2016**, *138*, 8781−8788.
58. (a) F. Medina, P. Salagre, J. E. Sueiras, J. L. G. Fierro, *J. Mol. Catal.* **1991**, *68*, L17-L20; (b) G. Cordier, P. Fouilloux, N. Laurain,J. F. Spindler, *Fr. Demande No. 2722784*, 26 Jan. 1996; (c) P. Roccatti, D. Letourneur, D. Philippe, *Fr. Demande No. 2905948*, 21 Mar. 2008; (d) D. Letourneur, P. Leconte, J.-F. Spindler, P. Lermusiaux, V. Boschat, *PCT Int. Appl. No. 2009/043906*, 09 Apr. 2009; (e) S. Alini, A. Bottino, G. Capannelli, R. Carbone, A. Comite, G. Vitulli, *J. Mol. Catal. A: Chemical* **2003**, *206*, 363-370.
59. (a) F. J. Weigert, *US Patent No. 5237088,* 17 Aug. 1993; (b) F. Medina, P. Salagre, J. E. Sueiras, *J. Mol. Catal.* **1993**, *81*, 387-395; (c) A. S. Ionkin *U.S. Pat. Appl. Publ. No. 2003/0065209*, 03 Apr. 2003; (d) L. Zhao, C. Y. Wang, J. X. Chen, J. Y. Zhang, *Chinese Chem. Lett.* **2007**, *18*, 685–688; (e) F. Mares, J. E. Galle, T. E. Diamond, F. J. Regina, *J. Catal.* **1988**, *112*, 145-156; (f) S. Alini, A. Bottino, G. Capannelli, A. Comite, S. Paganelli, *Appl. Catal. A: General* **2005**, *292*, 105-112; (g) M. Chatterjee, M. Sato, H. Kawanami, T. Yokoyama, T. Suzuki, T. Ishizaka, *Adv. Synth. Catal. (Abstract)* **2010**, *352*, 2394-2398.
60. L. Hegedîs, T. Mathé, *Appl. Catal. A Gen.* **2005**, *296*, 209–215.
61. M. Chatterjee, H. Kawanami, M. Sato, T. Ishizaka, T. Yokoyama, T. Suzuki, *Green Chem.* **2010**, *12*, 87–93.
62. W. H. Carothers, G. A. Jones, *J. Am. Chem. Soc.* **1925**, *47*, 3051-3057.
63. D. R. Levering, *US Patent No. 3152184*, 10 Jun. 1964.
64. K. C. Dewhirst, *US Patent No. 3454644*, 7 Aug. 1969.
65. S. Takemoto, H. Kawamura, Y. Yamada, T. Okada, A. Ono, E. Yoshikawa, Y. Mizobe, M. Hidai, *Organometallics* **2002**, *21*, 3897–3904.
66. (a) S. Enthaler, D. Addis, K. Junge, G. Erre, M. Beller, *Chem. Eur. J.* **2008**, *14*, 9491–9494; (b) S. Enthaler, K. Junge, D. Addis, G. Erre, M. Beller, *ChemSusChem* **2008**, *1*, 1006–1010.
67. D. Addis, S. Enthaler, K. Junge, B. Wendt, M. Beller, *Tetrahedron Lett.* **2009**, *50*, 3654–3656.
68. (a) R. A. Grey, G. P. Pez, A. Wallo, *J. Am. Chem. Soc.* **1981**, *103*, 7536–7542; (b) R. P. Beatty, R. A. Paciello, WO Patent WO/1996/ 23802-804, **1996**; (c) A. Toti, P. Frediani, A. Salvini, L. Rosi, C. Giolli, C. Giannelli, *C. R. Chim.* **2004**, *7*, 769; (d) T. Li, I. Bergner, F. N. Haque, M. Z. Iuliis, D. Song, R. H. Morris, *Organometallics* **2007**, *26*, 5940–5949; (e) R. Reguillo, M. Grellier, N. Vautravers, L. Vendier, S. Sabo-Etienne, *J. Am. Chem. Soc.* **2010**, *132*, 7854–7855; (f) C. Gunanathan, M. Hçlscher, W. Leitner, *Eur. J. Inorg. Chem.* **2011**, 3381–3386; (g) Z. Lu, T. J. Williams, *Chem. Commun.* **2014**, *50*, 5391– 5393.
69. T. Yoshida, T. Okano, S. Otsuka, *J. Chem. Soc. Chem. Commun.* **1979**, 870–871.
70. C. Chin, B. Lee, *Catal. Lett.* **1992**, *14*, 135 – 140.
71. K. Rajesh, B. Dudle, O. Blacque, H. Berke, *Adv. Synth. Catal.* **2011**, *353*, 1479 – 1484.

72. R. M. Bullock, *Science* **2013**, *342*, 1054.
73. C. Bornschein, S. Werkmeister, B. Wendt, H. Jiao, E. Alberico, W. Baumann, H. Junge, K. Junge, M. Beller, *Nat. Commun.* **2014**, *5*, 4111.
74. S. Chakraborty, G. Leitus, D. Milstein, *Chem. Commun.* **2016**, *52*, 1812-1815.
75. S. Elangovan, C. Topf, S. Fischer, H. Jiao, A. Spannenberg, W. Baumann, R. Ludwig, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2016**, *138*, 8809-8814.
76. R. Adam, C. B. Bheeter, J. R. Cabrero-Antonino, K. Junge, R. Jackstell, M. Beller, *ChemSusChem* **2017**, *10,* 1-6.
77. (a) D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; RSC Publishing: Cambridge, 2009; (b) H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351; (c) D. J. Edmonds, D. Johnston, D. Procter, *J. Chem. Rev.* **2004**, *104*, 3371; (d) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem., Int. Ed.* **2009**, *48*, 7140; (e) M. Szostak, D. J. Procter, *Angew. Chem., Int. Ed.* **2011**, *50*, 7737; (f) M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev.* **2013**, *42*, 9155.
78. M. Szostak, B. Sautier, M. Spain, D. J. Procter, *Org. Lett.* **2014**, *16*, 1092-1095.
79. S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226.
80. S. Gowda, D. C. Gowda, *Tetrahedron* **2002**, *58*, 2211.
81. R. C. Mebane, D. R. Jensen, K. R. Rickerd, B. H. Gross, *Synth. Commun.* **2003,** *33*, 3373-3379.
82. S. Werkmeister, C. Bornschein, K. Junge, M. Beller, *Chem. Eur. J.* **2013**, *19*, 4437–4440.
83. M. Vilches-Herrera, S. Werkmeister, K. Junge, A. Borner, M. Beller, *Catal. Sci. Technol.* **2014**, *4*, 629-632.
84. R. J. P. Corriu, J. J. E. Moreau, M. Pataud-Sat, *J. Organomet. Chem.* **1982**, *228*, 301-308.
85. T. Murai, T. Sakane, S. Kato, *Tetrahedron Lett.* **1985**, *26*, 5145-5148.
86. T. Murai, T. Sakane, S. Kato, *J. Org. Chem.* **1990**, *55*, 449-453.
87. A. M. Caporusso, N. Panziera, P. Pertici, E. Pitzalis, P. Salvadori, G. Vitulli, G. Martra, *J. Mol. Catal. A: Chemical* **1999**, *150*, 275-285.
88. M. Tanabe, K. Osakada, *Organometallics* **2001**, *20*, 2118-2120.
89. J. Kim, Y. Kang, J. Lee, Y. K. Kong, M. S. Gong, S. O. Kang J. Ko, *Organometallics* **2001**, *20*, 937-944.
90. I. Cabrita, A. C. Fernandes, *Tetrahedron* **2011**, *67*, 8183-8186.
91. C. Bornschein, S. Werkmeister, K. Junge, M. Beller, *New J. Chem.* **2013**, *37*, 2061-2065.
92. N. Gandhamsetty, J. Jeong, J. Park, S. Park, S. Chang, *J. Org. Chem.* **2015**, *80*, 7281-7287.
93. (a) S. Laval, W. Dayoub, A. F.-Reguillon, M. Berthod, P. Demonchaux, G. Mignani, M. Lemaire, *Tetrahedron Letters* **2009**, *50*, 7005-7007 ; (b) S. Laval, W. Dayoub, L. Pehlivan, E. Metay, A. F.-Reguillon, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron* **2014**, *70*, 975-*983.*
94. M. Sutter, L. Pehlivan, R. Lafon, W. Dayoub, Y. Raoul, E. Metay, M. Lemaire, *Green Chem.* **2013**, *15*, 3020-3026.
95. R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chem. Rev.* **1985**, *85*, 129–170.
96. M. D. Adam, M. D. Andrews, G. E. Gymer, D. Hepworth, H. R. Howard Jr., D. S. Middleton, A. Stobie, WO 2002/ 083643, 2002.
97. R. Eluri, B. Paul, *Materials Letters* **2012**, *76*, 36-39.
98. V. Aliev, R. Dolinina, S. C. R. Gadjiev, *C. R. Acad. Sci. II* **1990**, *310*, 1191–1194.

99. A. W. Frazier, K. R. Waerstad, *Fert. Res.* **1992**, *32*, 161– 168.
100. J. H. Clark, J. Emsley, T. B. Middleton, *J. Chem. Soc., Dalton Trans.* **1979**, 1693–1696.
101. D. R. Lide, in *Handbook of Chemistry and Physics*, CRC Press, 84th edn, 2004.
102. A. Wurtz, *Ann. Chim. Phys.* **1846**, *16*, 190–231.
103. (a) F. Medina, P. Salagre, J. E. Sueiras, *J. Mol. Catal.* **1993**, *81*, 387-395; (b) F. Medina, P. Salagre, J. E. Sueiras, J. L. G. Fierro, *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1455-1459; (c) M. Serra, P. Salagre, Y. Cesteros, F. Medina, J. E. Sueiras, *J. Catal.* **2002**, *209*, 202-209 ; (d) B. W. Hoffer, P. H. J. Schoenmakers, P. R. M. Mooijman, G. M. Hamminga, R. J. Berger, A. D. van Langeved, J. A. Moulijn, *Chem. Eng. Sci.* **2004**, *59*, 259-269; (e) P. Marion, Patent PCT WO2009/121704, 2009; (f) C. Shan-Yen, R. K. Shi-Hsin, US Patent US2010/0,152,452, 2010.
104. (a) K. Nakamura, M. Takagawa, Japanese Patent 08-020574, 1996; (b) I. Bertrand, M. Capet, J. -M. Lecomte, N. Levoin, X. Ligneau, O. Poupardin-Olivier, P. Robert, J. -C. Schwartz, O. Labeeuw, Patent WO2006/117609, 2006.
105. (a) E. J. Newson, T. –B. Truong, Patentschrift (Switz.) 654576, 1986; (b) J. -C. Souvie, C. Fugier, J. -P. Lecouve Eur. Pat. Appl. 1127876, 2001.
106. (a) J. Mauger, A. Robert, *Tetrahedron* **1988**, *44*, 2493e2502; (b) F. Qian, J. E. McCusker, Y. Zhang, A. D. Main, M. Chlebowski, M. Kokka, L. McElwee-White, *J. Org. Chem.* **2002**, *67*, 4086e4092; (c) Y. Kawanaka, K. Kobayashi, S. Kusuda, T. Tatsumi, M. Murota, T. Nishiyama, K. Hisaichi, A. Fujii, K. Hirai, M. Naka, M. Komeno, H. Nakai, M. Toda, *Eur. J. Med. Chem.* **2003**, *38*, 277e288, (d) J. de Mier-Vinue, M. Gay, A. M. Montana, R.-I. Saez, V. Moreno, J. Kasparkova, O. Vrana, P. Heringova, V. Brabec, A. Boccarelli, M. Coluccia, G. Natile, *J. Med. Chem.* **2008**, *51*, 424-431.
107. (a) R. Calas, *Pure and Applied Chem.* **1966**, *13*, 61-79; (b) R. J. P. Corriu, J. J. E. Moreau, M. Pataud-Sat, *J. Org. Chem.* **1981**, *46*, 3374-3376; (c) R. J. P. Corriu, J. J. E. Moreau, M. Pataud-Sat, *Organometallics* **1985**, *4*, 623-629; (d) Y. Kang, S. O. Kang, J. Ko, *Organometallics* **1999**, *18*, 1818-1820 and; *Organometallics* **2000**, *19*, 1216-1224.
108. S. Laval, W. Dayoub, L. Pehlivan, E. Metay, A. F.-Reguillon, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron* **2014**, *70*, 975-983.
109. (a) W. S. Emerson, *Org. React.* **1948**, *4*, 174; (b) K. A. Schellenberg, *J. Org. Chem*. **1963**, *28*, 3259.
110. J. Tadanier, R. Hallas, J. R. Martin, R. S. Stanaszek, *Tetrahedron* **1981**, *37*, 1309.
111. R. Leuckart, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2341-2344.
112. O. Wallach, *Justus. Liebigs. Ann. Chem.* **1892**, *272*, 99-122.
113. (a) F. S. Crossley, M. L. Moore, *J. Org. Chem.* **1944**, *6*, 529-536; (b) M. L. Moore, *Org. React.* **1949**, *5*, 301-330.
114. M. Kitmura, D. Lee, S. Hayashi, S. Tanaka, M. Yoshimura, *J. Org. Chem.* **2002**, *67*, 8685-8687.
115. (a) H. C. Brown, B. C. Subba Rao, *J. Amer. Chem. Soc.* 1956, *78*, 2582; (b) G. R. Pettit, D. M. Piatak, *J. Org. Chem.***1926**, *27*,2127; (c) R. Paul, N. Joseph, *Bull. Soc. Chem. Fr*. **1952**, 550; (d) H. C. Brown, E. J. Mead, *J. Amer. Chem. Soc*. **1953**, *75*, 6263.
116. (a) H. Noth, H. Beyer, *Chem. Ber.* **1960**, *93*, 1078; (b) J. H. Billman, J. W. McDowell, *J. Org. Chem.* **1961**, *26*, 1437; (c) S. S. White, Jr., H. C. Kelly, *J. Amer. Chem. Soc.* **1970**, *92*, 4203.

117. R. F. Borsch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.*, **1971**, *12*, 2897-2904.
118. (a) R. O. Hutchines, N. R. Natale, *Org. Prep. Proced. Int.* **1979**, *5*, 201; (b) C. F. Lane, *Synthesis* **1975**, 135.
119. (a) R. J. Mattson, K. M. Pham, D. J. Leuck, K, A. Cowen, *J. Org, Chem.* **1990**, *55*, 2552; (b) R. F. Borsch, A. I. Hassid, *J. Org. Chem.* **1972**, *37*, 1673; (c) P. Marchini, G. Liso, A. Reho, F. Liberatore, F. M. Moracci, *J. Org. Chem.* **1975**, *40*, 3453.
120. A. E. Moormann, *Synth. Commun.* **1993**, *23*, 789.
121. A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849-3862.
122. G. Verardo, A. G. Giumanin, P. Strazzolini, M. Poiana, *Synthesis* **1993**, 121.
123. A. Heydari, S. Khaksar, J. Akbari, M. Esfandyari, M. Pourayoubi, M. Tajbakhsh, *Tetrahedron Lett.* **2007**, *48,* 1135.
124. N. Jain, A. Kumar, S. Chauhan, S. M. S. Chauhan, *Tetrahedron* **2005**, *61*, 1015.
125. K. Nagaiah, V. N. Kumar, R. S. Rao, B. V. S. Reddy, A. V. Narsaiah, J. S. Yadav, *Synth. Commun.* **2006**, *36*, 3345–3352.
126. P. S. Reddy, S. Kanjilal, S. Sunitha, R. B. N. Prasad, *Tetrahedron Letters* **2007**, *48*, 8807-8810.
127. (a) H.-P. Zhu, F. Yang, J. Tang, M.-Y. He, *Green Chem.* **2003**, *5*, 38; (b) H.-H. Wu, F. Yang, P. Cui, J. Tang, M.-Y. He, *Tetrahedron Leters.* **2004**, *45*, 4963; (c) H. Wang, P. Cui, G. Zou, F. Yang, J. Tang, *Tetrahedron* **2006**, *62*, 3985.
128. (a) G. Chelucci, S. Baldino, S. Chessa, G.A. Pinna, F. Soccolini, *Tetrahedron: Asymmetry* **2006**, *17*, 3163–3169; (b) J.-U. Chung, S.Y. Kim, J.-O. Lim, H.-K. Choi, S.-U. Kang, H.-S. Yoon, H. Ryu, D.W. Kang, J. Lee, B. Kang, S. Choi, A. Toth, L.V. Pearce, V.A. Pavlyukovets, D.J. Lundberg, P.M. Blumberg, Bioorg. *Med. Chem.* **2007**, *15*, 6043–6053.
129. (a) Z. Han, S.G. Koenig, H. Zhao, X. Su, S.P. Singh, R.P. Bakale, *Org. Process Res. Dev*. **2007**, *11*, 726–730; (b) A. Grajewska, M.D. Rozwadowska, *Tetrahedron: Asymmetry* **2007**, *18*, 557– 561; (c) A.V. Reddy, S.U.B. Rao, G.L. Narasimha, P.K. Dubey, *Synth. Commun.* **2009**, *39*, 1451–1456.
130. (a) R. Annunziata, M. Cinquini, F. Cozzi, *J. Chem. Soc. Perkin Trans. 1* **1982**, *1*, 339– 343; (b) M. Cinquini, F. Cozzi, *J. Chem. Soc. Chem. Commun*. **1977**, 723–724.
131. (a) J. Tanuwidjaja, H.M. Peltier, J.A. Ellman, *J. Org. Chem*. **2007**, *72*, 626–629; (b) A. Watzke, R.M. Wilson, S.J. O'Malley, R.G. Bergman, J.A. Ellman, *Synlett* **2007**, 2383–2389; (c) T. Kochi, T.P. Tang, J.A. Ellman, *J. Am. Chem. Soc.* **2003**, *125*, 11276–11282; (d) T. Kochi, T.P. Tang, J.A. Ellman, *J. Am. Chem. Soc.* **2002**, *124*, 6518–6519.
132. (a) G. Borg, D.A. Cogan, J.A. Ellman, *Tetrahedron Lett.* **1999**, *40*, 6709–6712; (b) T. Kochi, J.A. Ellman, *J. Am. Chem. Soc*. **2004**, *126*, 15652–15653; (c) H.M. Peltier, J.A. Ellman, *J. Org. Chem.* **2005**, *70*, 7342–7345.
133. K. Yang, J.-T. Liu, *Journal of Fluorine Chemistry* **2015**, *173*, 18-22.
134. N. U. Kumar, B. S. Reddy, V. P. Reddy, R. Bandichhor, *Tetrahedron Letters* **2012**, *53*, 4354-4356.
135. H. C. Brown, C. A. Brown, *J. Am. Chem. Soc.* **1962**, *84*, 1493.
136. H. H. Seltzman, B. D. Berrang, *Tetrahedron Letters* **1993**, *34*, 3083; (b) R. H. Khan, R. C. Rastogi, *Indian J. Chem.* **1993**, *32B,* 898; (c) M. Yale, C. Keen, N. A. Bell, P. K. P. Drew, M. Coke, *Appl. Organomet. Chem.* **1995**, *9*, 297; (d) S. S. Zaman, J. C. Sarma, R. P. Sharma,

Chem. Ind. (*London*) **1991**, 509; (e) G. M. Singhal, J. C. Sarma, R. P. Sharma, *Indian J. Chem.* **1989**, *28B*, 853.
137. J. C. Sarma, R. P. Sharma, *Chem. Ind.* (*London*) **1987**, 764.
138. I. Saxena, R. Borah, J. C. Sarma, *J. Chem. Soc*., *Perkin Trans.1* **2000**, 503–504.
139. (a) M. Balogh, P. Laszlo, *Springer-Verlag: Berlin* **1993**; (b) P. Laszlo, P. *Academic Press, San Diego, California*, **1987**; (c) A. McKillop, D. W. Young *Synthesis* **1979**, 401 and 481; (d) G. H. Posner, *Angew. Chem.* **1978**, *90,* 527; (e) G. H. Posner, *Angew. Chem. Int. Ed. Engl.* **1978**, *17,* 487; (f) G. W. Kabalka, P.P. Wadgaonkar, N. Chatla, *Synth. Commun.* **1990**, *20,* 293; (g) G. W. Kabalka, R. M. Pagni, *Tetrahedron* **1997**, *53,* 7999.
140. (a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27,* 279; (b) R. J. Giguere, A. M. Namen, B. O. Lopez, A. Arepally, D. E. Ramos, G. Majetich, J. Defrauw, *Tetrahedron Lett.* **1987**, *28,* 6553; (c) A. K. Bose, B. K. Banik, N. Lavlinskaia, M. Jayaraman, M. S. Manhas, *Chemtech* **1997**, *27,* 18; (d) A. Oussaid, L. N. Thach, A. Loupy, *Tetrahedron Lett.* **1997**, *38,* 2451; (e) D. Villemin, A. B. Alloum, *Synth. Commun.* **1991**, *21,* 63; (f) J. M. Lerestif, L. Toupet, S. Sinbandhit, F. Tonnard, J. P. Bazureau, J. amelin, *Tetrahedron* **1997**, *53,* 6351; (g) R. S. Varma, A. K. Chatterjee, M. Varma, *Tetrahedron Lett* **1993**, 34, 3207*;* (h) R. S. Varma, R. K. Saini, *Synlett* **1997**, 857; (i) R. S. Varma, K. P. Naicker, *Molecules Online* **1998**, *2*, 94.
141. R. S. Varma, R. Dahiya, *Tetrahedron* **1998**, *54*, 6293-6298.
142. R. C Wade, *J. Mol. Catal.* **1983**, *18,* 273.
143. (a) T. Kawabata, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett*. **2003**, *44*, 9205; (b) L. Zatta, J. E. F. C. Gardolinski, F. Wypych, *Appl. Clay Sci.* **2011**, *51*, 165; (c) A. F. Shojaei, M. A. Rezvani, M. S. Baei, *World Appl. Sci. J.* **2010**, *11*, 727; (d) A. Khojastehnezhad, A. Davoodnia, M. Bakavoli, N. Tavakoli-Hoseini, M. Zeinali-Dastmalbaf, *Chin. J. Chem.* **2011**, *29*, 297; (e) R. Pal, T. Sarkar, S. Khasnobis, *ARKIVOC* **2012** (i), 570-609.
144. H. Alinezhad, M. Tajbakhsh, N. Mahdavi, *Synthetic Communications* **2010**, *40*, 951-956.
145. J. Brussee, R. A. T. M. van Benthem, C. G. Kruse, A. Van der Gen, *Tetrahedron: Asymmetry* **1990**, *1*, 163–166.
146. S. Bhattacharyya, *J. Org. Chem.* **1995**, *60*, 4928.
147. H. Takahashi, T. Tsubuki, K. Higashiyama, *Synthesis* **1988**,238 and references cited therein.
148. B. T. Cho, S. K. Kang, *Tetrahedron* **2005**, *61*, 5725-5734.
149. M.B. Smith, J. March, *Advanced Organic Chemistry,Wiley*, *NewYorkNY*, **2001**, 1187.
150. B. Miriyala, S. Bhattacharyya, J.S. Williamson, *Tetrahedron* **2004**, *60*, 1463, and references cited therein.
151. A. Heydari, A. Arefi, S. Khaksar, M. Tajbakhsh, *Catal. Commun*. **2006,** *7*, 982.
152. H. Akbar, A. Afsaneh, E. Maryam, *J. Mol. Catal. A-Chem*. **2007**, *274*, 169-172.
153. (a) Q. Zhang, K. D. O. Vigier, S. Royer, F. Jérôme, *Chem. Soc. Rev.* **2012**, *41*, 7108; (b) M. Francisco, A.V.D. Bruinhorst, M. C. Kroon, *Angew. Chem. Int. Ed.* **2013**, *52*, 3074.
154. (a) Y. A. Sonawane, S. B. Phadtare, B. N. Borse, A. R. Jagtap, G. S. Shankarling, *Org. Lett.* **2010**, *12*, 1456; (b) A. P. Abbott, T. J. Bell, S. Handa, B. Stoddart, *Green Chem.* **2007**, *7*, 705; (c) R. C. Morales, V. Tambyrajah, P. R. Jenkins, D. L. Davies, A. P. Abbott, *Chem. Commun*. **2004**, *2*, 158.
155. D. Saberi, J. Akbari, S. Mahdudi, A. Heydari, *Journal of Molecular Liquids* **2014**, *196*, 208–210.

156. (a) B. Singh, H. Lobo, G. Shankarling, *Catal. Lett*. **2011**, *141*, 178; (b) A. Zhu, T. Jiang, B. Han, J. Zhang, Y. Xie, X. Ma, *Green Chem*. **2007**, *9*, 169.
157. D. Menche, J. Hassfeld, J. Li, G. Menche, A. Ritter, S. Rudolph, *Org. Lett.* **2006**, *8*, 741-744.
158. S. Bhattacharyya, *Synth. Commun*. **1997**, *27*, 4265.
159. S. Bhattacharyya, *J. Org. Chem*. **1995**, *60*, 4928.
160. A. Shokrolahi, A. Zali, M. H. Keshavarz, *Green Chemistry Letters and Reviews* **2011**, *4*, 195-203.
161. H. W. Gibson, F. C. Baily, *J. Chem.* Soc., *Chem. Commun.* **1977**,815.
162. N. M. Yoon, K. B. Park, Y. S. Gyoung, *Tetrahedron Lett.* **1983**, *24*, 5367.
163. Y. S. Gyoung, N. M. Yoon, D. H. Jeon, *Bull. Korean Chem. Soc.* **1987**, *8*, 62.
164. G. W. Kabalka, P. P. Wadgaonkar, N. Chatla, *Synth. Commun.* **1990**, *20*, 293 and references there in.
165. N. M. Yoon, E. G. Kim, H. S. Son, J. Choi, *Synth. Commun.* **1993**, *23*, 1595-1599.
166. H. Kotsuki, N. Yoshimura, Y. Ushio, T. Ohtsuka, M. Ochi, *Chem. Lett.* **1986**, 1003.
167. B. C. Ranu, *Synlett.* **1993**,885-892.
168. H. Kotsuki, N. Yoshimura, I. Kadota, Y. Ushio, M. Ochi, *Synthesis* **1990**,401-402.
169. W. S. Emerson, F. W. Neumann, T. P. Moundres, *J. Am. Chem. Soc.* **1941**, *63*, 972.
170. A. R. Surrey, H. F. Hammer, *J. Am. Chem. Soc.* **1944**, *66*, 2127.
171. S. Cacchi, G. Palmiori, *Tetrahedron* **1983**, *39*, 3373.
172. I. V. Micc´ovic´ , M. D. Ivanovic´ , D. M. Piatak, V. D. Bojic´, *Synthesis* **1991**, 1043.
173. S. Bhattacharyya, A. Chatterjee, S. K. Duttachoudhury*, J. Chem Soc. Perkin Trans 1* **1994**, 1.
174. S. Bhattacharyya, A. Chatterjee, J. S. Williamson, *Synth. Commun.* **1997**, *27*, 4265-4274.
175. B. C. Ranu, A. Majee, A. Sarkar, *J. Org. Chem.* **1998**, *63*, 370-373.
176. (a) B. C. Ranu, S. Bhar, D. C. Sarkar, *Tetrahedron Lett*. **1991**, *32*, 2811; (b) B. C. Ranu, S. Bhar, R. Chakraborti, *J. Org. Chem*. **1992**, *57*, 7349; (c) B. C. Ranu, S. Bhar, *J. Chem. Soc., Perkin Trans. 1* **1992**, 365; (d) B. C. Ranu, M. Saha, S. Bhar, *Tetrahedron Lett*. **1993**, *34*, 1989; (e) B. C. Ranu, M. Saha, S. Bhar, *J. Chem. Soc*., *Perkin Trans. 1* **1994**, 2197; (f) B. C. Ranu, M. Saha, *J. Org. Chem*. **1994**, *59*, 8269; (g) B. C. Ranu, A. Majee, A. R. Das, *Synth. Commun*. **1995**, *25*, 363; (h) B. C. Ranu, A. Sarkar, M. Saha, S. Bhar, *Pure Appl. Chem*. **1996**, *68*, 775; (i) B. C. Ranu, K. Ghosh, U. Jana, *J. Org. Chem*. **1996**, *61*,9546.
177. A. Nose, T. Kudo, *Chem. Pharm. Bull*. **1986**, *34*, 4817-4820.
178. J. W. Bae, S. H. Lee, Y. J. Cho, C. M. Yoon, *J. Chem. Soc., Perkin Trans. 1* **2000**,145-146.
179. (a) K. Matos, S. Pichlmair, E. R. Burkhardt, *Chim. Oggi/Chem. Today* **2007**, *25*, 17; (b) H. C. Brown, J. V. B. Kanth, P. V. Dalvi, M. Zaidlewicz, *J. Org. Chem.* **1999**, *64*, 6263.
180. A. Pelter, R. M. Rosser, S. Mills, *J. Chem. Soc. Perkin Trans* **1984**, *1*, 717.
181. M. D. Bomann, I. C. Guch, M. DiMare, *J. Org. Chem.* **1995**, *60*, 5995-5996.
182. (a) G. E. Ryschkewitsch, E. R. Birnbaum, *Inorg. Chem.* **1965**, *4*, 575; (b) R. A. Baldwin, R. M. Washburn, *J. Org. Chem.* **1961**, *26*, 3549; (c) H. C. Brown, L. Domash, *J. Am. Chem. Soc*. **1956**, *78*, 5384.
183. JP Patent 112, 988, **1995.**
184. S. Sato, T. Sakamoto, E. Miyazawa, Y. Kikugawa, *Tetrahedron* **2004**, *60*, 7899-7906.

185. (a) J. H. Billman, J. W. McDowell, *J. Org. Chem.* **1961**, *26*, 1437; (b) L. T. Plante, *J. Org. Chem.* **1971**, *36*, 860; (c) B. A. Behnam, D. M. Hall, *J. Chem., Soc., Perkin Trans. 1* **1980**, 107.
186. M. A. Peterson, A. Bowman, S. Morgan, *Synth. Commun.* **2002**, *32*, 443–448.
187. M. D. Bomann, I. C. Guch, M. DiMare, *J. Org. Chem.* **1995**, *60*, 5995.
188. U.S. Patent Application 60/846144, EP2007/060003.
189. E. R. Burkhardt, B. M. Coleridge, *Tetrahedron Letters* **2008**, *49*, 5152–5155.
190. M. Tajbakhsh, M. M. Lakowraj, F. Shirini, S. Habibzadeh, A. Nikdoost, *Tetrahedron Lett*. **2004**, *45*, 3295
191. A. Heydari, S. Khaksar, M. Esfandyaria, M. Tajbakhsh, Tetrahedron **2007**, *63*, 3363–3366.
192. (a) N. J. Lawrence, M. D. Drew, S. M. Bushell, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381; (b) K. K. Senapati, *Synlett* **2005**, 1960; (c) J.-F. Carpentier, V. Bette, *Curr. Org. Chem.* **2002**, *6*, 913.
193. (a) H. Mimoun, J. Y. de Laumer, L. Giannini, R. Scopelliti, C. Floriani, *J. Am. Chem. Soc.* **1999**, *121*, 6158; (b) V. Bette, A. Mortreux, D. Savoia, , J.- F. Carpentier, *Tetrahedron* **2004**, *60*, 2837; (c) V. Bette, A. Mortreux, C. W. Lehmann, , J.- F. Carpentier, *Chem. Commun.* **2003**, 332.
194. Y. Motoyama, K. Mitsui, T. Ishida, H. Nagashima, *J. Am. Chem. Soc.* **2005**, *127*,13150.
195. (a) D. Kim, B.-M. Park, J. Yun, *Chem. Commun.* **2005**, 1755; (b) B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352; (c) B. H. Lipshutz, K. Noson, W. Chrisman, J. *Am. Chem. Soc.* **2001**, *123*, 12917.
196. (a) D. Nadkarni, J. Hallissey, C. Mojica, *J. Org. Chem.* **2003**, *68*, 594; (b) W. P. Gallagher, R. E. Maleczka, *J. Org. Chem.* **2003**, *68*, 6775; (c) W. P. Gallagher, R. E. Maleczka, *Synlett* **2003**, 537; (d) M. D. Drew, N. J. Lawrence, D. Fontaine, L. Sehkri, S. A. Bowles, W. Watson, *Synlett* **1997**, 989.
197. M. Pereyre, J.-P. Quintard, A. Rahm, *Tin in Organic Synthesis;* Butterworths: Boston, **1987**.
198. R. M. Lopez, G. C. Fu, *Tetrahedron* **1997**, *53*, 16349-16354.
199. S. Chandrasekhar, C. R. Reddy, L. Chandraiah, L. *Synth. Commun.* **1999**, *29*, 3981-3987.
200. S. Chandrasekhar, C. R. Reddy, M. Ahmed, M. *Synlett* **2000**, 1655-1657.
201. J. P. Patel, A.-H Li, H. Dong, V. L. Korlipara, M. J. Mulvihill, *Tetrahedron Lett.* **2009**, *50*, 5975-5977.
202. V. A. Pestunovich, A. I. Albanov, M. F. Larin, L. P. Ignat'eva, M. G. Voronkov, *Izv. Akadem. Nauk SSSR, Ser. Khim.* **1978**, 2185; (b) S. Brownstein, *Can. J. Chem.* **1980**, *58*, 1407.
203. S. Enthaler, *Catal. Lett.* **2011**, *141*, 55-61.
204. V. Bette, A. Mortreux, C. W. Lehmann, J.-F. Carpentier, *Chem. Commun.* **2003**, *3*, 332–333; (b) V. Bette, A. Mortreux, D. Savoia, J.-F. Carpentier, Adv. Synth. Catal. **2005**, *347*, 289–302; (c) M. Bandini, M. Melucci, F. Piccinelli, R. Sinisi, S. Tommasi, A. Umani-Ronchi, *Chem. Commun.* **2007**, 4519–452; (d) B.-M. Park, S. Mun, J. Yun, *Adv. Synth. Catal.* **2006**, *348*, 1029–1032.
205. (a) B. Le-Khac, W. Chester, U.S. Pat., 5, 714, 428, **1998** ; (b) M.V. Patil, M.K. Yadav, R.V. Jasra, *J. Mol. Catal. A: Chem*. **2007**, *273*, 39–47; (c) P.S. Sreeprasanth, R. Srivastava, D. Srinivas, P. Ratnasamy, *Appl. Catal. A* **2006**, *314*, 148–159; (d) J. Sebastian, D. Srinivas, *Chem. Commun.* **2011**, 47, 10449–10451; (e) J.K. Satyarthi, D. Srinivas, P. Ratnasamy, *Appl.*

Catal. A **2011**, *391*, 427–435; (f) T. Ostrowski, R. Ruppel, S. Baum, U.S. Pat., 2006/223979 A1, **2006**.
206. A. Peeters, P. Valvekens, F. Vermoortele, R. Ameloot, C. Kirschhock, D. De Vos, *Chem. Commun.* **2011**, *47*, 4114–4116.
207. A. R. Jadhav, H. A. Bandal, H. Kim, *Chem. Eng. J.* **2016**, *295*, 376-383.
208. (a) F. Iwasaki, T. Maki, O. Onomura, W. Nakashima, Y. Matsumura, *J. Org. Chem*. **2000**, *65*, 996; (b) A. Orita, K. Sakamoto, Y. Hamada, A. Mitsutome, J. Otera, *Tetrahedron* **1999**, *55*, 2899; (c) J. K. Whitesell, R. Apodaca, *Tetrahedron Lett.* **1996**, *37*, 2525; (d) J. K. Whitesell, R. Apodaca, *Tetrahedron Lett.* **1996**, *37*, 3955.
209. C. Stetin, B, de Jeso, J. C. Pommier, *Synth. Commun*. **1982**, *12*, 495.
210. R. M. Lopez, G. C. Fu, *Tetrahedron* **1997**, *53*, 16349.
211. R. Apodaca, W. Xiao, *Org. Lett.* **2001**, *3*, 1745-1748.
212. J. J. Kangasmetsa, T. Johnson, *Org. Lett.* **2005**, *7*, 5653-5655.
213. J. T. Hunt, C. Z. Ding, R. Batorsky, M. Bednarz, R. Bhide, Y. Cho, S. Chong, S. Chao, J. Gullo-Brown, P. Guo, S. H. Kim, F. Y. F. Lee, K. Leftheris, A. Miller, T. Mitt, M. Patel, B. A. Penhallow, C. Ricca, W. C. Rose, R. Schmidt, W. A. Slusarchyk, G. Vite, V. Manne, *J. Med. Chem*. **2000**, *43*, 3587.
214. B.-C. Chen, J. E. Sundeen, P. Guo, M. S. Bednarz, R. Zhao, *Tetrahedron Lett.* **2001**, *42*, 1245-1246.
215. T. Matsumura, M. Nakada, *Tetrahedron Lett.* **2014**, *55*, 1829-1834.
216. (a) J. S. Bajwa, X. Jiang, J. Slade, K. Prasad, O. Repic, T. J. Blacklock, *Tetrahedron Lett.* **2002**, *4*3, 6709–6713; (b) P. A. Evans, J. Cui, S. J. Gharpure, *Org. Lett.* **2003**, *5*, 3883–3885.
217. J. M. Blackwell, E. R. Sonmor, T. Scoccitti, W. E. Piers, *Org. Lett.* **2000**, *2*, 3921-3923.
218. I. Shibata, T. Yoshida, A. Baba, H. Matsuda, *Chem. Lett.* **1989**, 619; (b)I. Shibata, T. Yoshida, T. Kawakami, A. Baba, H. Matsuda, *J. Org. Chem.* **1992**, *57*, 4049; (c) T. Kawakami, I. Shibata, A. Baba, H. Matsuda, *J. Org. Chem.***1993**, *58*, 7608; (d) T. Kawakami, I. Shibata, A. Baba, *J. Org. Chem.* **1996**, *61*, 82; (e) T. Kawakami, M. Miyatake, I. Shibataa, A. Baba, H. Matsuda, *J. Org. Chem.* **1996**, *61*, 376.
219. I. Shibata, T. M.- Kawakami, D. Tanizawa, T. Suwa, E. Sugiyama, H. Matsuda, A. Baba, *J. Org. Chem.* **1998,** *63,* 383-385.
220. I. Shibata, T. Suwa, E. Sugiyama, A. Baba, *Synlett* 1998, 1081-1082.
221. R. Hiroi, N. Miyoshi, M. Wada, *Chemistry Letters* **2002**, 274-275.
222. *Applied Homogenous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 1996, vol. 1 and 2; *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 1998, vol. 1 and 2.
223. V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz and A. Börner, *Tetrahedron: Asymmetry* **1999**, *10*, 4009.
224. V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron Lett.* **2000**, *41*, 2351.
225. V. I. Tararov, R. Kadyrov, T. H. Riermeier, A. Börner, *Chem. Commun.* **2000**, 1867-1868.
226. R. Kadyrov, T. H. Riermeier, U. Dingerdissen, V. I. Tararov, A. Börner, *J. Org. Chem.* **2003**, *68*, 4067-4070.
227. T. Gross, A. M. Seayad, M. Ahamd, M. Beller, *Org. Lett.* **2002**, *4*, 2055-2058.
228. D. Xiao, X. Zhang, *Angew. Chem., Int. Ed.* **2001**, *40*, 3425-3428.

229. Y. Chi, Y.-G. Zhou, X. Zhang, *J. Org. Chem.* **2003**, *68*, 4120-4122.
230. D. Imao, S. Fujihara, T. Yamamoto, T. Ohta, Y. Ito, *Tetrahedron* **2006**, *61*, 6988–6992.
231. A. Robichaud , A. N. Ajjou, *Tetraherdon Lett.* **2006**, *47*, 3633-3636.
232. M. D. Bhor, M. J. Bhanushali, N. S. Nandurkar, B. M. Bhanage, *Tetraherdon Lett.* **2008**, *49*, 965-969.
233. (a) J. W. Sprengers, J. Wassenaar, N. D. Clement, K. J. Cavell, C. J. Elsevier, *Angew. Chem., Int. Ed.* **2005**, *44*, 2026; (b) H. J. Kim, M. Kim, S. Chang, *Org. Let.* **2011**, *13*, 2368; (c) P. Hauwert, R. Boerleider, S. Warsink, J. J. Weigand, C. J. Elsevier, *J. Am. Chem. Soc*. **2010**, *132*, 16900; (d) N. Patil, *Angew. Chem., Int. Ed*. **2011**, *50*, 1759; (e) J. H. Park, S. V. Bhilare, S. W. Youn, *Org. Lett*. **2011**, *13*, 2228; (f) T. Droge, F. Glorius, *Angew. Chem., Int. E*d. **2010**, *49*, 6940.
234. (a) J.-W. Byun, Y.-S. Lee, *Tetrahedron Lett*. **2004**, *45*, 1837; (b) Z. S. Qureshi, K. M. Deshmukh, P. J. Tambade, B. M. Bhanage, *Synthesis* **2011**, 243; (c) J. Kim, B. Jun, J. Byun, Y. Lee, *Tetrahedron Lett*. **2004**, *45*, 5827; (d) W. A. Herrmann, *Angew. Chem., Int. Ed*. **2002**, *41*, 1290; (e) L. Li, J. Wang, C. Zhou, R. Wang, M. Hong, *Green Chem.* **2011**, *13*, 2071; (f) B. S. Yong, S. P. Nolan, *Chemtracts* **2003**, *16*, 205; (g) K. J. Cavell, D. S. McGuinness, *Coord. Chem. Rev.* **2004**, *248*, 671; (h) K. V. S. Ranganath, J. Kloesges, A. H. Schafer, F. Glorius, *Angew.Chem., Int. Ed*. **2010**, *49*, 7786.
235. D. B. Bagal, Z. S. Qureshi, K. P. Dhake, S. R. Khan, B. M. Bhanage, *Green Chem*. **2011**, *13*, 1490.
236. D. B. Bagal, R. A. Watile, M. V. Khedkar, K. P. Dhake, B. M. Bhanage, *Catal. Sci. Technol.* **2012**, *2*, 354–358.
237. J. Kim, H. J. Kim, S. Chang, *Eur. J. Org. Chem.* **2013**, *2013*, 3201–3213.
238. G. Mignonac, *Comptes Rendus* **1921**, *172*, 223–225.
239. H. S. Broadbent, L. H. Slaugh, N. L. Jarvis, *J. Am. Chem. Soc.* **1954**, *76*, 1519 and refernces there in.
240. F. S. Dovell, H. Greenfield, *J. Org. Chem.* **1964**, *29*, 1265–1267.
241. A. W. Heinen, J. A. Peters,H. van Bekkum, *Eur. J. Org. Chem.* **2000**, 2501-2506.
242. A. Villa, K. Dumoleijn, C. Evangelisti, K. Moonen, L. Prati, *RSC Adv.* **2018**, *8*, 15202-15206.
243. C. Cheng, X. Wang, L. Xing, B. Liu, R. Zhu, Y. Hu, *Adv. Synth. Catal.* **2007**, *349*, 1775–1780.
244. S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons: New York, NY, **2001**; Charter 2, pp 53–59.
245. (a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev*. **2002**, *102*, 4009–4092; (b) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons: New York, NY, **2001**; Chart 13, pp 623–639; (c) P. N. Rylander, *Hydrogenation Methods;* Academic: London, **1985**; Charter 12, pp 148–156.
246. L. Xing, C. Cheng, R. Zhu, B. Zhang, X. Wang, Y. Hu, *Tetraherdon* **2008**, *64*, 11783-11788.
247. N. M. Patil, B. M. Bhanage, *Catal. Today* **2015**, *247*, 182-189.
248. J. Bódis, L. Lefferts, T. E. Müller, R. Pestman, J. A. Lercher, *Catal. Lett.* **2005**, *104*, 23-28.
249. Bo Dong, X. Guo, B. Zhang, X. Chen, J. Guan, Y. Qi, S. Han, X. Mu, *Catalysts* **2015**, *5*, 2258-2270.

250. M. E. Domine, M. C. Hernandez-Soto, M. T. Navarro, Y. Perez, *Catal. Today* **2011**, *172*, 13-20.
251. T. Ikenaga, K. Matsushita, J. Shinozawa, S. Yada, Y. Takagi, *Tetrahedron* **2005**, *61*, 2105-2109.
252. E. R. Alexander, L. A. Misegades, *J. Am. Chem. Soc*. **1948**, *70*, 1315.
253. (a) E. E. Nifant'ev, L. P. Levitan, *J. Gen. Chem. USSR* **1965**, *35*, 762 ; (b) S. Deprèle, J. Montchamp, *J. Organomet. Chem.* **2002**, 643-644,154-163.