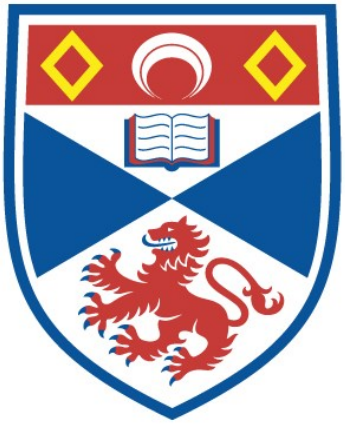
CONVERSION OF RENEWABLE FEEDSTOCKS INTO POLYMER PRECURSORS AND PHARMACEUTICAL DRUGS

Yiping Shi

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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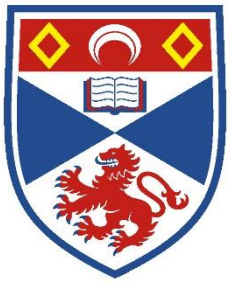

University of
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This thesis is submitted in partial fulfilment for the degree of

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at the University of St Andrews

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"A scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales."

– Mary Curie

General acknowledgements

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Table of contents

Table of abbreviations

Ac	Acetyl
1,4-BD	1,4-Butanediol
BNPA	BINOL-phosphoric acid
BPy-*t*-PNN	6-Di-*tert*-butylphosphinomethyl-2,2'-bipyridine
Bpy	2,2'-bipyridy
br	Broad
Cat.	Catalyst
CI engine	Compression-ignition engine
CNSL	Cashew nut shell liquid
cod	1,4-Cyclooctadiene
Conv.	Conversion
Cp	Cyclopentadienyl
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublet
DFT	Density functional theory
DIBALH	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMO	Dimethyl oxalate
DMSO	Dimethyl sulfoxide
DPPB	1,4-Bis(diphenylphosphino)butane
DPPP	1,3-Bis(diphenylphosphino)propane

DTBPMB	1,2-Bis(di-*tert*-butylphosphinomethyl)benzene
ED	Ethane-1,2-diol
e.e.	Enantiomeric excess
E_f	Environmental (E) factor
Equiv.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FA	Formic acid
G1	Grubbs catalyst 1st generation
G2	Grubbs catalyst 2nd generation
GC-FID	Gas Chromatography with Flame Ionisation Detector
GC-MS	Gas chromatography–mass spectrometry
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HG1	Hoveyda-Grubbs Catalyst 1st Generation
HG2	Hoveyda-Grubbs Catalyst 2nd Generation
$HNTf_2$	Trifluoromethanesulfonimide
IA	Itaconic acid
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
KO^tBu	Potassium *tert*-butoxide
K_3PO_4	Tripotassium phosphate
LA	Levulinic acid

LAB	Linear alkyl benzenes
LC_{50}	Lethal concentration 50
$LiAlH_4$	Lithium aluminium hydride
m	Multiplet
M1	Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]{[2-(1-methylacetoxy)phenyl]methylene}ruthenium(II)
M2	Dichloro(3-phenyl-1H-inden-1-ylidene) - bis(tricyclohexylphosphine)ruthenium(II)
Me	Methyl
MeOH	Methanol
MG	Methyl glycolate
MO	Methyl oleate
MSA	Methane sulfonic acid
$NaBH_4$	Sodium borohydride
n.d.	Not detetermined
NHC	*N*-heterocyclic carbenes
NMR	Nuclear magnetic resonance
NSAID	Nonsteroidal anti-inflammatory drug
OTf	Triflate
Ph	Phenyl
PVC	Polyvinyl chloride
rac	Racemic
RCM	Ring closing metathesis

rt	Room temperature
s	Singlet
Sel.	Selectivity
t	Time
t	Triplet
T	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilane
TOF	Turnover frequency
TOFA	Tall oil fatty acid
TONs	Turnover number
triphos	1,1,1-Tri(diphenylphosphinemethyl)ethane

Abstract

Fossils fuels are highly demanded in everyday life domestically or industrially. Fossil fuels are finite resources and they are rapidly depleting, as such alternative renewable feedstocks are sought to replace fossil fuels. Tall oil from paper processing and cashew nut shell liquid from the cashew nut industry are the two major renewable sources we studied, they are both waste byproducts, and have the potential to be converted into value-added materials.

Tall oil from the paper industry mainly contained tall oil fatty acid, and under isomerising methoxycarbonylation with palladium catalyst, dimethyl 1,19-dimethyl nonadecanedioate can be obtained. This difunctional ester, dimethyl 1,19-dimethyl nonadecanedioate, is converted to diols, secondary and primary diamines by a hydrogenation reaction with ruthenium complexes of 1,1,1-tris(diphenylphosphinometyl)ethane (triphos) as catalysts in the presence of water, amine or aqueous ammonia respectively. In the case of aqueous ammonia it is necessary to use a two step reaction *via* diol to obtain 1,19-diaminononadecane. Diesters, diols and diamines are useful precursors for the synthesis of polyesters and polyamides. Difunctional substrates with 8-19 carbon chains are all tolerated under the reaction conditions and are successfully converted to the corresponding diols and diamines in high yields.

Under similar hydrogenation conditions with the same ruthenium catalyst, cyclic products were predominantly produced with decreased chain length. *N*-heterocycles, which are important building blocks for the synthesis of drug molecules, were formed from the hydrogenation of diesters with 4-7 carbon chains in the presence of an amine. Another polymer precursor, ε-caprolactam, which is the precursor for Nylon 6, is obtained in a reasonable yield from both adipic acid and adipate esters together with aqueous ammonia in the presence of ruthenium catalyst.

Cashew nut shell liquid was also converted into useful medical drugs, such as norfenefrine, *rac*-phenylephrine, etilefrine and fenoprofene in reasonable yields. Most of these drug molecules have been formed from 3-vinylphenol by catalytic hydroxyamination followed by methylation or ethylation. 3-Vinylphenol was

synthesised from cardanol by ethenolysis to 3-non-8-enylphenol followed by isomerising ethenolysis, whilst the *N*-alkylation reactions used methyl or ethyl triflate to avoid dialkylation. Fenoprofene was formed by firstly *O*-phenylating cardanol then ethenolysis followed by isomerising ethenolysis to form 1-phenoxy-3-vinylbenzene. Methoxycarbonyation followed by hydrolysis formed the final product in good yield.

Our methods start from renewable waste materials and avoid unpleasant reagents in the original stoichiometric synthesis of those drugs, for example, cyanide is no longer essential for the synthesis of fenoprofene.

Chapter 1 General introduction

1.1 Chemical industry and green chemistry

The chemical industry is one of the most important industries in the world, and it converts raw materials, especially fossil oil, into a large variety of products. Fossil fuels are generally considered to be non-renewable feedstocks. Although fossil fuels are continually being formed *via* natural processes, it takes over millions of years for them to be formed from dead organism remains. Because of the high demand for fossil fuels in everyday life, either in domestic or in industrial use, fossil fuels are consumed faster than they can be replenished; so the limited amount of fossil oil feedstock on earth will eventually be depleted. The use of fossil fuels can also cause serious environmental concerns because of the emission of carbon dioxide, which is a greenhouse gas and contributes to climate change. It is now a major challenge to find alternative resources, which should be renewable and produce less pollution, to replace fossil fuels. This led to the concept of sustainable development, which is defined as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs".[1] Sustainable development will be progressively more critical as the population of the world increases. Green chemistry is one of the key methods for the chemical industry to work towards sustainable development.

Green chemistry, which is also known as sustainable chemistry, is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Paul Anastas together with John C. Warner came up with 12 principles of green chemistry:[2]

1. *Prevent waste instead of treat or clean up waste after it is formed.*
   Environmental (E) factor is a useful measure of the potential environmental acceptability of chemical process and is used to calculate the ratio of the mass of waste per unit of product (Equation 1.1). The waste can be byproducts and solvents from the reaction. The smaller the E-factor, the "greener" the reaction is. Profit and total amount of waste will also be taken into account before applying a novel methodology in industry. The pharmaceutical industry has a larger E

factor ($25<E_f<100$) than oil refining ($E_f \sim 0.1$), but oil refining produces 10^6 tonnes of waste annually, while pharmaceuticals produce 10^3 tonnes.[34] The pharmaceutical industry is focused more on molecule manufacture and quality because of the high profit it can make, while the oil industry has to minimize the waste as less profit can be made.

$$E - factor = \frac{total\ waste\ (kg)}{product\ (kg)} \qquad \text{Equation 1.1}$$

2. *Maximize atom economy.*

   Atom economy is used to measure the "greenness" of a chemical process. It calculates the efficiency of a chemical conversion with equation shown in Equation 1.2. In an ideal process, the atom economy should be 100% with no loss of atoms.

$$Atom\ economy = \frac{molecular\ mass\ of\ desired\ product}{molecular\ mass\ of\ all\ reactants} \times 100\ \% \qquad \text{Equation 1.2}$$

3. *The synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and environment.*

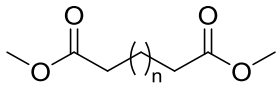
4. *Design safer chemicals.* The designed products should have the desired function while toxicity is kept to its minimum.

5. *Safer solvent and auxiliaries should be considered.* Wherever possible, the use of auxiliary substances should be made unnecessary.

6. *Design for energy efficiency.* Energy requirement should be minimized, and if possible, ambient temperature and pressure should be used in production.

7. *Use of renewable feedstock.* Renewable feedstocks such as biomass should be used instead of depleting limited material. An example of some of the renewable feedstocks of potential interest in the synthesis of dicarboxylic acids is given in Table 1.1.

Table 1.1. Difunctional carboxylic acid derived from biomass.



Entry	n	Chain length	source	Ref
1	0	4	soybean carbohydrates	[5]
2	2	6	glucose	[6]
3	4	8	oleic acid	[7]
4	6	10	castor oil	[8]
5	8	12	castor oil	[9]
6	15	19	waste tall oil	[10]

The linear difunctional carboxylic acid esters which can be obtained from non-food natural oils or waste oils, especially tall oil, which will be discussed in detail in the next chapter, are preferred over edible oils as waste oils do not compete for land with the food industry.

8. *Reduce derivatives.* Unnecessary derivatization (blocking groups, protection/deprotection, temporary modification) should be avoided whenever possible.

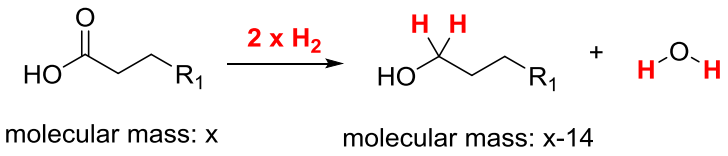
9. *Catalysis.* Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. *Design for degradation.* Chemical products should be designed so that at the end of their function they do not persist in the environment but break down into innocuous degradation products.

11. *Real- time analysis for pollution prevention.* Analytical methodologies need to be developed to allow real-time monitoring and control prior to the formation of hazardous substances.

12. *Inherently safer chemistry for accident prevention.* Substances in a chemical process should have the minimum potential for chemical accidents (eg. releases, explosions, and fires).

The aim of the research in this thesis is based on these green chemistry principles, in which the renewable feedstocks are transformed into value-added materials using selective catalytic methods. The methods used should minimize the usage and generation of toxic substances, and have less influence on the environment compared to stoichiometry chemistry. Catalytic hydrogenation using hydrogen molecule is close to be an ideal reaction as it has high atom economy and, in the case of carboxylic acid derivatives has water as the only byproduct (Scheme 1.1). Therefore, hydrogenations of this kind are heavily studied both industrially and academically.



$$atom\ economy = \frac{x-14}{x+4} \times 100 \approx 100\%\ when\ x \gg 14$$

Scheme 1.1. Example of hydrogenation using molecular hydrogen.

1.2 Homogeneous reduction of carboxylic acids and their derivatives

Part of the work presented in this section was published in the Science of Synthesis series entitled "Catalytic Reduction in Organic Synthesis".[11]

The catalytic hydrogenation of carboxylic acids and their derivatives such as esters, amides, acid chlorides and anhydrides is a fundamental reaction for organic synthesis and chemical production. The resulting products are useful building blocks for the pharmaceutical, agrochemical, flavor and fragrance industries.[12] These catalytic hydrogenations are beginning to replace the use of stoichiometric reagents such as aluminium and boron hydrides. Catalytic reactions are favored for sustainable chemistry as less harmful reagents are used, and less hazardous waste products are formed.[13] Molecular hydrogen is a more attractive reducing agent due to its price, the lack of

formation of waste products and general environmental friendliness.[14] Homogeneous catalysis usually requires less harsh conditions compared to heterogeneous catalysis. Lower reaction temperature and hydrogen pressure might lead to higher selectivity to the desired products.[14]

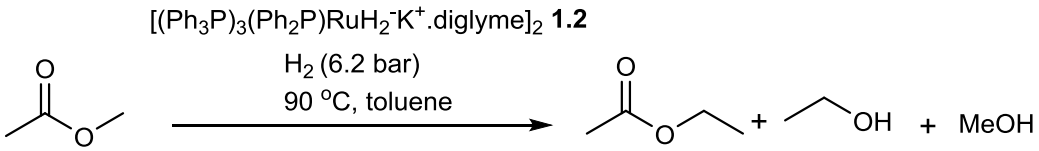
1.2.1 Reduction of esters

Traditionally, esters are reduced by using stoichiometric amounts of $LiAlH_4$,[15] diisobutylaluminium hydride (DIBALH),[16] lithium cyanoaluminium hydride[17] or boron hydride.[18] Due to the high cost, poor atom economy, severe safety issues and difficulties in work up, catalytic hydrogenations are preferred especially on larger scales, and no waste is generated from the catalytic hydrogenation of esters to alcohols. Heterogeneous metal oxide based catalysts are applied for large scale ester hydrogenation. Unfortunately, high temperature and pressure are required. Homogeneous hydrogenation of esters with ruthenium, iridium and osmium complexes has been studied in order to obtain performance under milder condition. These metals are chosen because of their potential activity.

1.2.1.1 Hydrogenation of aliphatic, aromatic, difunctional esters and lactones

1.2.1.1.1 Triphos ligands

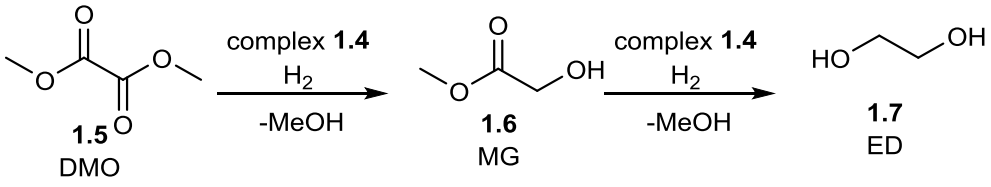
A facially-capping tripodal phosphine ligand was originally found to be the optimal choice for catalytic ester hydrogenation with ruthenium as the metal centre.[19] In 1980, Grey and Pez developed anionic ruthenium hydride complexes $[(Ph_3P)_2Ph_2P(C_6H_4)RuH_2]^-K^+(Et_2O)\cdot C_{10}H_{18}$, **1.1**, and $[(Ph_3P)_3(Ph_2P)RuH_2^-K^+\cdot diglyme]_2$, **1.2**, which can hydrogenate carboxylic acid esters under mild condition (Scheme 1.2).[20] However complex **1.1** was found only to be effective for the hydrogenation of polar organic compounds such as dimethyl oxalate and 2,2,2-trifluoroethyl trifluoroacetate, but not for simple aliphatic esters. Complex **1.2** was then designed to overcome this problem. A relatively non coordinating solvent such as toluene was required for the hydrogenation of an aliphatic ester, methyl acetate. When THF was used as the solvent, or if 18-crown-6 was added, the conversion of the reaction was greatly reduced. The reaction did not proceed in the absence of solvent.



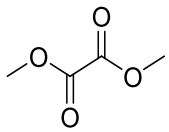
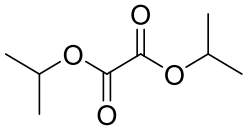
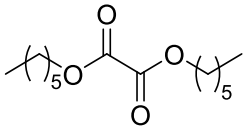
Scheme 1.2. Hydrogenation of esters by Grey and Pez.[20]

Bianchi, Matteoli and co-workers tried the neutral ruthenium carbonyl hydride complex $[Ru_4H_4(CO)_8(PBu_3)_4]$, **1.3**, for hydrogenation reactions of carboxylic acids and their anhydride derivatives in the same year. The reaction required 100 to 200 bar of hydrogen, which were very harsh conditions. However, esters could not be reduced under these conditions.[21] Matteoli and co-workers further investigated this reaction by using the related complexes $[Ru(CO)_2(CH_3COO)_2(PBu_3)_2]$, **1.4**.[22] In this case, dimethyl oxalate (DMO), **1.5**, could be fully converted to methyl glycolate (MG), **1.6**, with 100% selectivity at 130 bar of hydrogen and 180 °C in 50 h (Table 1.2, Entry 1). Increasing the reaction time to 144 h led to a decrease of methyl glycolate, **1.6,** selectivity to 93.2%, but it gave 6.8% selectivity to the dihydrogenated ethane-1,2-diol (ED), **1.7** (Table 1.2, Entry 2). A range of dialkyl oxalates (**1.8** and **1.9**) had been proved to be reactive under such reaction conditions (Table 1.2, Entry 4 and 5). Heavier ester alcohols are less reactive for the further reduction to the corresponding diols, and only methyl esters are further reduced to glycols. Aromatic solvents such as benzene or hydroxylated solvents such as methanol are preferred for the subsequent reduction and afford the glycol (Table 1.2, Entry 2 and 3). Kinetic studies revealed a first order reaction relative to the substrate.

Table 1.2. Hydrogenation of dialkyl oxalates.[a]

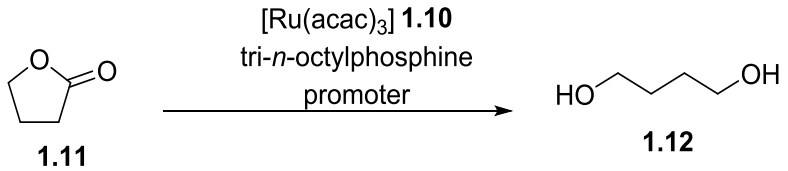


Entry	Substrates	Solvent	t (h)	Conv. (%)	Sel. MG, 1.6 (%)	Sel. ED, 1.7 (%)	ref

1	 **1.5**	benzene	50	100	100	-	[22]
2		benzene	144	100	93.2	6.8	[22]
3		MeOH	144	100	73.3	26.7	[22]
4	 **1.8**	benzene	144	100	100	-	[22]
5	 **1.9**	benzene	144	69.7	100	-	[22]

[(a)]Ester (11 mmol), $[Ru(CO)_2(CH_3COO)_2(PBu_3)_2]$, **1.4**, (6.5 mol%), solvent (15 ml), H_2 (132 bar), 180 °C.

In 1991, Hara and Wada reported a catalytic system ($[Ru(acac)_3]$, **1.10** /tri-*n*-octylphosphine/*p*-TsOH) which could be used for the reduction of lactones and anhydrides.[23] They found that, with addition of a strong acid to the system, the rate of hydrogenation of anhydride could be accelerated dramatically. Later in 1992, they published another paper on the hydrogenation of cyclic esters (lactones) into the corresponding α,ω-diols with only small modifications of the original conditions (Scheme 1.3).[24] Ammonium hexafluorophosphate, phosphoric acid, or its derivatives were used as promoters for the $[Ru(acac)_3]$, **1.10** /tri-*n*-octylphosphine system, and improved the conversion to up to 29% for γ-butyrolactone, **1.11**, to 1,4-butanediol, **1.12**.

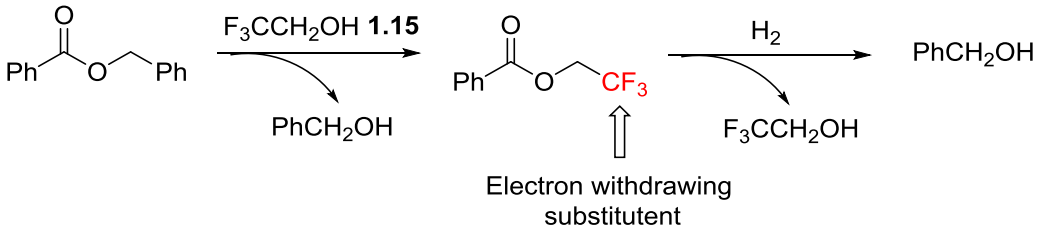


Scheme 1.3.Hydrogenation of cyclic esters into the corresponding α,ω-diols.[24]

Elsevier developed a system in 1997 with milder conditions[25] than those used by Hara and Wada.[24] It was found that the hydrogenation of methyl glycolate, **1.6**, to ethylene glycol, **1.7**, required drastic conditions, while the hydrogenation of dimethyl oxalate, **1.5**, to methyl glycolate, **1.6**, was relatively easy. The reason is that the esters activated by electron withdrawing substituents could be converted more efficiently to the

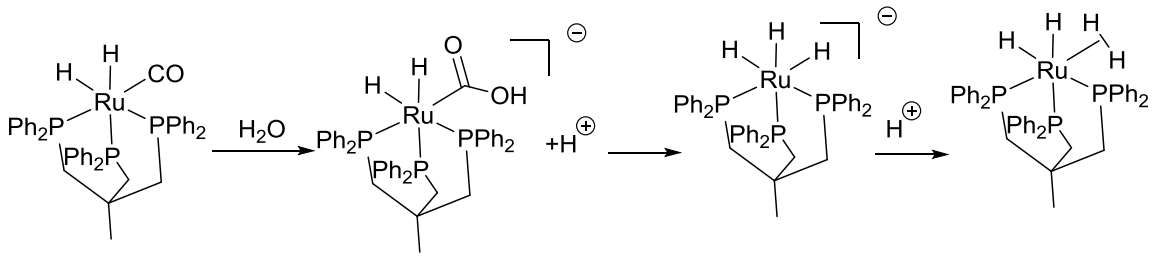
corresponding alcohols. A series of phosphine ligands was tested along with [Ru(acac)$_3$], **1.10**, as metal source, and the activity of dimethyl oxalate hydrogenation with ruthenium-phosphine increased in the order: P(C_6H_{11})$_3$< $PPh_2PCH_4PPh_2$< PPh_3< $PhP(C_2H_4PPh_2)_2$≈ $[CH_2P(Ph)C_2H_4PPh_2]_2$<<$MeC(CH_2PPh_2)_3$, 1,1,1-Tris(diphenylphosphinomethyl)ethane (triphos), **1.13**, (Scheme 1.6) was found to be the most reactive ligand for the direct hydrogenation of dimethyl oxalate, **1.5**, to ethylene glycol, **1.7** (95% selectivity) with zinc as an additive. Zinc in this case was used to initiate the reduction of the ruthenium acetylacetonate complex.[25]

The [Ru(acac)$_3$], **1.10** / triphos, **1.13**, system was further optimised by the same group in 1998.[26] The hydrogenation of dimethyl maleate, **1.14**, to 1,4-butanediol, **1.12**, could be achieved in 100% conversion and 100% yield at 85 bar of H_2 and 120 °C with trimethylamine as base in the fluorinated solvent, 1,1,1,3,3,3-hexafluoropropan-2-ol (TON=2019). Fluorinated solvents such as 1,1,1,3,3,3-hexafluoropropan-2-ol or 2,2,2-trifluoroethanol, **1.15**, were used to facilitate the hydrogenation reaction, which could possibly suggest transesterification between the fluorinated solvent and the ester to produce an ester with a more electron withdrawing substituent adjacent to the carbonyl group (Scheme 1.4).[26]



Scheme 1.4. Transesterification between solvent and an ester.[26]

Crabtree and co-workers further studied the [Ru(acac)$_3$], **1.10**/ triphos, **1.13**, system.[27,28] Dimethyl maleate, **1.14**, was converted into butanediol, **1.12**, in 99.5% of conversion and 66% selectivity at 48 bar of H_2 and 191 °C for 53 h. Water was found to be necessary as an additive for this hydrogenation reaction because it can activate and stabilise the catalyst at the same time. In the absence of water, the conversion of methyl propionate was only 16.4% while in the presence of water, the conversion increased to 100%. The role of water is believed to be to regenerate the active species from inactive [RuH_2CO(triphos)] by water gas shift type chemistry (Scheme 1.5).



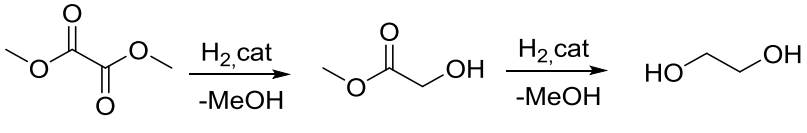
Scheme 1.5. Regeneration of active species by water.[27]

In 2014, Leitner and co-workers developed another ruthenium complex [Ru(triphos)(TMM)], **1.16** (Scheme 1.6) for the hydrogenation of carboxylic acids and their derivatives, such as esters and amides.[29] At 140°C, dimethyl succinate was hydrogenated to the corresponding diol in excellent yield (99%) after 16 h. Double bonds, alcohol and ketone groups are all tolerated under these conditions with C=C and ketonic C=O bonds not being hydrogenated.

Ruthenium triphos complexes provide good catalysts for ester hydrogenation. However, improvements are constantly required because of the disadvantages these reactions possess, such as high pressure, long reaction times and limited functional group tolerance.

The first ruthenium/sulfur catalyst for ester hydrogenation was developed by Tooze and co-workers in 2006.[30] Examination of the literature suggested that soft, electron-rich door ligands were preferred for this reaction. Sulfur-based ligands were studied due to their catalytic activity in alkene and ketone hydrogenation.[31] The tripodal sulfur ligand, $MeC(CH_2SMe)_3$, **1.17** (Scheme 1.6),[32] was extensively used because of its wide application scope in the coordination chemistry of transition metals.[33,34] Dimethyl oxalate, **1.5**, was chosen as the substrate in this paper because of the industrial interest of its alcohol product, ethane-1,2-diol (ED, **1.7**).[27] The ruthenium/sulfur system could convert dimethyl oxalate (DMO, **1.5**) to the monohydrogenated product methyl glycolate (MG, **1.6**) in high conversion with or without an additive (Table 1.3, Entry 1 and 2). However, the addition of zinc could greatly increase the reaction rate (Table 1.3, Entry 2). It was found that this reaction was zero order with respect to the substrate DMO, **1.5**.

Table 1.3. Hydrogenation of DMO with various ligands.[a]

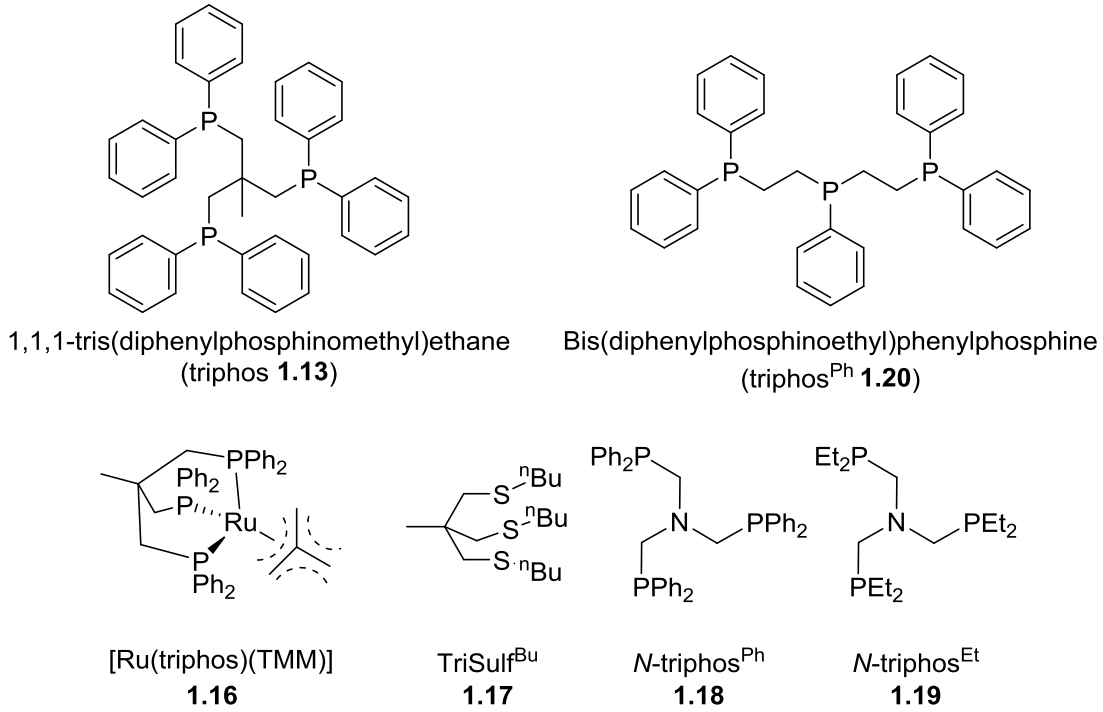


DMO **1.5** MG **1.6** ED **1.7**

Entry	Ligand	Additive	t (h)	Conv. to MG 1.6 (%)	Conv. to ED 1.7 (%)	ref
1	TriSulf^{Bu}, **1.17**	-	136	100	-	[30]
2	TriSulf^{Bu}, **1.17**	Zn	69	87.2	-	[30]
3	*N*-triphos^{Ph} **1.18**	Zn	20.9	96.6	-	[35]
4	*N*-triphos^{Et} **1.19**	Zn	20.6	93	5.6	[35]
5	triphos^{Ph}, **1.20**	Zn	7	-	98.6	[35]

[(a)]Conditions: [Ru(acac)$_3$], **1.10** (1 mol%), ligand (1.3 mol%), Zn (0.3 mol%), 100 °C, H_2 (80 bar), MeOH (30 mL).

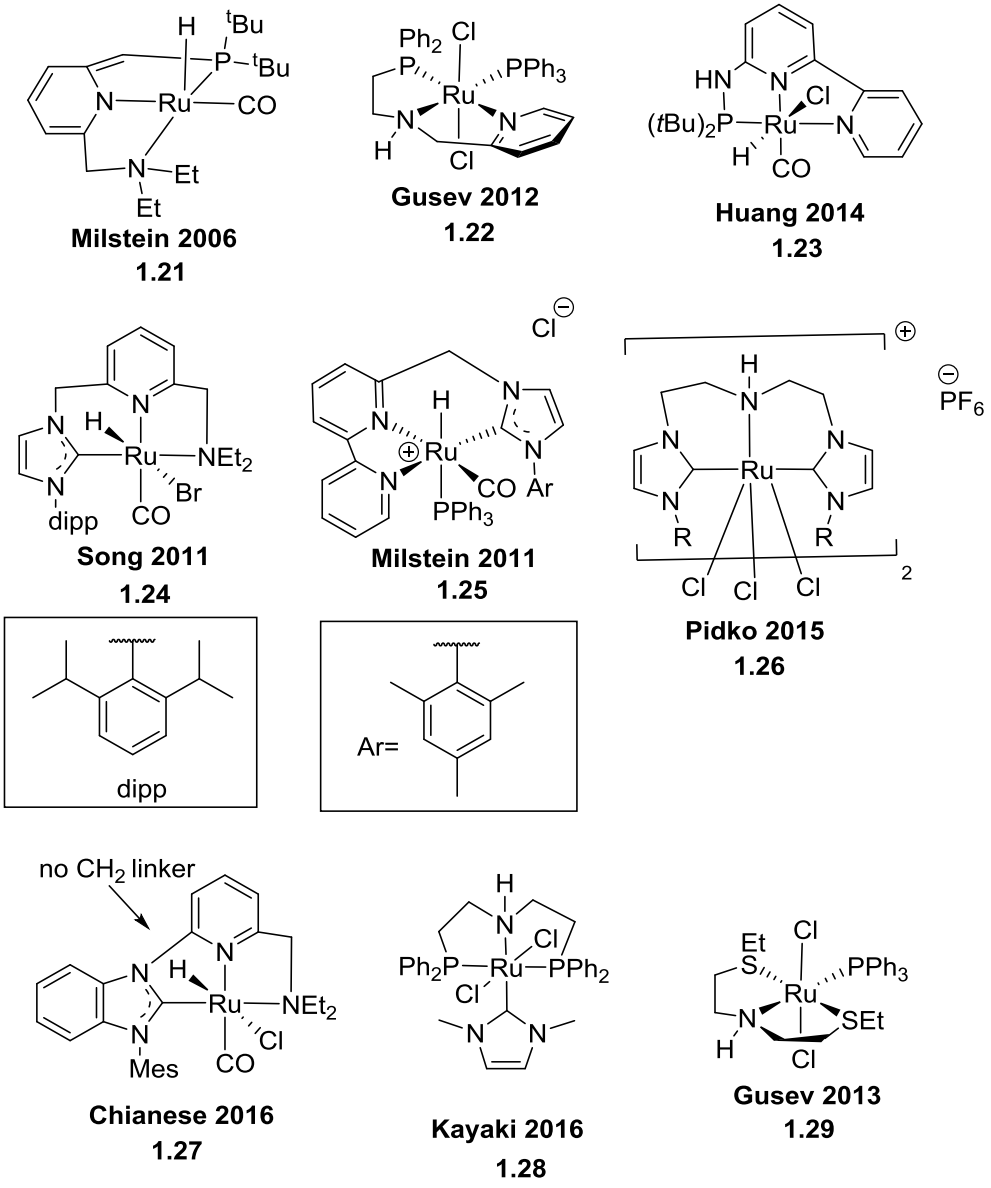
N-triphos^{Et}, **1.19**, and *N*-triphos^{Ph}, **1.18** (Scheme 1.6) were studied by Hanton et al. in 2011.[35] The reaction was found to be first order in substrate when using *N*-triphos^{Et}, **1.19**, and *N*-triphos^{Ph}, **1.18**. The reaction rate was greatly improved (Table 1.3, Entry 3 and 4) compared with that when using the sulfur ligand (Table 1.3, Entry 1 and 2). However, the rate was lower if comparing with triphos^{Ph} **1.20**) ligand (Table 1.3, Entry 5), which might be due to the decomposition of the *N*-triphos^{Ph} ligand, **1.18**, during catalysis. Various additives such as water, Me_3NO and AuI were also tested for this reaction, but unfortunately, the reaction rate could not be increased.



Scheme 1.6. Structures of triphos and derivative ligands.

1.2.1.1.2 Hydrogenation with Pincer Ligands

Ruthenium complexes with *N*, *P*-ligands are known to be efficient catalysts for ketone hydrogenation to alcohols under mild conditions.[36,37] In 2006, Milstein and co-workers reported the ruthenium hydride complex with the pincer ligand PNN (2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine), **1.21** (Scheme 1.7) for the hydrogenation of non-activated esters to the corresponding alcohols in the absence of additives (Table 1.4).[38] Simple aromatic (Table 1.4, Entry 1), aliphatic (Table 1.4, Entry 3) and difunctional esters (Table 1.4, Entry 6) were converted to the alcohols in excellent yields at 115 °C and 5 bar of hydrogen. Hydrogenation of bulky esters gave a much lower yield (10.5%) even after 24 hours (Table 1.4, Entry 7). The analogous PNP complex had much lower activity, therefore, it was proposed that the reaction mechanism contains both pincer ligand hemilability[39] and ester coordination.



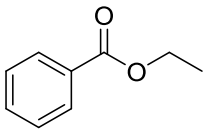
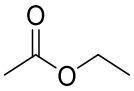
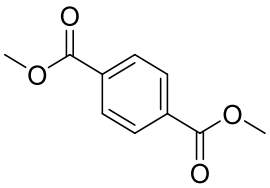
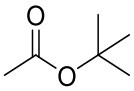
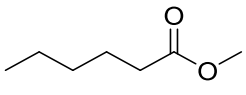
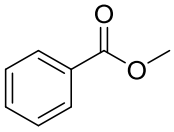
Scheme 1.7. Structure of Pincer ligands for ester hydrogenation.

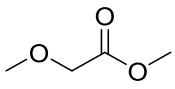
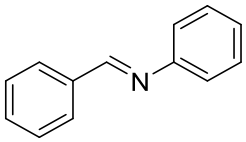
In 2012, Gusev and co-workers developed an air stable catalyst $[RuCl_2(PPh_3)[PyCH_2NHC_2H_4PPh_2]]$, **1.22**, for ester reduction aiming for a reduced reaction temperature and lower catalyst loading compared to the previous results.[40] The hydrogenation results are summarised in Table 1.4. Low catalyst loading (0.002-0.025 mol%) was applied for the hydrogenation of aromatic and aliphatic esters (Table 1.4, Entry 4, 8, 10 and 12). Reaction can be successfully achieved at only 40 °C for esters and even for imines (Table 1.4, Entry 13). Reduction of ethyl acetate gave 20000 turnovers in 16 h with catalyst **1.22** (Table 1.4, Entry 4), and 18800 for methyl

hexanoate reduction in 18 h at 40 ºC (Table 1.4, Entry 8). This catalyst is also known as an alcohol dehydrogenation catalyst.[40]

Stable Ruthenium PN^3-Pincer complex, **1.23** (Scheme 1.7) with an aminophosphine arm was reported by Huang and co-workers in 2014.[41] Excellent yields were obtained for the hydrogenation of aromatic (Table 1.4, Entry 2 and 11) and aliphatic esters (Table 1.4, Entry 5 and 9). Benchtop solvent can be used for this reaction as water can be tolerated; anhydrous solvents are no longer necessary, which is more practically favourable.

Table 1.4. Hydrogenation with ruthenium complexes containing *P,N*-pincer ligands.[a]

Entry	Substrate	Cat.	Cat. loading (mol%)	t(h)	T (°C)	P(H_2) (bar)	Yield (%)	ref
1		**1.21**	1	4	115	5.4	96	38
2[b]		**1.23**	1	2	120	28	98	41
3		**1.21**	1	12	115	5.4	85.6	38
4[c,g]		**1.22**	0.005	16	40	50	100	40
5[b]		**1.23**	1	2	120	28	98	41
6[h]		**1.21**	1	5	115	5.4	97	38
7		**1.21**	1	24	115	5.4	10.5[b]	38
8[d,f]		**1.22**	0.005	18	40	50	100	40
9[b]		**1.23**	1	2	120	28	96	41
10[d,f]		**1.22**	0.025	16	40	50	98	40
11[b]		**1.23**	1	2	120	28	95	41

12[e,f]		**1.22**	0.025	16	40	50	100	[40]
13[e,f]		**1.22**	0.002	16	40	50	100	[40]

[a]Conditions: esters (2 mmol), H_2 (5.4 bar), 1,4-dioxane (2 mL). [b]KO^{t}Bu (8 mol%) was added. [c]NaOEt (1 mol%) was added. [d]KOMe (5 mol%) was added [e]KO^{t}Bu (1 mol%) was added. [f]THF. [g]Neat condition. [h]1,4-dimethanolbenzene is the product of this reaction.

Milstein type catalysts have been extended by exchanging the "one phosphine-two tertiary amine" donor set for an *N*-heterocyclic carbene ligand (NHC) and two tertiary amines in complex **1.21** (Scheme 1.7).[42,43] NHC ligands are usually regarded as replacements for phosphine ligands; they are more electron-donating than phosphines, and therefore are more strongly bonded to the metal. Song and co-workers reported a new Ru-CNN pincer complex, **1.24** (Scheme 1.7),[43] which showed an over 100-fold increase in TOF at a lower temperature compared to Milstein's catalytic system (105 °C instead of 115 °C). Unactivated aromatic and aliphatic esters were efficiently converted to the corresponding alcohols in the presence of KO^{t}Bu or KHMDS within 2 or 3 hours. Simple ethyl acetate was hydrogenated in 99% yield after only 2 hours (Table 1.5, Entry 2), while Milstein's catalyst, **1.21**, required 12 hours to afford 86% yield (Table 1.4, Entry 3). Surprisingly, the bulky ester, *tert*-butyl acetate, could be transformed to the alcohol in 92% yield in 2 hours (Table 1.5, Entry 3), while with Milstein's catalyst, the yield was only 10.5% after 24 hours (Table 1.4, Entry 7).

Another CNN-type ruthenium NHC complex, **1.25**, (Scheme 1.7) was developed by Milstein and co-workers in the same year.[42] Complex **1.25** together with one equivalent of KO^{t}Bu relatively to the catalyst gave up to 97% yield in 2 hours when hydrogenating non-activated esters to the corresponding alcohols under mild conditions (Table 1.5, Entry 4 and 5). These results suggested a better catalytic activity compared to the PNN ligands.

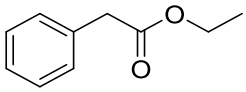
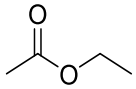
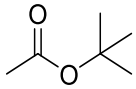
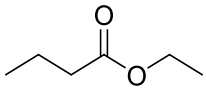
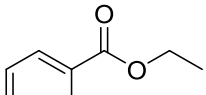
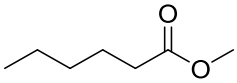
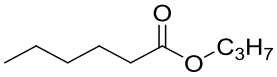
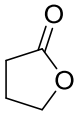
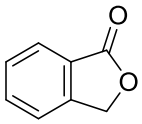
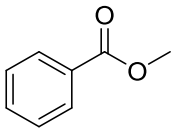
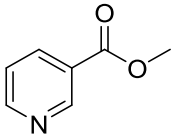
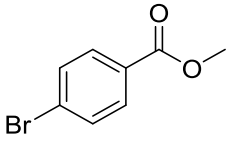
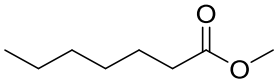
In 2015, Pidko and co-workers developed the first *bis*-NHC amino pincer ligand, **1.26**, (Scheme 1.7) for ester hydrogenation. Under 50 bar of hydrogen and 70 °C, only 12.5

ppm of Ru loading is required for efficient conversion (Table 1.5).[44] Aromatic (Table 1.5, Entry 6), aliphatic esters (Table 1.5, Entry 8 and 9) and lactones (Table 1.5, Entry 10) can be hydrogenated with a low catalyst loading (0.0067-0.01 mol%) under mild conditions (50 bar H_2, 70 °C). Surprisingly, dimethyl itaconate was chemoselectivily reduced at the double bond, whereas methyl cinnamate was reduced to a mixture of the allylic alcohol (72%) and the saturated alcohol.

Complex **1.27** (Scheme 1.7), which has similar structure compared to Song's catalyst was synthesised in 2016 by Chianese and co-workers. By deuteration experiments carried out by Song and co-workers, a complete deprotonation was observed with a strong base at the NHC site. A new Ru-CNN complex, **1.27**, was synthesised in the absence of a CH_2 linker on the NHC site, in order to understand the catalytic relevance of reversible deprotonation at different positions of a pincer ligand.[45] Various esters such as ethyl, benzyl, hexyl esters and lactones were successfully converted to the alcohols by complex **1.27**. However, methyl esters tended to give poor yields using complex **1.27** (Table 1.5, Entry 13). The hypothesis given in Chianese's paper was that the byproduct methanol is a strong catalyst poison which resulted in the lack of reactivity of methyl esters.

A new PNP pincer ruthenium complex which additionally contained a monodentate *N*-heterocyclic carbene ligand (complex **1.28**) was developed by Kayaki and coworkers in 2016. They managed to hydrogenate esters under atmospheric pressure of hydrogen, and therefore, no autoclave is needed under their conditions.[46] Aliphatic and aromatic ester hydrogenations were successfully achieved in over 90% yield (Table 1.5, Entry 11, 14 and 17). Hydrogenation of methyl 3-pyridinecarboxylate gave the alcohol in 90% yield and the pyridine moiety remained intact (Table 1.5, Entry 15). Bromo-substituted benzoates were successfully hydrogenated to the corresponding alcohols in 94% yield without concomitant hydrogenolysis of the bromide (Table 1.5, Entry 16).

Table 1.5. Hydrogenation with ruthenium pincer complexes containing NHC ligands.

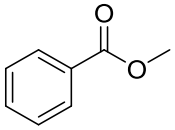
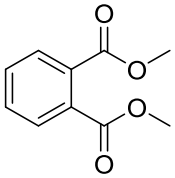
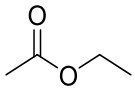
Entry	Substrate	Cat	Cat. loading (mol%)	T (°C)	t (h)	P(H_2) (bar)	Yield (%)	ref
1[a]		**1.24**	1	105	2	5.4	99.7	[43]
2[a]		**1.24**	1	105	2	5.4	99	[43]
3[a]		**1.24**	1	105	2	5.4	92	[43]
4[b]		**1.25**	1	135	2	5.4	97	[42]
5[b]		**1.25**	1	135	2	5.4	97	[42]
6[c]		**1.26**	0.01	70	16	50	93.7	[44]
7[d]		**1.27**	0.4	105	20	6	>99	[45]
8[c]		**1.26**	0.0067	70	16	50	100	[44]
9[c]		**1.26**	0.01	70	16	50	100	[44]
10[c]		**1.26**	0.0067	70	16	50	100	[44]
11[e,f]		**1.28**	2	50	5	1	73	[46]
12[d]		**1.27**	0.2	105	20	30	99	[45]
13[d]		**1.27**	0.8	105	20	6	8	[45]
14[e]		**1.28**	2	50	5	1	90	[46]
15[e]		**1.28**	2	50	5	1	90	[46]
16[e]		**1.28**	2	50	5	1	94	[46]
17[e]		**1.28**	2	50	5	1	94	[46]

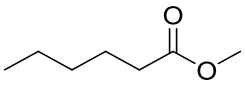
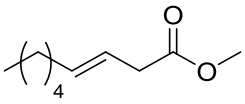
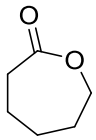
[(a)]Conditions: esters (1 mmol), catalyst (1 mol%), KO^{t}Bu (8 mol%), toluene (2 mL).
[(b)]Conditions: ester (1 mmol), catalyst (1 mol%), KO^{t}Bu (1 mol%), toluene (2 mL).

[c]Conditions: ester (5 mmol), catalyst (0.0067-0.01 mol%), KO^{t}Bu (2 mol%), THF (2 mL). [d]Conditions: toluene (2 mL), NaO^{t}Bu (6 equiv to [Ru]). [e]Conditions: Ester (1 mmol), catalyst (2 mol%), KO^{t}Bu (0.2 mmol), THF (2 mL). [f]NaOMe (0.2 mmol) was used instead.

Phosphorus ligands have shown great activity in ester hydrogenation developed by different groups. However, there are still disadvantages using phosphine ligands. They are very sensitive to both water and oxygen, and therefore need to be handled under an inert atmosphere, which also leads to an increase in price for the phosphine ligands. In 2013, pincer complexes with sulfur ligands instead of phosphorus were studied by the Gusev group.[47] A few sulfur containing catalysts were tested, and it turned out that complex **1.29** has the best activity in ester hydrogenation. Aromatic (Table 1.6, Entry 1 and 2), aliphatic (Table 1.6, Entry 3 and 4), unsaturated esters (Table 1.6, Entry 5) and lactones (Table 1.6, Entry 6) were effectively reduced in the presence of the air stable catalyst, **1.29**. Therefore, the phosphine moieties in Noyori-type catalysts can be replaced by sulfur donors successfully to give a higher stability and lower cost. Later on, complex **1.29** was shown to be a good ester metathesis catalyst by Khaskin and co-workers.[48]

Table 1.6. Hydrogenation with catalyst **1.29**.[a]

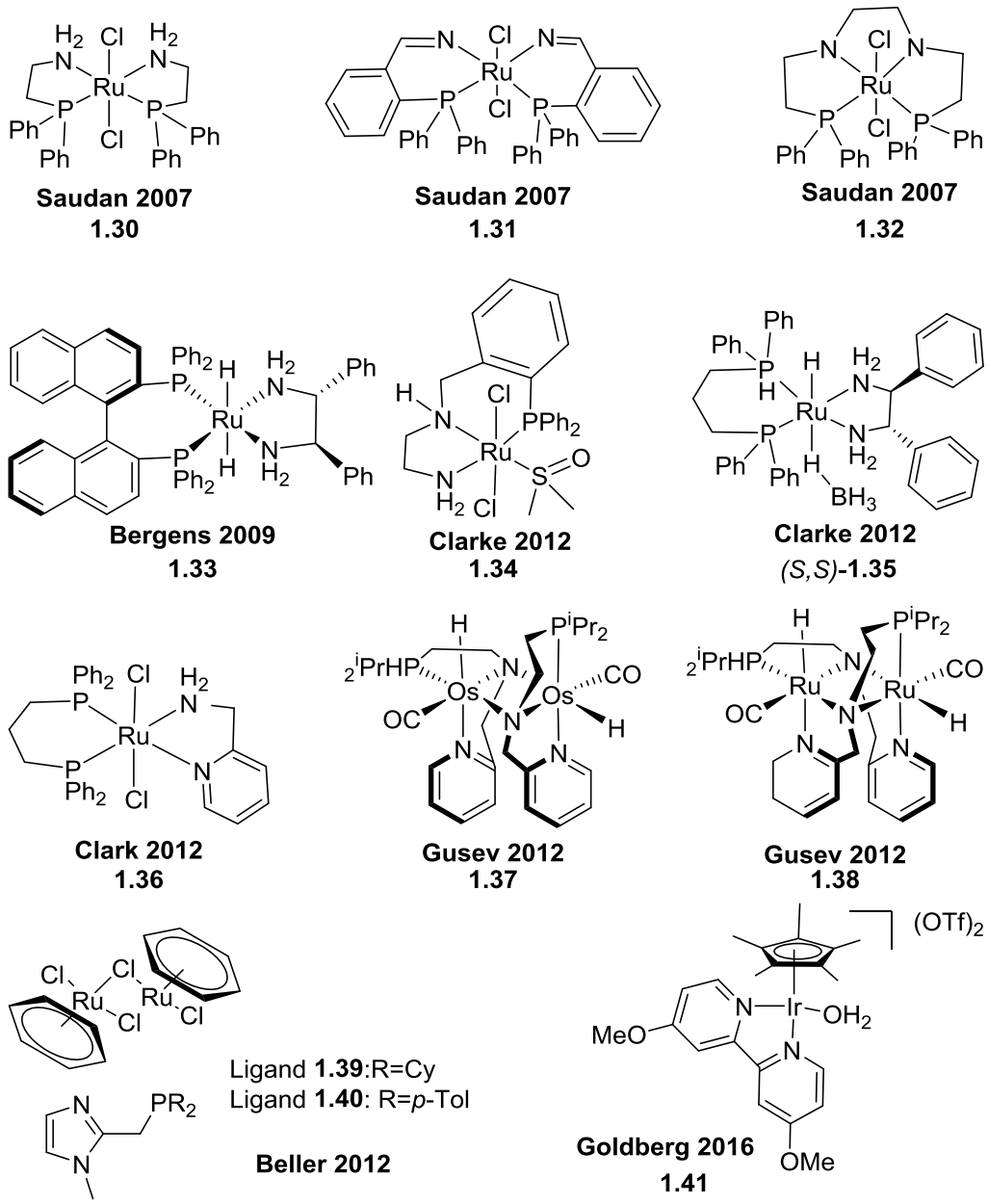
Entry	Substrate	Cat	Cat. loading (mol%)	T (°C)	t (h)	P(H_2) (bar)	Conv. (%)	ref
1[b]		**1.29**	0.025	40	6	50	95	47
2[c]		**1.29**	0.1	100	1.2	50	96	47
3[d]		**1.29**	0.0025	40	14	50	95	47

4[c]		**1.29**	0.01	100	2	50	98	[47]
5[b,e]		**1.29**	0.05	40	8	50	100	[47]
6[c]		**1.29**	0.01	100	2	50	99	[47]

[(a)]Conditions: substrate (0.02 mol), base additive (1 mol%), THF (6 mL). [(b)]^{t}BuOK as base. [(c)]MeOK as base. [(d)]EtONa as base. [(e)]Double bond not reduced.

1.2.1.1.3 Hydrogenation with other ligands

Saudan and co-workers developed a few more active P, N ligands (complex **1.30**, **1.31**, **1.32**) for ester hydrogenation in 2007.[49]



Scheme 1.8. Other complexes for ester hydrogenation.

Aliphatic and aromatic esters can be easily hydrogenated to the corresponding alcohols in high yield (Table 1.7, Entry 1, 6-9, 11-14). Linear and branched esters were reduced efficiently. Interestingly, when isopropyl benzoate is used as substrate instead of methyl benzoate, either the catalyst loading or the hydrogen pressure can be decreased (Table 1.7, Entry 6 and 7). This is possibly due to the presence of the methanol byproduct during the hydrogenation of methyl benzoate, which could act as a catalyst poison through carbonylation of the metal. Esters with an isolated C=C bond (Table 1.7, Entry

13 and 14) were successfully hydrogenated with high chemoselectivity (98:2, C=O:C=C). The author suggested this reduction of the C=C bond probably requires coordination to the metal center, and therefore is more sterically demanding than the C=O bond which is proposed to proceed by an outer-sphere hydrogenation. However, it is also possible that there is no vacant site for the coordination of the C=C bond hence the C=O is hydrogenated preferentially.

In 2009, Bergens and co-workers developed a Noyori-type catalyst.[50] *Trans*-[Ru(*R*)-BINAP$(H)_2$(1,2-diaminoethane)], **1.33**, was found to provide good activity for ester hydrogenation even at very low temperature (-20 °C). However, product inhibition slowed these reactions over time at low temperature and pressure. When the temperature was increased to 30 or 50 °C, the hydrogenation could result in 100% yield using complex **1.33** (Table 1.7, Entry 15). For the hydrogenation of methyl cinnamate, both C=O and C=C bonds were reduced in 100% yield (Table 1.7, Entry 17). Larger amounts of base are needed to retain good reactivity compared to Milstein's Ru-hydride complex.

In 2012, Clarke and co-workers developed a few more catalysts (Catalyst **1.34**, **1.35**, **1.36**) for the hydrogenation of esters. Aromatic and heteroaromatic esters were successfully reduced in very high isolated yields (98% for methyl 4-chlorobenzoate using catalyst **1.35**-(*S.S*)).[51]

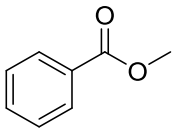
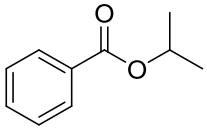
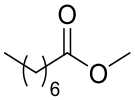
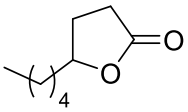
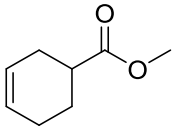
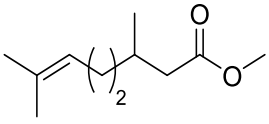
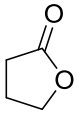
New Ru and Os catalysts were investigated by the same group for the hydrogenation of esters under neutral conditions. Their work is based on the dehydrogenation catalyst [MH_2(CO)(HN($C_2H_4P^iPr_2$)$_2$)] (M=Ru, Os). Hemilabile NNHP^{i}Pr is used to replace the PNHP^{i}Pr ligand which is believed to facilitate the hydrogenation.[52] Dimers **1.37** and **1.38** (Scheme 1.8) can hydrogenate various esters with high efficiency (Table 1.7, Entry 3, 4, 18, 20-23). Hydrogenation of isopropyl 2-bromobenzoate was not successful, possibly due to catalyst deactivation (Table 1.7, Entry 19).

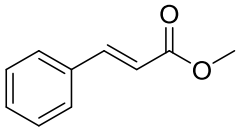
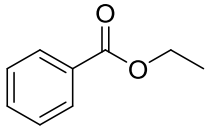
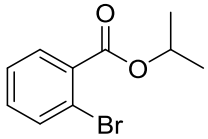
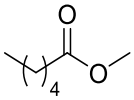
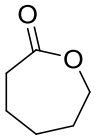
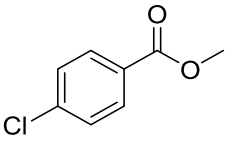
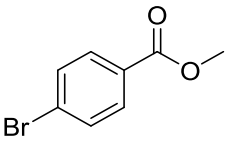
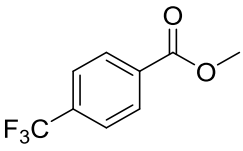
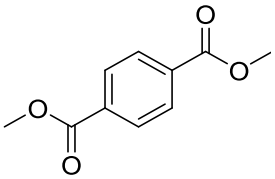
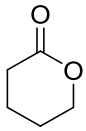
In 2012 Beller and co-workers developed several P-N ligands, which contain phosphorus and imidazolyl nitrogen donor atoms (Ligands **1.39** and **1.40**).[53] Ruthenium catalysts based on these ligands were found to be active in the hydrogenation of both

aromatic and aliphatic esters (Table 1.7, Entry 5, 10, 16, 24-28) after activation with KO^{t}Bu. Ethyl 2-bromobenzoate (Table 1.7, Entry 25) was not hydrogenated in a reasonable yield. However, *para* positioned chloride (Table 1.7, Entry 24) and trifluoromethyl (Table 1.7, Entry 26) did not influence the results when they were present on the substrate.

An iridium catalyst was also found to be active in ester hydrogenation. [Cp*Ir(bpy-OMe)OH_2][OTf]$_2$, **1.41**, was described by Goldberg and co-workers in 2016.[54] Hydrogenation of esters and lactones were carried out effectively without adding base. Mild conditions (30 bar of H_2, 100 °C, 16 h) are particularly effective for formate esters, giving a TON of 1317.

Table 1.7. Hydrogenation with other catalysts.

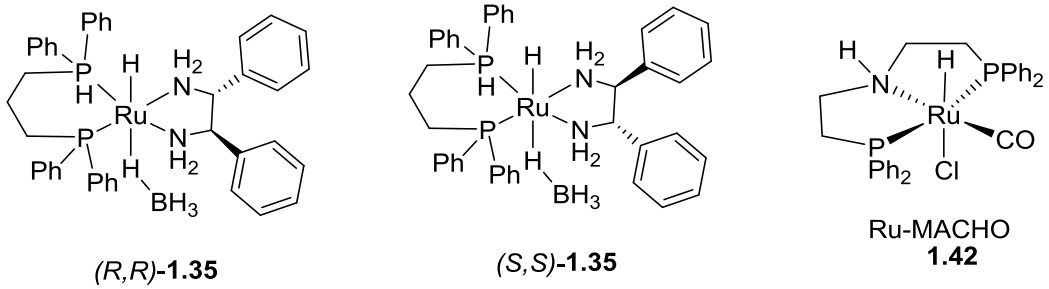
Entry	Substrate	Cat	Cat. Loading (mol%)	T (°C)	t (h)	P(H_2) (bar)	Yield (%)	ref
1[a]		**1.30**	0.05	100	1	50	99	49
2[c]		**1.33**	1	30	3	4	100	50
3[d]		**1.37**	0.05	100	1.5	50	99	52
4[d]		**1.38**	0.05	100	1	50	99	52
5[e]		**1.39**	0.25	100	2	50	94	53
6[a]		**1.30**	0.01	100	4	50	99	49
7[a]		**1.30**	0.05	100	4	10	99	49
8[a]		**1.30**	0.05	100	2.5	50	94	49
9[a]		**1.31**	0.05	100	2.5	50	87	49
10[e]		**1.40**	0.25	100	4.5	50	75	53
11[a]		**1.30**	0.05	100	4	50	87	49
12[a]		**1.31**	0.05	100	4	50	91	49
13[a]		**1.31**	0.05	100	2.5	50	98:2[b]	49
14[a]		**1.31**	0.05	100	2.5	50	99:1[b]	49
15[c]		**1.33**	1	30	4	4	100	50
16[e]		**1.40**	0.25	100	4.5	50	99	53

17[c]		**1.33**	2	30	3	4	100[i]	50
18[d]		**1.37**	0.05	100	1.6	50	99	52
19[d,g]		**1.37**	0.05	100	17	50	0	52
20[d]		**1.37**	0.05	100	2	50	100	52
21[d]		**1.38**	0.05	100	1.5	50	93	52
22[d]		**1.37**	0.05	100	1.4	50	99	52
23[d]		**1.38**	0.05	100	5	50	67	52
24[e,h]		**1.39**	0.25	100	4.5	50	92	53
25[e,h]		**1.39**	0.25	100	4.5	50	24	53
26[e]		**1.39**	0.25	100	4.5	50	84	53
27[e,f]		**1.39**	0.25	100	4.5	50	67	53
28[e]		**1.40**	0.25	100	4.5	50	73	53

[a]Conditions: ester (20 mmol), catalyst (0.05 mol%), NaOMe (5 mol%). [b]Ratio of unsaturated alcohol to saturated alcohol. [c]9 equiv. of KOBu relative to Ru. [d]Conditions: Substrate (20 mmol), catalyst (0.05 mol%), THF (7 mL), 100 °C, H_2 (50 bar). [e]Conditions: ester (10 mmol), [{Ru(benzene)Cl_2}$_2$] (0.25 mol%), ligand **1.39** or **1.40** (1 mol%), KO^{t}Bu (10 mol%), THF (10 mL), 100 °C, 4.5 h, H_2 (50 bar). [f]13% monoreduction. [g]100% starting material recovered. [h]Without concomitant hydogenolysis of the halogen. [i]Saturated alcohol is obtained as the product.

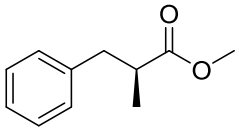
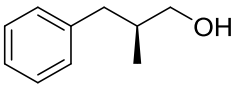
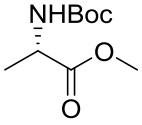
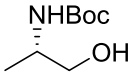
1.2.1.2 Hydrogenation of optically active esters

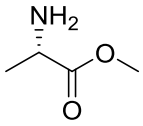
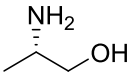
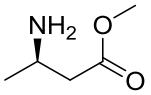
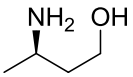
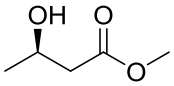
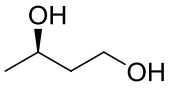
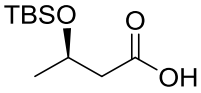
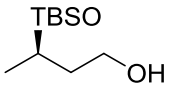
[$RuCl_2$(aminophosphine)$_2$], **1.30**, was reported to be a highly active catalyst for ester hydrogenation by Saudan in 2007.[49] Kuriyama and co-workers tested its activity for optically active esters in 2010.[55] Unfortunately, there was a substantial loss in enantiomeric excess during the hydrogenation reaction (62% Δe.e. for methyl (*S*)-2-methyl-3-phenylpropanoate). Screening of diamine and diphosphine ligands with the [$RuCl_2$(bisphosphine)(diamine)] precursor suggested that 1,3-bis(diphenylphosphino)propane (dppp) together with 1,2-diphenyl-1,2-ethylenediamine (dpen) gives the best performance. Complex (*R,R*)-**1.35** and (*S,S*)-**1.35** (Scheme 1.9) were therefore developed for the hydrogenation of chiral esters. Optically active esters were successfully reduced to the corresponding alcohols in high yield with no loss of optical purity.



Scheme 1.9. Complexes used for optical pure esters.[55,56]

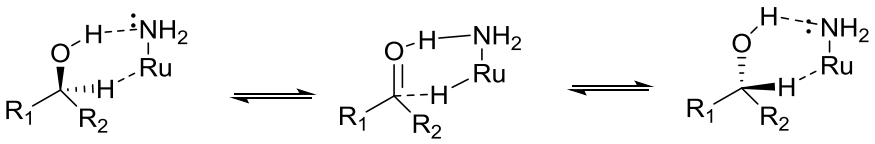
Table 1.8. Hydrogenation of optically pure esters.[a]

Entry	Substrate	Cat.	product	Yield (Δe.e.)[b]	ref
1		(*R,R*)-**1.35**		95 (<2)	55
2		(*S,S*)-**1.35**		95 (1)	55
3		(*R,R*)-**1.35**		92 (1)	55

4		(*S*,*S*)-**1.35**		96 (<1)	[55]
5		(*R*,*R*)-**1.35**		0[c] (-)	[55]
6		(*S*,*S*)-**1.35**		0[c] (-)	[55]
7		(*R*,*R*)-**1.35**		64[d] (<1)	[55]
8		(*S*,*S*)-**1.35**		53[d] (<1)	[55]
9		(*R*,*R*)-**1.35**		98 (19)	[55]
10		(*S*,*S*)-**1.35**		95 (24)	[55]
11		(*R*,*R*)-**1.35**		87 (<1)	[55]
12		(*S*,*S*)-**1.35**		92 (<1)	[55]

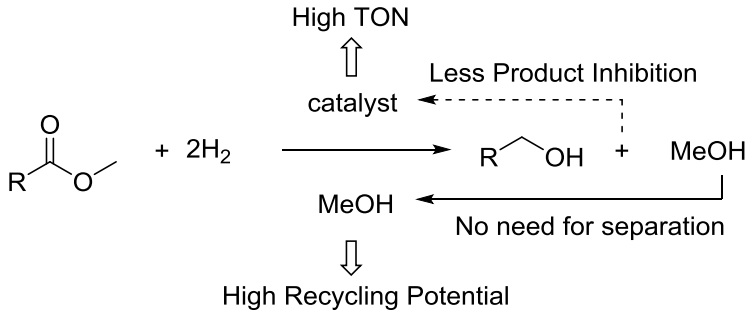
[a]Conditions: Substrate (5 mmol), complex (1 mol%) in THF (2 mL), H_2 (50 bar), 80 °C. Purification: silica gel column chromatography. [b]Δe.e.=(e.e. of substrate)-(e.e. of product) [c]GC analysis. [d]Purification by distillation.

Reduction of α-alkyl substituted chiral esters (Table 1.8, Entry 1 and 2) and *N*-Boc-α-amino acid esters (Table 1.8, Entry 3 and 4) occurred with excellent yields without loss of optical purity (Δe.e. = <1). However, no product was obtained for the unprotected α-amino acid esters (Table 1.8, Entry 5 and 6). β-Substituted esters gave better results especially the unprotected β-hydroxy ester (Table 1.8, Entry 7-10). The enantiomeric excesses were perfectly retained excepted for the unprotected alcohol (Table 1.8, Entry 9 and 10). This might be due to the hydrogen transfer process shown in Scheme 1.10. No racemization was obtained when the hydroxyl group was protected (Table 1.8, Entry 11 and 12).



Scheme 1.10. Racemisation process through transfer hydrogenation.[55]

This system successfully hydrogenated optically active esters to the corresponding alcohols with no loss of optical purity. However, the activities of these complexes were only moderate. Therefore, more studies should be carried out to find a catalyst with better activity. Despite the fact that the Ru-PNP system was shown not to be effective in ester hydrogenation by Milstein. Kuriyama and co-workers developed Ru-MACHO, **1.42**, for the hydrogenation of esters under mild and neutral conditions in 2012.[56] [RuHCl(CO)(HN($CH_2CH_2PPh_2$)$_2$] (Ru-MACHO, **1.42**) shows high catalytic activity when methanol is used as solvent whereas [$RuCl_2$($H_2NCH_2CH_2PPh_2$)$_2$] hardly gave any conversion, which means that Ru-MACHO was not deactivated by methanol. The use of solvents has a high environmental impact especially in the pharmaceutical industry. There is no need to remove the produced methanol as it can be reused as the solvent (Scheme 1.11). The optical purity of (*R*)-1,2-propanediol *via* methyl (*R*)-lactate hydrogenation was higher than that from hydroxyacetone under asymmetric hydrogenation with ruthenium-SEGPHOS.[56]

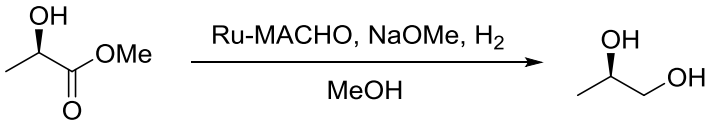


Scheme 1.11. Advantages of [RuHCl(CO)(HN(CH2CH2PPh2)2)], Ru-MACHO, **1.42**.[56]

Hydrogenation with Ru-MACHO was first tested on simple aromatic and aliphatic esters. Excellent yields (up to 100%) were obtained when NaOMe was used as an additive at 100 °C and 5 bar of H_2. Most interestingly, Ru-MACHO showed high activity for chiral esters and the optical purity was retained in the product alcohols. (*R*)-1,2-propanediol which is a useful chiral building block in the pharmaceutical industry

could be produced by the hydrogenation of methyl (*R*)-lactate. Low temperature (30-40 °C) was found to be crucial for the optical purity (Table 1.9).

Table 1.9. Hydrogenation of methyl (*R*)-lactate.[a]

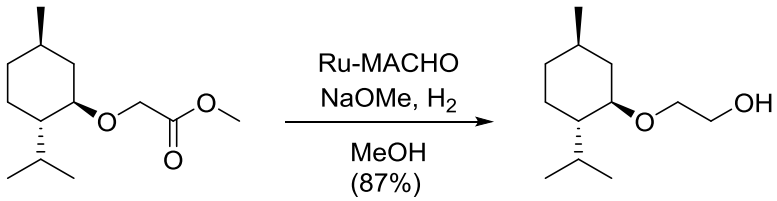


Entry	S/C	Temp.	diol	e.e.	ref
1	1000	80	99	35.9	56
2	1000	40	98	98.6	56
3[b]	4000	30	87[c]	98.6	56

[(a)]Reaction conditions: Substrate (10 mmol), Ru-MACHO, **1.42** (0.01 mmol), NaOMe (2 M in MeOH, 0.5 mmol), MeOH (5.5 mL), H_2 (5 MPa), 16 h. [(b)]Substrate (48 mmol), Ru-MACHO, **1.42** (0.012 mmol), NaOMe (2 M in MeOH, 0.96 mmol), MeOH (5 mL), H_2 (4 to 6 MPa), 24 h. [(c)]Isolated yield after silica gel column chromatography.

The optical purity decreased as the temperature increased. At 80 °C, the e.e. dropped from 99.2% to only 35.9% (Table 1.9, Entry 1), while at 40 °C, the e.e. only decreased by <1% (Table 1.9, Entry 2). At 30 °C, even with a substrate/catalyst ratio of 4000, the desired 1,2-propanediol could be obtained with 87% yield and less than 1% e.e. loss (Table 1.9, Entry 3). This hydrogenation reaction was carried out on a large scale to test its industrial potential (2200 kg substrate). The product 1,2-propanediol was obtained in 78% yield after distillation, and 99.2% e.e. was achieved from 99.6% e.e. of the starting ester.

2-(*L*-Menthoxy)ethanol, a flavouring compound which imparts a cooling sensation, can also be produced in 87% yield after distillation using Ru-MACHO with a S/C ratio of 2000 at 80 °C for 5 h (Scheme 1.12).

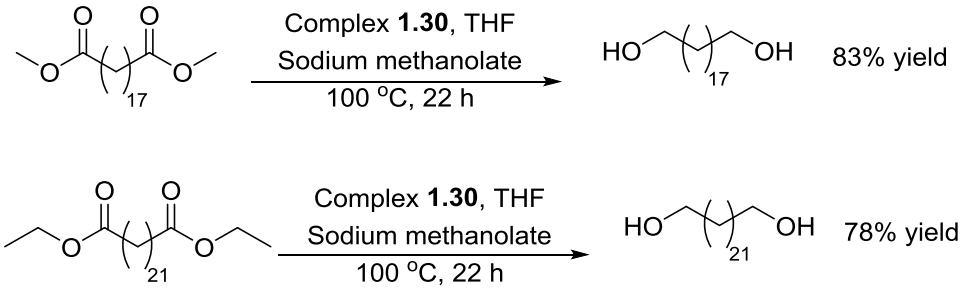


Scheme 1.12. Hydrogenation of methyl *L*-menthoxyacetate. Reagents and conditions: Substrate (160 mmol), Ru-MACHO (0.08 mmol), NaOMe (28% in MeOH, 1.55 g, 8 mmol), MeOH (73.2 mL), H_2 (4.5 MPa), 80 °C, 5 h.[56]

1.2.1.3 Hydrogenation of Fatty Acid Esters

Fatty alcohols are generally used as surfactant precursors industrially. The hydrogenation of fatty acid methyl esters (FAMEs) to the corresponding fatty alcohols is performed on a multimillion ton scale each year using a copper chromate catalyst in industrial plants. Relatively high temperatures (200-300 °C) and hydrogen pressure (200-300 bar) are required.[57] Nowadays, polymer production mainly starts from fossil feedstocks. The development of polymer synthesis from renewable feedstocks is therefore highly desired. Fatty acids obtained from plant oils are attractive starting materials because of their long chain linear segments.

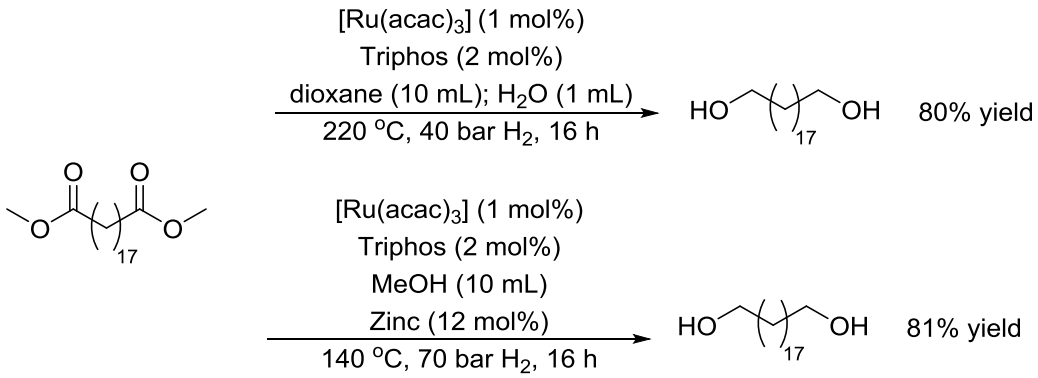
In 2011, Mecking and co-workers[58] successfully hydrogenated the diesters obtained by isomerising methoxycarbonylation of oleic acid ester and erucic acid ester (Scheme 1.13) to their corresponding diols by applying Saudan's ruthenium catalyst, **1.30**.



Scheme 1.13. Hydrogenation of fatty acid-derived di-esters by Mecking and co-workers.[58]

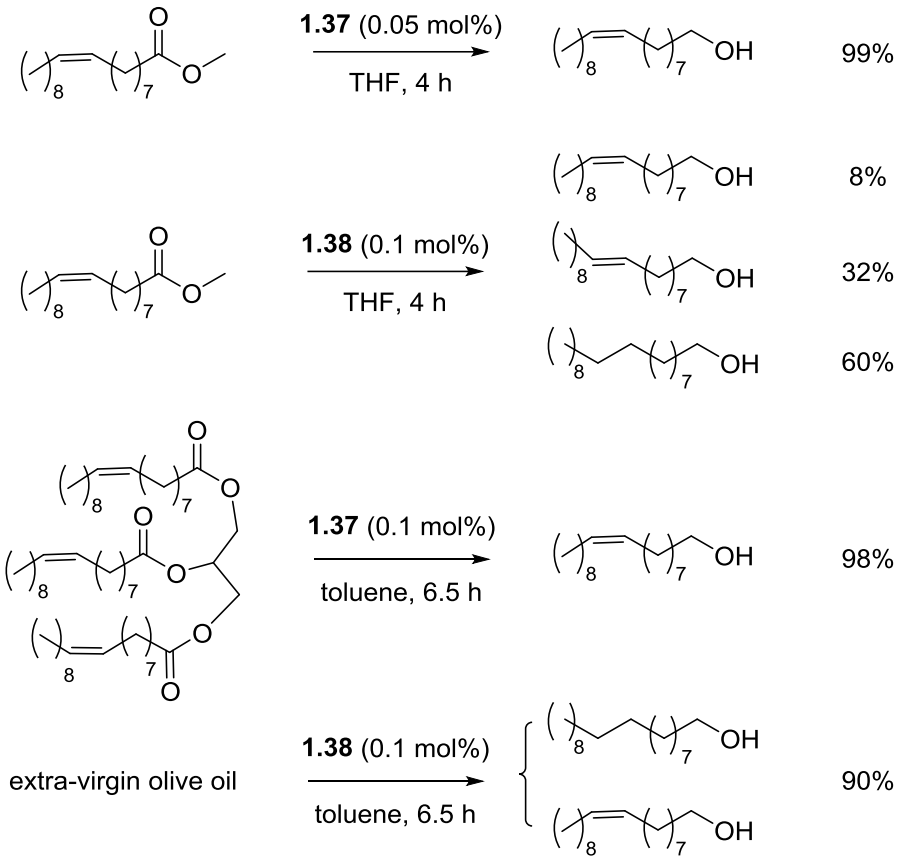
Köckritz and co-workers hydrogenated 1,19-dimethylnonadecanedioate to the nonadecane 1,19-diol in 98% yield using Milstein's catalyst, **1.21**, under less than 10 bar of H_2, 115 °C and 0.5 mol% catalyst loading.[59]

Later in 2011, Cole-Hamilton and co-workers managed to hydrogenate 1,19-dimethyl nonadioate to 1,19-nonadiol using [Ru(acac)$_3$], **1.10**, and triphos, **1.13**.[60] Around 80% yield was obtained either with or without a zinc additive (Scheme 1.14).



Scheme 1.14. Hydrogenation of fatty acid esters by Cole-Hamilton and co-workers.[60]

Fatty acid esters can also be successfully hydrogenated to the corresponding alcohols (Scheme 1.15) by applying the complexes **1.37** and **1.38** developed by Gusev in 2012.[52] Methyl oleate was hydrogenated with complex **1.37** with retention of the C=C double bond. When complex **1.38** was used, the selectivity was lost, and a mixture of *E* and *Z* octadec-9-en-1-ol was obtained, together with a larger percentage of the saturated alcohol. Glyceryl trioleate and a sample of extra-virgin olive oil which contains around 85% oleic acid, 2-3% linoleic acid, and palmitic acids were also tested under this condition. Hydrogenation of glyceryl trioleate afforded *Z*-octadec-9-enol quantitatively (98%). Reduction of the olive oil afford a mixture of oleyl (85%) and palmityl alcohols after aqueous washing.

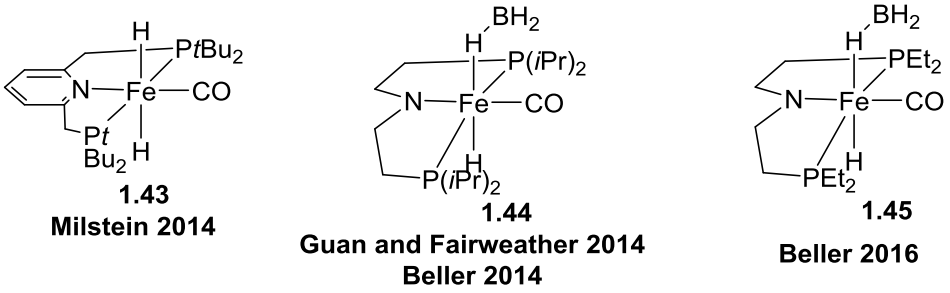


Scheme 1.15. Hydrogenation of fatty acid esters by Gusev and co-workers.[52]

1.2.1.4 Hydrogenation of esters with iron catalysts

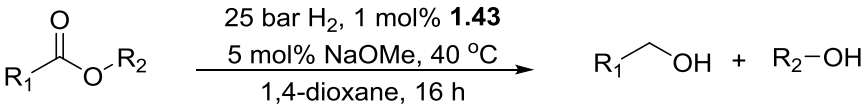
The first example of iron-catalysed hydrogenation of activated ester was reported by Milstein and co-workers in 2014.[61] Trifluoroacetic esters can be efficiently and selectively hydrogenated to the corresponding alcohols by iron pincer complex **1.43** (Scheme 1.16) in the presence a strong base, such as NaOMe. Aliphatic, aromatic and olefinic esters were all successfully hydrogenated to the corresponding alcohols in good to excellent yields and selectivities. Ether (Table 1.10, Entry 2), aryl groups (Table 1.10, Entry 5-8), terminal and internal C=C double bonds (Table 1.10, Entry 3-4) in ester substrates stayed intact under this condition. Esters with bulky substituents at the ester alkoxy group gave much lower reaction rate (Table 1.10, Entry 9). However, increasing reaction time could improve the result (Table 1.10, Entry 10). Esters with only two fluoro substituents at the methyl carbon atom of the acetate moiety, such as ethyl

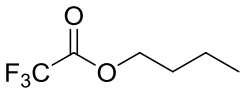
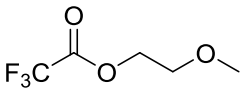
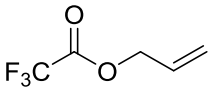
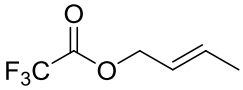
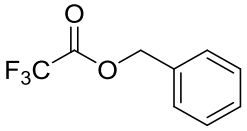
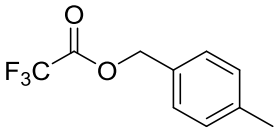
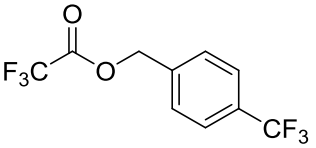
chlorodifluoroacetate, ethyl bromodifluoroacetate and ethyl difluoroacetate, cannot be hydrogenated under these reaction conditions.

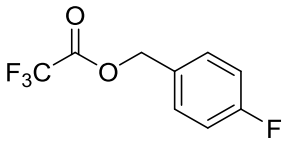
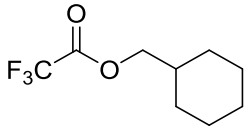


Scheme 1.16. Iron catalysts for the hydrogneation of esters.

Table 1.10. Hydrogenation of esters with Iron catalyst.[a]



Entry	Substrate	Conv. (%)	ref
1		77	61
2		80	61
3		95	61
4		84	61
5		>99	61
6		>99	61
7		>99	61

8		97	61
9		52	61
10[b]		95	61

[(a)]Reaction conditions: Substrate (2.0 mmol), **1.43** (1 mol%), NaOMe (5 mol%), 1,4-dioxane (2 mL), H_2 (25 bar), 16 h, 40 °C, performed in an autoclave. Yields based on integration of the ^{19}F {^1H} NMR spectra of the crude products. [(b)]48 h.

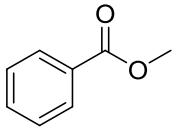
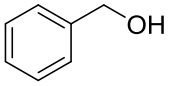
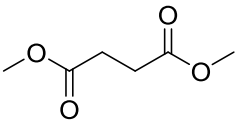
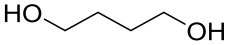
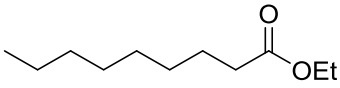
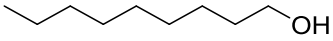
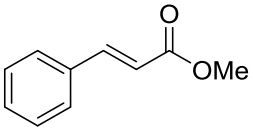
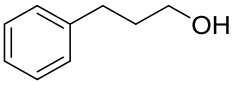
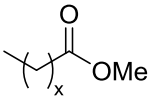
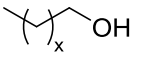
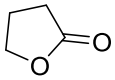
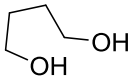
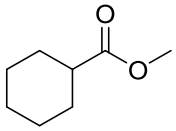
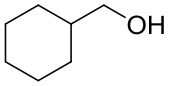
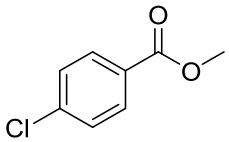
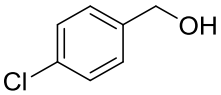
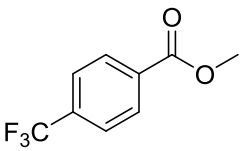
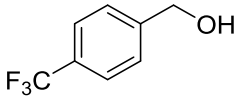
Milstein's iron catalyst is only limited to trifluoroacetic esters. Later in the same year, Fairweather and Guan and Beller's group both reported aliphatic PNP-pincer iron complex, **1.44**, for non-activated ester hydrogenation. Aliphatic and aromatic esters can both be reduced to the corresponding alcohols in excellent yields in the absence of a base (Table 1.11, Entry 1-4). For the hydrogenation of methyl cinnamate, the saturated alcohol is obtained with both C=O and C=C bonds reduced (Table 1.11, Entry 5-6). Fairweather and Guan's group reported that complex **1.44** can also be applied to fatty acid methyl esters under neat conditions (Table 1.11, Entry 7-8).[62] The desired alcohols can be obtained in 99% yield under 52 bar of hydrogen (Table 1.11, Entry 7), while decreasing the hydrogen pressure to 21 bar decreased the yield to 73% (Table 1.11, Entry 8). Addition of a base is detrimental to this hydrogenation reaction.

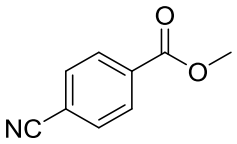
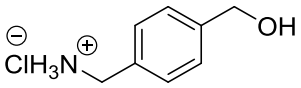
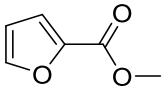
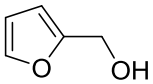
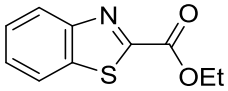
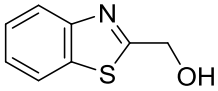
Beller and co-workers[63] extended the substrate scope to nitrile (Table 1.11, Entry 13) and heteroaromatic containing esters (Table 1.11, Entry 14-15) using complex **1.44**. Lactones (Table 1.11, Entry 9) and pharmaceutical intermediate, dodecapetide (Scheme 1.17), can also be reduced to the corresponding alcohols using these conditions. The methyl ester in the dodecapetide is chemoselectively hydrogenated to the alcohol in the presence of an olefin, an acetate, a carbamate, and secondary and tertiary amides (Scheme 1.17).

In 2016, Beller and co-workers[64] developed another PNP iron complex **1.45**, which has less sterically hindered ^{Et2}PNP instead of ^{iPr2}PNP compared to complex **1.44** (Scheme 1.16). Similar results are obtained for both PNP catalysts, **1.44** and **1.45**. Lower

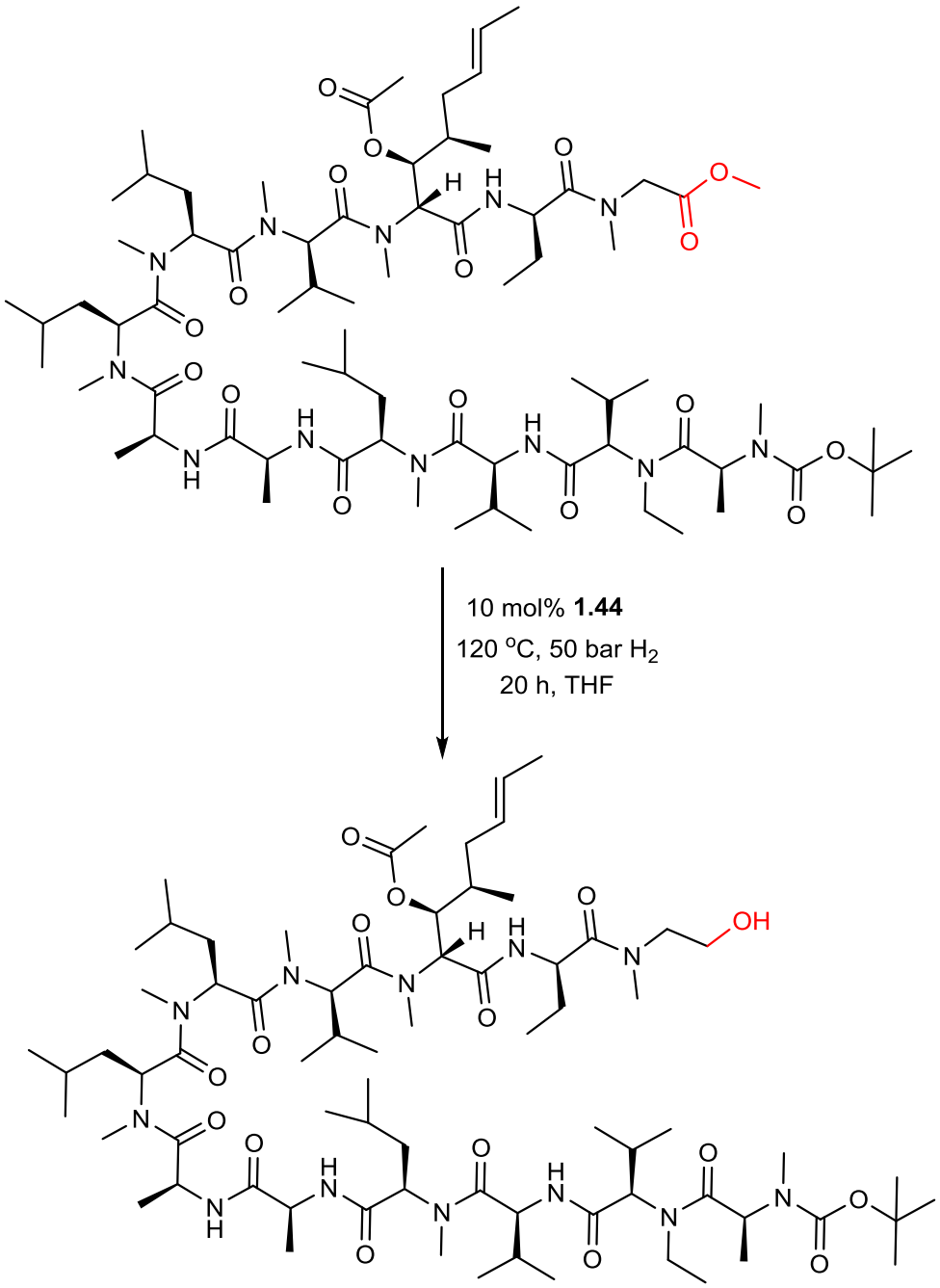
temperature (60 °C) is needed for the latter when hydrogenating simple esters, such as methyl benzoate and methyl cinnamate.

Table 1.11. Hydrogenation with non-activated esters with iron catalysts.

Entry	Substrate	Cat	Product	Conv. (%)	ref
1[a]		**1.44**		92	62
2[f]		**1.44**		97	63
3[b]		**1.44**		75	62
4[c]		**1.44**		91	62
5[c]		**1.44**		93	62
6[f]		**1.44**		99	63
7[d]		**1.44**		99	62
8[e]	x=8,10,12,14	**1.44**	x=8,10,12,14	73	62
9[g]		**1.44**		89	63
10[h]		**1.44**		92	63
11[d]		**1.44**		85	63
12[i]		**1.44**		62	63

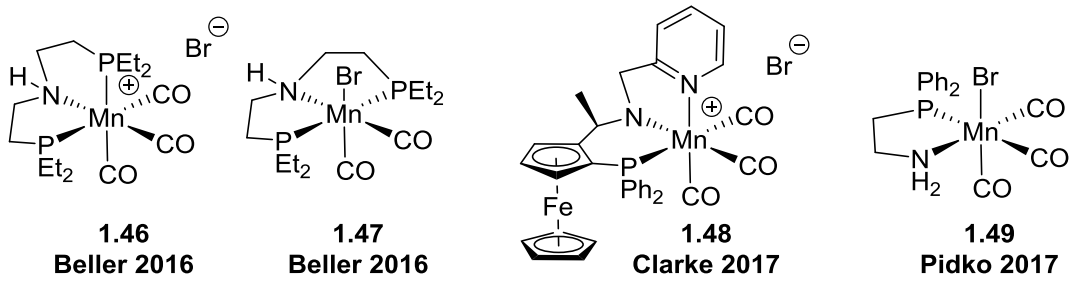
13[h]		**1.44**		86[k]	63
14[h]		**1.44**		90	63
15[d]		**1.44**		63	63

[(a)]Reaction conditions: Substrate (0.83 mmol), **1.44** (25 μmol, 3 mol% loading), toluene (0.5 mL), H_2 (10 bar), 3 h, 115 °C, isolate yield. [(b)]Same as [a], 24 h. [(c)]Same as [(a)], 24 h, H_2 (16 bar). [(d)]Reaction conditions: **1.44** (1 mol% loading), H_2 (52 bar), 3 h, 135 °C, combined GC yield of all fatty alcohols. [(e)]Same as [(d)], H_2 (21 bar). [(f)]Reaction conditions: Substrate (0.5 mmol), **1.44** (0.005 mol), THF (1 mL), H_2 (30 bar), 6 h, 100 °C, yield determined by GC using hexadecane as an internal standard. [(g)]Same as [f], 19 h, 120 °C. [(h)]Reaction conditions: Substrate (2 mmol), **1.44** (0.025 mol), THF (4 mL), H_2 (50 bar), 19 h, 120 °C, yield determined by GC using hexadecane as an internal standard. [(i)]Substrate (0.5 mmol), **1.44** (0.025 mmol), THF (1 mL), H_2 (50 bar), 120 °C, 19 h. [(j)]Same as [(f)], **1.44** (0.025 mmol). [(k)]Yield of isolated HCl salt.



Scheme 1.17. Hydrogenation of a pharmaceutically relevant dodecapeptide.[63]

1.2.1.5 Hydrogenation of ester with Manganese catalysts



Scheme 1.18. Mn catalysts for the hydrogenation of esters.

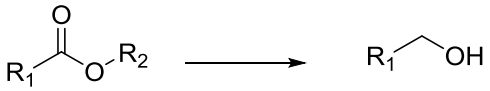
The first manganese-catalyst for ester hydrogenation was reported by Beller in 2016.[65] Complex **1.46** and **1.47** (Scheme 1.18) were found to have the same activity for ester hydrogenation. Esters with electron-donating and electron-withdrawing groups can all be hydrogenated to the corresponding alcohols with moderate to good yields (Table 1.12, Entry 3, 5 and 6). For the hydrogenation of 3-cyclohexene-1-carboxylate (Table 1.12, Entry 8) and methyl oleate (Table 1.12, Entry 23), the double bond remained intact, however, hydrogenation of conjugated methyl cinnamate (Table 1.12, Entry 9) gave the saturated alcohol under these conditions. Lactones (Table 1.12, Entry 11-12) and diesters (Table 1.12, Entry 13-14) can also be converted to the corresponding diols in excellent yields.

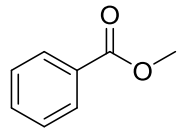
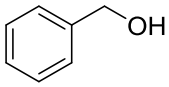
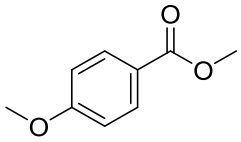
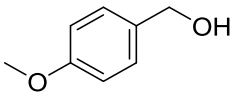
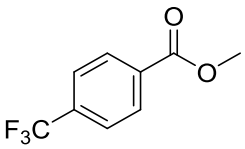
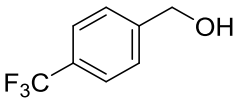
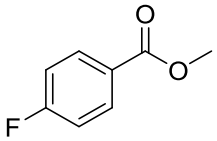
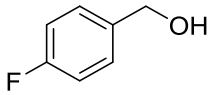
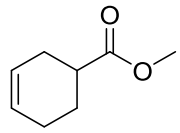
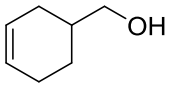
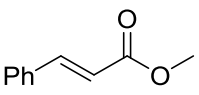
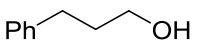
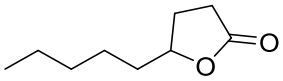
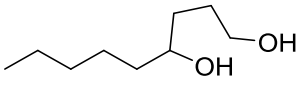
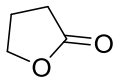
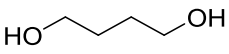
In 2017, Clarke and co-workers published another manganese-PNN type catalyst **1.48** for the hydrogenation of esters.[66] This method can be applied to both aromatic and aliphatic esters with good to excellent yields. Halogens (Table 1.12, Entry 7, 15), amino groups (Table 1.12, Entry 16) and unsaturated bonds (Table 1.12, Entry 20) are all tolerant, however, alkyne groups are also slightly hydrogenated to alkene in around 20% yield. Esters containing a nitro group cannot be converted at all (Table 1.12, Entry 17). Difunctional esters can also be reduced to the corresponding diols under this reaction conditions in excellent yields (Table 1.12, Entry 13-14).

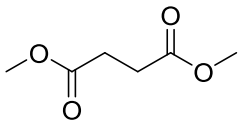
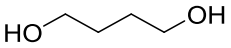
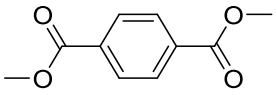
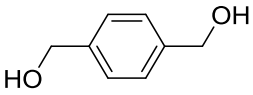
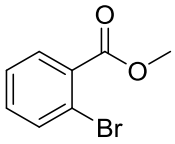
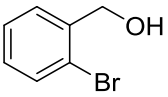
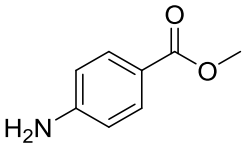
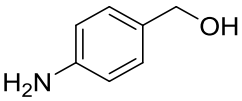
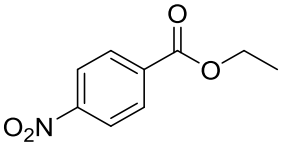
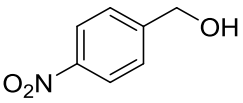
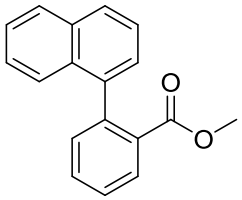
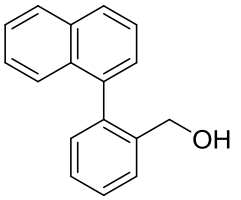
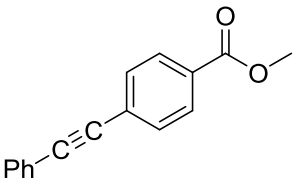
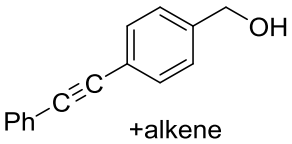
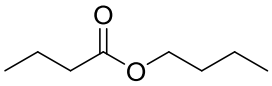
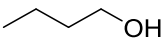
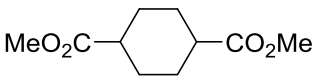
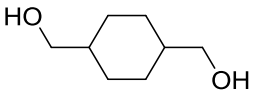
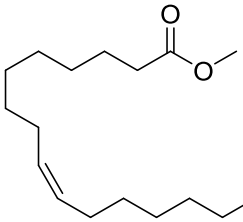
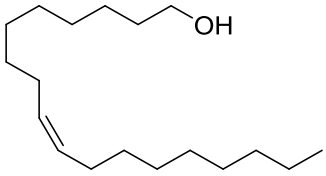
The only non-pincer type Mn PN catalyst (Catalyst **1.49**) was reported by Pidko in 2017.[67] Temperature was found to be crucial for this reaction, in the case of methyl benzoate hydrogenation, 65% yield of benzyl alcohol is obtained with complex **1.49** at 80 °C. Increasing the temperature to 100 °C, 66% yield was obtained, while a further

increase to 120 °C led to a substantial decrease to 43% yield because of the formation of methyl benzyl ether. Aromatic and aliphatic esters can be converted to the alcohols in excellent yields. Similar to Beller's results, hydrogenation of substrates containing an unsaturated bond distant from the ester moiety, leave the unsaturated bond intact (Table 1.12, Entry 24). While, conjugated methyl cinnamate is converted to saturated hydrocinnamyl alcohol (Table 1.12, Entry 10).

Table 1.12. Hydrogenation of esters with Mn catalysts.



Entry	Substrate	Cat.	Product	Conv. (%)	ref
1[a]		**1.46**		97	65
2[h]		**1.49**		95 (87)	67
3[a]		**1.46**		(95)	65
4[h]		**1.49**		89 (81)	67
5[a]		**1.46**		(75)	65
6[a]		**1.46**		(89)	65
7[d]		**1.48**		99 (86)	66
8[c]		**1.46**		93 (83)	65
9[a]		**1.46**		>99 (93)	65
10[i]		**1.49**		99 (99)	67
11[a]		**1.46**		>99 (82)	65
12[a]		**1.46**		>99 (88)	65

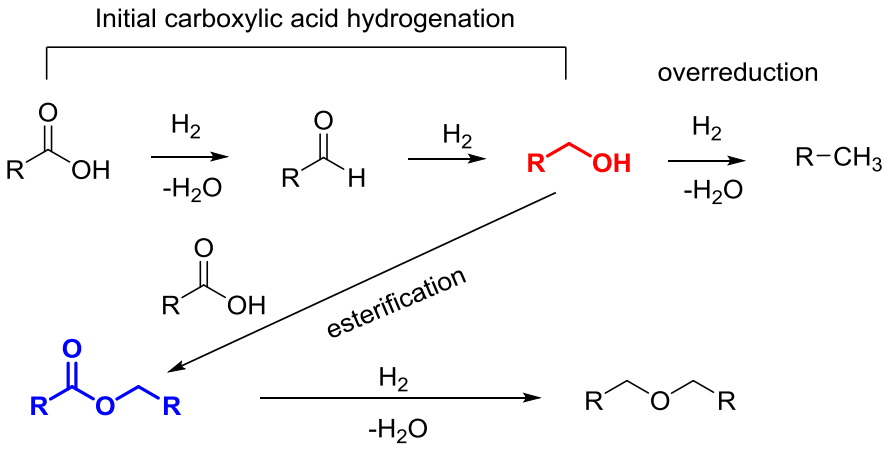
13[b]		**1.46**		>93 (66)	65
14[a]		**1.46**		>99 (95)	65
15[d]		**1.48**		99 (90)	66
16[d]		**1.48**		91 (80)	66
17[d]		**1.48**		0	66
18[a]		**1.46**		(86)	65
19[d]		**1.48**		99 (87)	66
20[d]		**1.48**		99[d,e]	66
21[f]		**1.48**		82	66
22[d]		**1.48**		99 (86)[g]	66
23[a]		**1.46**		95 (89)	65
24[i]		**1.49**		95 (95)	67

[(a)]Reaction conditions: Substrate (1 mmol), **1.46** (2 mol% loading), 1,4-dioxane (2 mL), H_2 (30 bar), 24 h, 110 °C, GC yield using hexadecane as an internal standard. Isolated yields in parentheses. [(b)]Same as [(a)], **1.46** (3 mol% loading), 48 h, 120 °C. [(c)]Same as [(a)], 48 h. [(d)]Reaction conditions: Substrate (0.34 mmol), **1.48** (0.003 mmol), ^{t}BuOK (0.034 mmol), internal standard in isopropanol (0.5 M, 1.6 mL), H_2 (50 bar), 16 h, 75 °C, Conversion was estimated by ^{1}H NMR using 1-methylnaphthalene as internal standard.

[e]^{1}H NMR showed the presence of ≈20% alkene. [f]Same as [a], neat reaction with **1.48** (0.1 mol%), ^{t}BuOK (2 mol%). [g]A 50:50 mixture of *cis* and *trans* isomers. [h]Reaction conditions: Substrate (1 mmol), **1.49** (0.2 mol% loading), 1,4-dioxane (2 mL), H_2 (50 bar), 16 h, 100 °C, yield determined by GC. [i]Same as [h], **1.49** (0.5 mol% loading), 6 h.

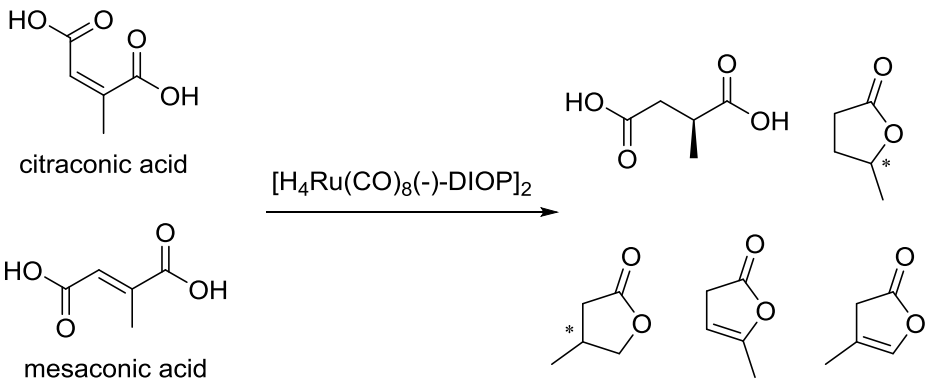
1.2.2 Reduction of carboxylic acids

Hydrogenation of carboxylic acid is also a significant transformation because of its industrial importance. In general, the catalysts for ester hydrogenation should also be effective in carboxylic acid hydrogenation. However, hydrogenation of carboxylic acids is much less selective because of the pathway it undergoes or because of the higher temperature involved (Scheme 1.19). The authors proposed that the carboxylic acid is firstly hydrogenated to the aldehyde, and then to the primary alcohol. However, the produced alcohol could undergo either esterification with the acid or over-reduction to the alkane depending on the activity of catalyst.[21] Alcohols can be obtained as the final products if the catalyst is active enough. Under very harsh condition, the alcohol could also be over-reduced to the alkane, and the ester product may be further hydrogenated to the ether.



Scheme 1.19. Chemoselectivity in carboxylic acid hydrogenation.[21]

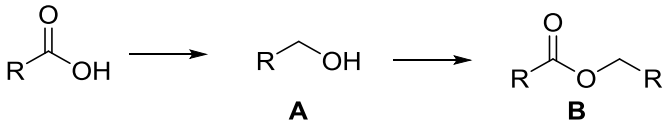
To the best of our knowledge, the first homogeneous hydrogenation of a free COOH group was reported by Bianchi and co-workers in 1977.[68] Citraconic and mesaconic acids were hydrogenated to a mixture of (*S*)-methyl succinic acid, saturated γ-lactones and unsaturated γ-lactones using $[H_4Ru(CO)_8$(-)-DIOP$]_2$ **1.50** (Scheme 1.20) in poor selectivity.

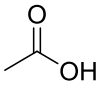
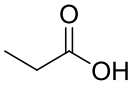
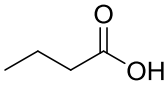
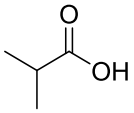
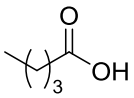


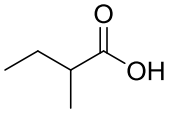
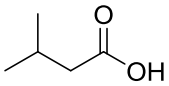
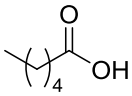
Scheme 1.20. Hydrogenation with $[H_4Ru(CO)_8(-)\text{-DIOP}]_2$, **1.50**.[68]

Bianchi, Matteoli and co-workers tried the neutral ruthenium carbonyl hydride complex $[Ru_4H_4(CO)_8(PBu_3)_4]$, **1.3**, for the hydrogenation reactions of carboxylic acids and their anhydride derivatives in 1980.[21] The reaction required 100 to 200 atm of hydrogen, making the conditions very harsh. The hydrogenation results of *mono*-carboxylic acids and *di*-carboxylic acids are illustrated in Table 1.13 and Table 1.14.

Table 1.13. Hydrogenation of *mono*-carboxylic acids using complex **1.3**.[a]



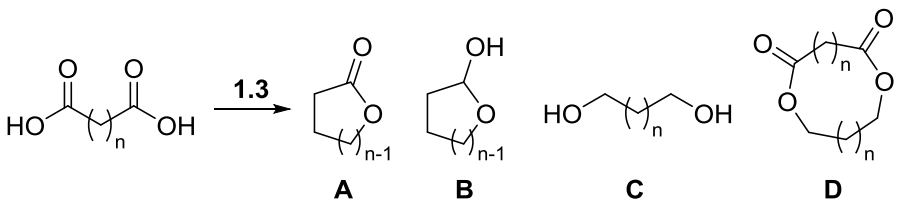
Entry	Substrate	T(°C)	Conv. (%)	Sel. A (%)	Sel.B (%)	ref
1		180	37.5	-	100	21
2		200	69.5	28	72	21
3		200	46.7	9.5	90.5	21
4		200	73.9	10	90	21
5		200	38.6	6	94	21
6		200	26	-	100	21

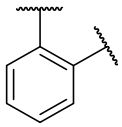
7		200	21.2	-	100	[21]
8		200	18.2	-	100	[21]
9		200	2	-	100	[21]

[a]Condtions: Substrate (220 mmol), complex **1.3** (25 mg), H_2 (132 bar), 48 h.

For the hydrogenation of mono-carboxylic acids, the conversion and the alcohol selectivity both increase when the temperature increases from 180 °C to 200 °C (Table 1.13, Entry 1 and 2). The conversion of the reaction decreases as the steric bulk of the substrates increases with butanoic acid as an exception (Table 1.13, Entry 4). The rate of the reaction decreases for branched substrates, and the conversion is much lower compared to the linear compounds (Table 1.13, Entry 4 vs. 5).

Table 1.14. Hydrogenation of *di*-carboxylic acids using complex **1.3**.[a]



Entry	n	Cat.	T(°C)	Conv.	Sel. A (%)	Sel. B (%)	Sel. C (%)	Sel. D (%)	ref
1	2	**1.3**	180	100	100	-	-	-	[21]
2	3	**1.3**	180	76.2	4.8	63.5	13	18.7	[21]
3	3	**1.3**	200	96.8	2.9	28.7	47.7	20.7	[21]
4	4	**1.3**	220	27	100	-	-	-	[21]
5		**1.3**	200	100	100	-	-	-	[21]

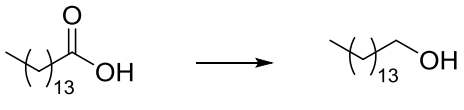
[a]Conditions: Substrate (22 mmol), solvent dioxane (30 mL), complex **1.3** (100 mg), H_2 (132 bar), 48 h.

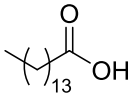
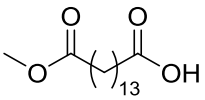
Succinic acid was fully converted to the corresponding lactone in 100% selectivity at 180 °C (Table 1.14, Entry 1). However, the selectivity of glutaric acid decreases

dramatically even at higher temperature (200 °C). Four compounds can be formed including δ-valerolactone (A, n=3), 2-hydroxytetrahydropyran (B, n=3), 1,5-pentanediol (C, n=3) and the cyclic diester 1,7-dioxacyclododecane-2,6-dione (D, n=3) (Table 1.14, Entry 2 and 3). Hydrogenation of adipic acid gave purely ε-caprolactone in 100% selectivity albeit with low conversion. The conversion did not exceed 27% even at 220 °C (Table 1.14, Entry 4). Aromatic dicarboxylic acids gave excellent conversion (100%) and selectivity to the lactone (100%) under the same conditions.

In 1995, Fuchikami and co-workers developed catalysts containing mixtures of late transition metal compounds (Group 8 to 10) and early transition metal carbonyls (Group 6 or 7) for the selective conversion to alcohols (Table 1.15).[69] Tetradecanoic acid was selectively converted to tetradecanol in up to 97% yield at 160 °C (Table 1.15, Entries 1-3). Dicarboxylic acid monoesters (Table 1.15, Entry 4 and 5) can be hydrogenated to both the ester alcohols and the diols, but the reduction is more effective on the carboxylic acid moiety rather than the ester moiety (88% yield of ester alcohol and 7% yield of diol).

Table 1.15. Hydrogenation of carboxylic acid with two metal complexes.[a]



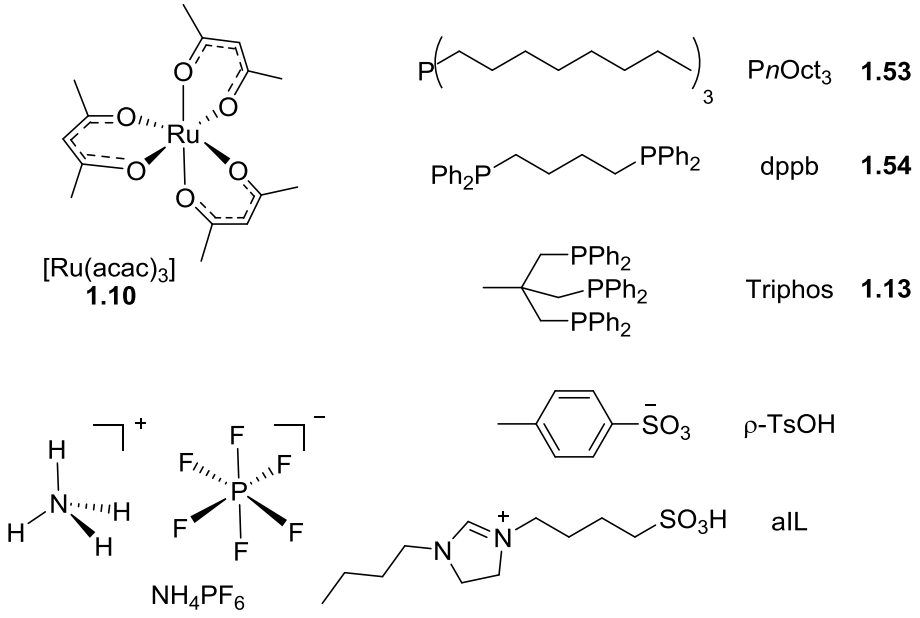
Entry	Substrate	Cat. 1	Cat. 2	T (°C)	Yield (%)	ref
1		$[Rh(acac)_3]$	$[Re_2(CO)_{10}]$	160	97	69
2		$[Rh(acac)_3]$	$[Mo(CO)_6]$	160	93	69
3		$[Ru_3(CO)_{12}]$	$[Re_2(CO)_{10}]$	160	95	69
4[b]		$[Rh(acac)_3]$	$[Re_2(CO)_{10}]$	160	88[c]	69
5[b]		$[Rh(acac)_3]$	$[Mo(CO)_6]$	170	85[c]	69

[(a)]Substrate (1 mmol), catalyst (0.01 equiv.), DME (1 mL), 16 h, H_2 (101 bar). [(b)]Substrate (0.5 mmol). [(c)]Yield to the ester alcohol; 7% yield to the diol for Entry 4; 11% yield to the diol for Entry 5.

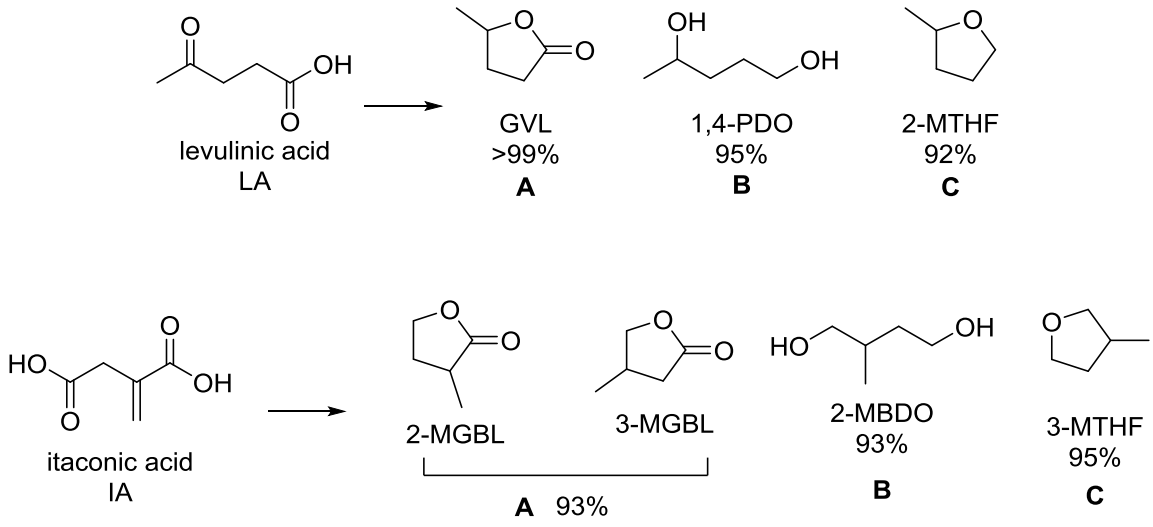
In 2005, Frediani and co-workers developed ruthenium complexes, $[Ru_2(CO)_4(\mu\text{-}MeCOO)_2(PBu_3)_2]$, **1.51**, and $[Ru_4(CO)_8(\mu\text{-}MeCOO)_4(PBu_3)_2]$, **1.52**, for the

hydrogenation of acetic acid.[70] However, only around 30% yield of ethyl acetate was obtained with 0.03 mol% of catalyst loading at 180 °C for 48 h.

Hydrogenations of levulinic acid (LA) and itaconic acid (IA), two compounds that can be obtained from renewable resources were studied by Leitner and co-workers in 2010 because of the industrial applications of the products which can be used as fuels, chemicals solvents and materials.[71] [Ru(acac)$_3$], **1.10**, was used together with various phosphine ligands (**1.13**, **1.53**, **1.54**) to produce the lactone, diol and cyclic ether (Scheme 1.21 and Scheme 1.22). The selectivity to different products highly depends on the ligands and additives used. The different conditions are summarised in Table 1.16.



Scheme 1.21. Catalysts and additives for the hydrogenation of LA and IA.[71]



Scheme 1.22. Hydrogenation of LA and IA and the maximum yield for the possible products under different conditions as shown in Table 1.16.[71]

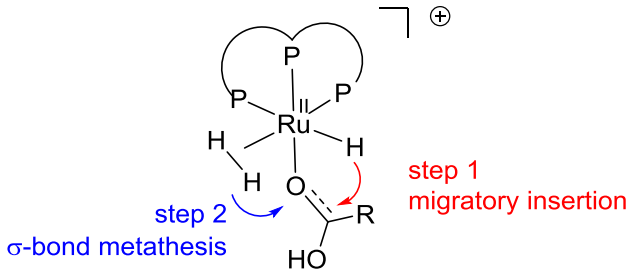
Table 1.16. Hydrogenation of LA and IA.

Entry	Substrate	Cat.	additive	T (°C)	Conv (%)	Yield A (%)	Yield B (%)	Yield C (%)	ref
1[a]	LA	**1.10**+ **1.53**	NH_4PF_6	160	100	>99	0	0	[71]
2[a]	LA	**1.10**+ **1.13**	-	160	100	3	95	0	[71]
3[a]	LA	**1.10**+ **1.13**	aIL+ NH_4PF_6	160	100	1	0	92	[71]
4[b,c]	IA	**1.10**+ **1.54**	-	195	95	80	2	0	[71]
5[b,d]	IA	**1.10**+ **1.13**	-	195	>99	6	93	0	[71]
6[b]	IA	**1.10**+ **1.13**	ρ-TsOH +NH_4PF_6	195	>99	2	0	97	[71]

[(a)]Conditions: LA (10 mmol), **1.10** (0.1 mol%), **1.53** (1 mol%) or **1.13** (0.2 mol%), 1 mol% additive, 18h, H_2 (100 bar). [(b)]Conditions: IA (2.4 mmol), **(1.10** (0.5 mol%), **1.54** or **1.13** (0.6 mol%), 2 mol% additive, 18 h, H_2 (100 bar), dioxane (2 mL). [(c)]THF (2 mL) used as solvent. [(d)]Dioxane (1 mL).

LA was selectively converted in over 99% yield to GVL when P*n*Oct$_3$ was used as ligand together with [Ru(acac)$_3$], **1.10**, in the presence of NH_4PF_6 as additive (Table 1.16,

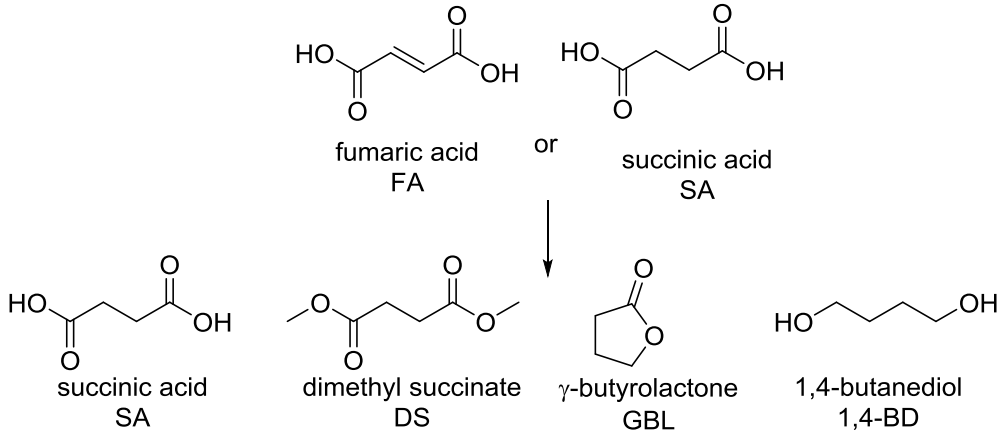
Entry 1). In comparison, 1,4-PDO could be obtained in 95% yield in the absence of additive (Table 1.16, Entry 2). When a combination of aIL (acid ionic liquid) and NH_4PF_6 was added, 2-MTHF was selectively obtained in 92% yield (Table 1.16, Entry 3). With the successful results in hand, the studies moved on to IA hydrogenation. A 1.2:1 mixture of 2- and 3-MGBL was achieved in 80% yield when DPPB was used as the ligand in the absence of the additive (Table 1.16, Entry 4). The selectivity of 2-MBDO improved to 93% when triphos was used without additives (Table 1.16, Entry 5). A combination of p-TsOH and NH_4PF_6 gave 97% yield of 3-MTHF (Table 1.16, Entry 6). The mechanism of this reaction was further explored by the same group in 2011 by using density functional theory (DFT) together with NMR analysis.[72] This reaction was believed to take place *via* a cationic cycle starting with hydride transfer from the catalyst to the carbonyl carbon followed by σ-bond metathesis (Scheme 1.23).



Scheme 1.23. Cationic cycle including hydride transfer and σ-bond metathesis.[72]

In 2010, Frediani and co-workers studied the hydrogenation of unsaturated and saturated dicarboxylic acids by applying the $[Ru(acac)_3]$, **1.10** /triphos, **1.13**, system.[73] Fumaric acid was hydrogenated to a mixture of compounds as shown in Table 1.17. When the reaction was carried out for 16 h, only a trace amount of 1,4-butanediol (1,4-BD) was obtained (Table 1.17, Entry 1), while when the reaction time was increased, the yield of 1,4-BD increased, reaching 56% after 96 h (Table 1.17, Entry 4). When succinic acid was used as the substrate, a slightly better selectivity to 1,4-BD was obtained compared to fumaric acid (Table 1.17, Entry 5). Changing the solvent from methanol to THF decreased the 1,4-BD selectivity from 23% to 0% while the selectivity of SA and GBL increased significantly (Table 1.17, Entry 6). Higher temperatures were preferred for the formation of 1,4-BD, and the yield improved to 81% at 180 °C (Table 1.17, Entry 8).

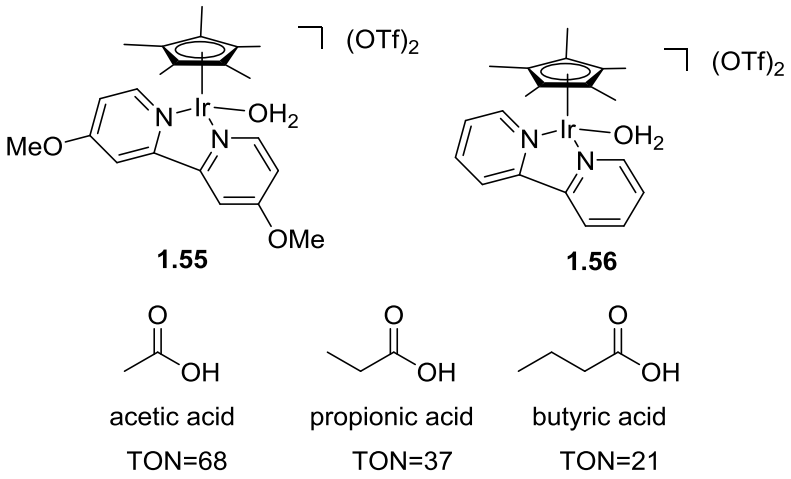
Table 1.17. Hydrogenation of fumaric acid and succinic acid with [Ru(acac)$_3$], **1.10** /triphos **1.13**.[a]



Entry	Substrate	t (h)	solvent	T (°C)	Yield SA (%)	Yield DS (%)	Yield GBL (%)	Yield 1,4-BD (%)	ref
1	FA	16	MeOH	120	38	48	14	Trace	[73]
2	FA	48	MeOH	120	3	38	36	23	[73]
3	FA	72	MeOH	120	2	37	31	30	[73]
4	FA	96	MeOH	120	2	28	14	56	[73]
5	SA	48	MeOH	120	3	12	56	29	[73]
6	FA	48	THF	120	52	-	48	-	[73]
7	FA	48	MeOH	150	4	11	33	52	[73]
8	FA	48	MeOH	180	1	9	9	81	[73]

[(a)]Substrate (1.770 mmol), solvent (12 mL), H_2 (80 bar), [Ru(acac)$_3$], **1.10** (0.021 mmol), triphos, **1.13** (0.029 mmol), Zn (4.6×10^{-3} mmol).

In 2013, Goldberg and co-workers developed a series of iridium complexes for carboxylic acid hydrogenation, and among them, catalyst **1.55**, shown in Scheme 1.24, was found to be the most active.[74] Hydrogenation results for acetic, propanoic and butanoic acids are summarised in Scheme 1.24. The reaction was carried out at 120 °C, and 30 bar of H_2 for 18 h in the presence of 3:1 H_2O/HBF_4. As the chain length of the carboxylic acid increased from acetic acid (C_1) to butyric acid (C_3) a decrease in reactivity was observed. The decreasing reactivity is mostly likely due to the increasing electron donating ability of the alkyl chain, the carboxylate carbon becomes more electron-rich and less electrophilic for the iridium hydride to attack.

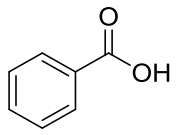
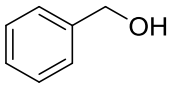
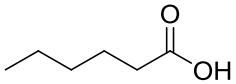
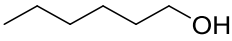


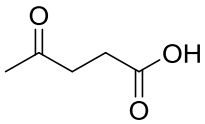
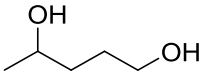
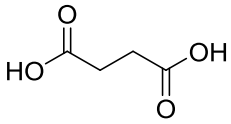
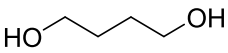
Scheme 1.24. Structure of complexes and substrates used and turnover numbers obtained under 30 bar of H_2, 120 °C and 18 h in the presence of complex **1.55**.

Goldberg and co-workers reported the first catalyst, **1.56**, for the disproportion of formic acid to methanol, carbon dioxide and water in 2013.[75] This reaction was carried out with 0.0083 mol% of catalyst at 80 °C for 24 h in aqueous solution, affording a TON of 156 in the absence of hydrogen and organic solvent. The selectivity to methanol was low (7%), but this reaction has the potential to be an important method for the renewable production of methanol.

In 2014, Leitner and co-workers reported another complex [Ru(triphos)(TMM)], **1.16**, for carboxylic acid hydrogenation.[29] This catalyst is also active for ester and amide hydrogenation as described in Section 1.2.1 and 1.2.3. The results for hydrogenation of various carboxylic acids are illustrated in Table 1.18.

Table 1.18. Hydrogenation of carboxylic acids with [Ru(triphos)(TMM)], **1.16**.[a]

Entry	Substrate	Product	t (h)	Temp (°C)	Conv. (%)	Sel. (%)	ref
1[b]			24	220	93	95	29
2			16	195	50	98	29

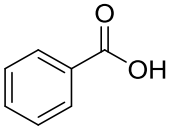
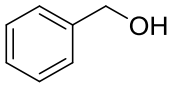
3			16	140	99	99	29
4			24	195	92	92	29

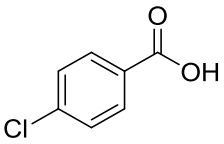
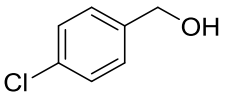
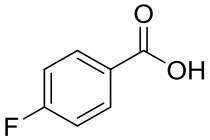
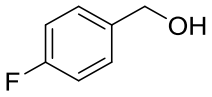
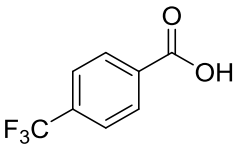
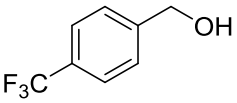
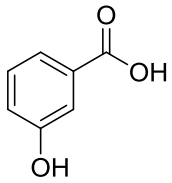
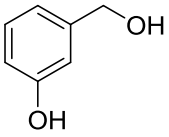
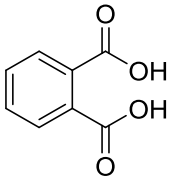
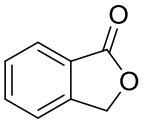
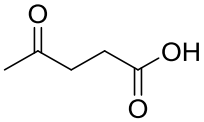
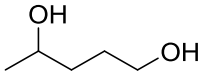
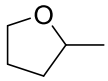
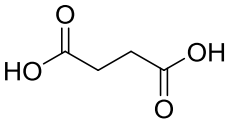
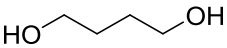
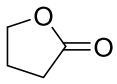
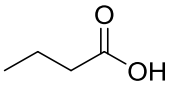
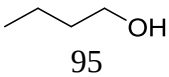
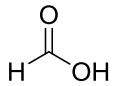
[(a)]Conditions: Substrate (1 mmol), [Ru(triphos)(TMM)], **1.16** (0.02 mmol), 1,4-dioxane (1 mL), H_2 (50 bar), conversion and selectivity determined by ^{1}H NMR using mesitylene as internal standard. [(b)] [Ru(triphos)(TMM)], **1.16** (0.01 mmol).

Aromatic (Table 1.18, Entry 1), aliphatic (Table 1.18, Entry 2) and dicarboxylic acids (Table 1.18, Entry 3 and 4) were all successfully hydrogenated to the corresponding alcohols in excellent selectivity (above 92%) under additive free conditions. However, the conversion of hexanoic acid was only 50% (Table 1.18, Entry 2). Cyclisation which usually occurs *in situ* during dicarboxylic acid hydrogenation was not observed for succinic acid in the absence of strong acid (Table 1.18, Entry 4). The aromatic ring is tolerated under this condition (Table 1.18, Entry 1), while the keto- group is hydrogenated to the alcohol (Table 1.18, Entry 3).

The use of earth-abundant and cheap cobalt was developed in 2015 by de Bruin and co-workers for the hydrogenation of carboxylic acids and esters.[76] A combination of $Co(BF_4)_2{\cdot}6H_2O$, **1.57**, and triphos, **1.13**, gives high conversion and yield for both aliphatic and aromatic acids under relatively mild conditions (100 °C, 80 bar H_2) (Table 1.19).

Table 1.19. Hydrogenation with Co catalyst, **1.57**/**1.13**.[a]

Entry	Substrate	Cat. Loading (mol%)	Conv. (%)	Product (yield %)	Ref
1[b]		2.5	>85	 62	76

2		5	>99	 82	76
3		5	>99	 96	76
4		5	98	 98	76
5		5	>90	 89	76
6		2.5	>99	 71	76
7		10	>99	 47  14	76
8		2.5	>85	 61  23	76
9		5	>99	 95	76
10		0.5	>99	MeOH 76	76

[(a)]Conditions: Substrate (0.15 M), 1:1 ratio of $Co(BF_4)_2.6H_2O$, **1.57**, and triphos, **1.13**, distilled THF, H_2 (80 bar), 100 °C, 22 h. [(b)]4 h.

Aromatic (Table 1.19, Entry 1-6) and aliphatic carboxylic acids (Table 1.19, Entry 7-9) were converted to the corresponding alcohols in excellent yields and good to excellent selectivities. Electron withdrawing and donating substituents on the aromatic ring did not have a significant impact on the results (Table 1.19, Entry 1-5). Hydrogenation of LA and succinic acid gave 47% and 61% yield to the corresponding diols, which are

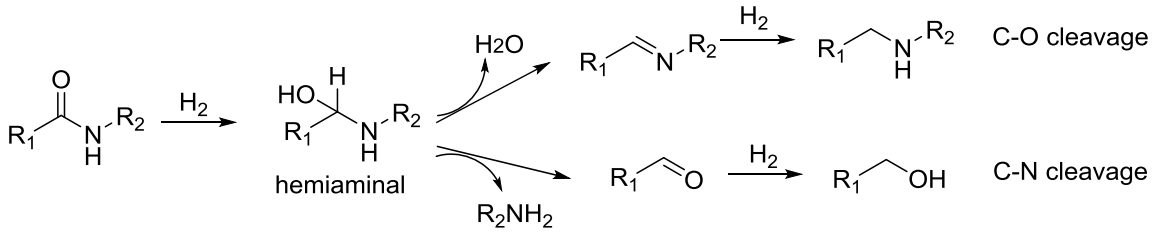
much lower than the results obtained by Leitner in 2014 (Table 1.18, Entry 3 and 4).[29] Formic acid was hydrogenated to methanol in 76% yield with 0.5 mol% catalyst loading, which is a noteworthy improvement compared to Goldberg's catalyst (7%), although the mechanism is different.[75]

Conclusion

To the best of our knowledge, the ruthenium complex, [Ru(triphos)(TMM)], **1.16**, is the best catalyst for the selective hydrogenation of carboxylic acids to alcohols so far with perfect conversion and selectivity. Earth-abundant cobalt was also found to be active in the carboxylic acid hydrogenation with good yield. However, higher catalyst loadings (2.5-10 mol%) are required compared to the use of ruthenium catalysts. The low cost of cobalt, however, means that the higher catalyst loading may still provide a cheaper catalytic system.

1.2.3 Reduction of amides

Amines are an important class of chemicals because of their use in organic synthesis.[77] Amines have a high annual production, and have a large variety of applications, such as the production of dyes and drugs. Amides can be reduced to amines using $LiAlH_4$[78] or borane[79] as reducing agents which are not only difficult to handle and remove during work up, but also produce a large amount of waste. Catalytic hydrogenation will only produce water as a by-product which is much more environmental friendly and easier to separate from the desired products. Due to the scarcity of environmentally friendly catalytic hydrogenation reactions for amides, the American Chemical Society Green Chemistry Institute (GCI) and the Pharmaceutical Round Table members identified amide hydrogenation as one of their priority reactions in 2005.[80] Homogeneous catalytic hydrogenation of amides can undergo two possible pathways: C-N cleavage and C-O cleavage (Scheme 1.25).[14] Amide hydrogenation using homogeneous and heterogeneous catalysts have recently been reviewed.[81]



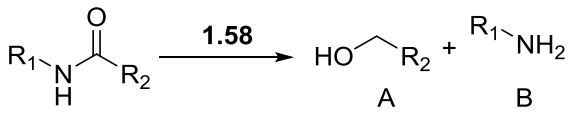
Scheme 1.25. Reduction of amides through C-O cleavage and C-N cleavage.[14]

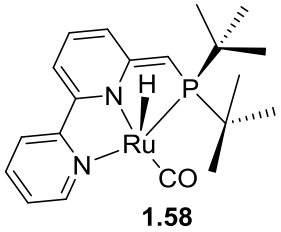
1.2.3.1 C-N Cleavage

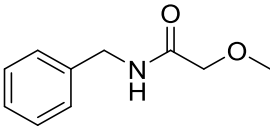
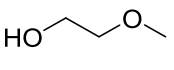
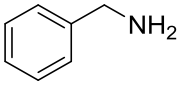
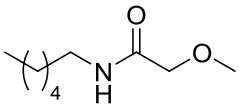
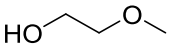
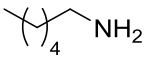
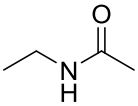
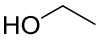
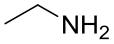
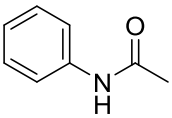
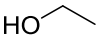
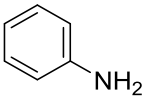
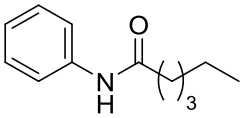
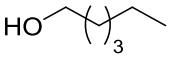
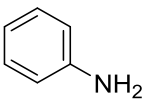
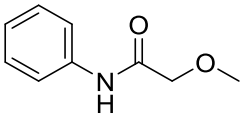
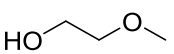
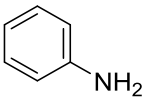
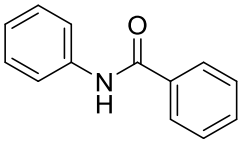
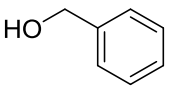
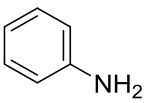
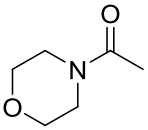
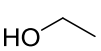
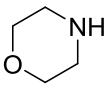
Amides can be hydrogenated to the corresponding alcohol and amine though C-N cleavage. Although some C-N bond cleavage was observed in early hydrogenations of propanamide catalysed by [Ru(acac)$_3$], **1.10**, in the presence of 1,1,1-tri(diphenylphosphinemethyl)ethane (triphos, **1.13**),[82] the predominant products arose from C-O cleavage, see Section 1.2.3.2.

A PNN ligand together with a ruthenium complex was later found to be a good catalytic system for amide hydrogenation *via* selective C-N cleavage. Ruthenium complexes of 6-di-*tert*-butylphosphinomethyl-2,2'-bipyridine (BPy-*t*-PNN), **1.58**, can effectively hydrogenate amides to amines and alcohols with no additives needed. The reaction was carried out under anhydrous conditions, and hydrolytic cleavage of the amide is not involved in this reaction.[83] A summary of representative amide hydrogenation to alcohols using BPy-*t*-PNN as ligand is depicted in Table 1.20.

Table 1.20. Amide hydrogenation with ruthenium complex of (BPy-*t*-PNN) ligand, **1.58**.





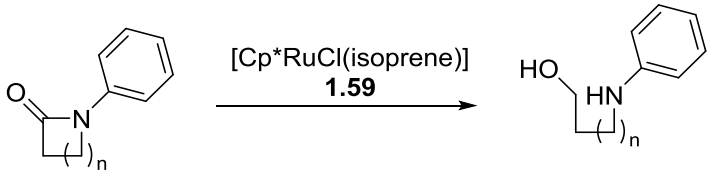
Entry	Substrate	Products		Yield[b] A (%)	Yield[b] B (%)	Ref
		A	B			
1				89	90	83
2				91	90	83
3				71	-[c]	83
4				94	95[d]	83
5				92	92	83
6				95	95	83
7				92	91	83
8				97	98	83

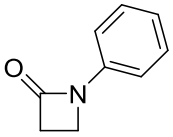
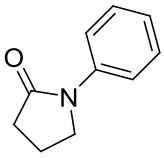
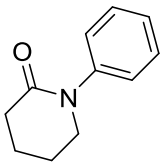
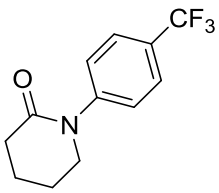
[a]Conditions: Complex **1.58** (0.01 mmol), amide (1 mmol), H_2 (10 atm), and dry THF (2 mL) were heated in a Fischer-Porter tube at 110 °C (bath temperature) for 48 h. [b]Yields of products were analyzed by GC. [c]The amines ($EtNH_2$) were analyzed in the gas phase by GC-MS. [d]In the reactions involving anilide derivatives (Entries 4-7), trace amounts of the corresponding secondary amines were detected by GC-MS.

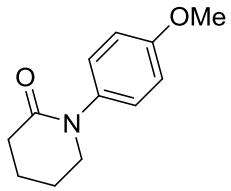
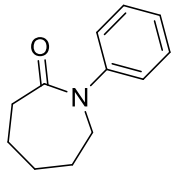
Amide hydrogenation afforded the corresponding alcohols and amines in high yields, and no C-O hydrogenolysis took place at all. Aliphatic and aromatic amides with different chain lengths were tested, and good yields were achieved under these conditions (Table 1.20, Entry 1-7). Heterocyclic amides also afforded the alcohols and amines in up to 98% yield (Table 1.20, Entry 8). Mild conditions (110 °C) are required when using BPy-PNN-Ru (II) hydride pincer catalyst for this amide C-N cleavage hydrogenation reaction.

Ikariya and co-workers reported similar findings in 2011 using lactams as substrates.[84] Linear amino alcohols are obtained *via* this C-N cleavage using [Cp*RuCl(isoprene)] **1.59** and a ligand (Table 1.21).

Table 1.21. Hydrogenation of lactams using [Cp*RuCl(isoprene)], **1.59**.[a]

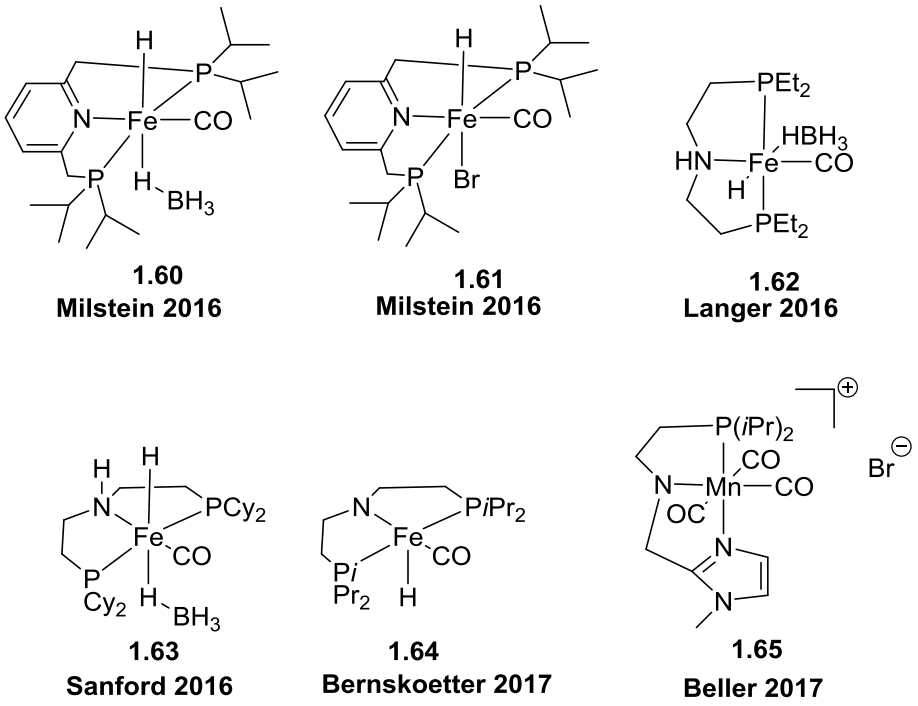


Entry	Substrate	Conv. (%)	Yield[b] (%)	ref
1		>99	83	84
2		84	73	84
3		>99	96	84
4		>99	90	84

5		88	78	[84]
6[c]		60	60[d]	[84]

[(a)]Conditions: lactam (1 M in 2-propanol), [Cp*RuCl(isoprene)], **1.59** (10 mol%), KO*t*-Bu (25 mmol), 100°C, H_2 (50 bar), 24 h. [(b)]Isolated yield. [(c)]72 h. [(d)]Product yield determined by ^{1}H NMR spectroscopy, using triphenylmethane as an internal standard.

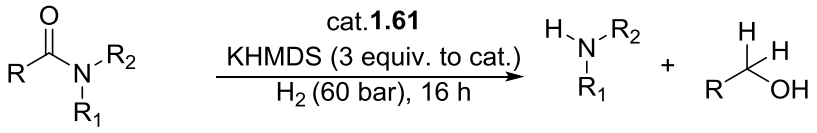
A series of lactams was studied, and reactions with 4- and 6-membered ring lactams gave high conversions (up to 99%) (Table 1.21, Entry 1, 3-5). However, lactams with 5- or 7- membered rings gave much lower conversions and yields (Table 1.21, Entry 2 and 6). Lactams with an electron withdrawing group do not have a significant impact on the results (Table 1.21, Entry 4). However, a methoxy group led to a 10% decrease of the conversions and yields (Table 1.21, Entry 5).

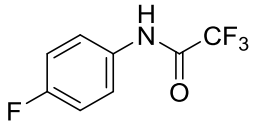
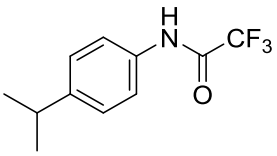
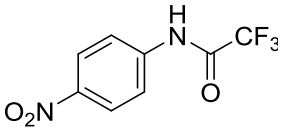
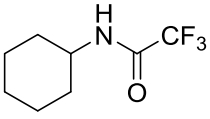
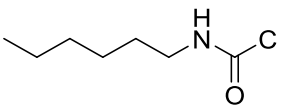


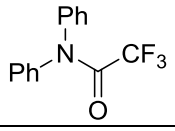
Scheme 1.26. Fe and Mn catalysts for the hydrogenation of amides.

Other earth-abundant metal complexes have also been studied for amide hydrogenation. The first examples of iron complexes, **1.60** and **1.61**, containing PNP ligands were reported in 2016 by Milstein.[85] However, these complexes only work on activated amides (Table 1.22). Both of the complexes gave very similar results. Activated amides with a *para* fluro or isopropyl group on the aromatic ring can be hydrogenated to the corresponding amines and alcohols in excellent yields (Table 1.22, Entry 1 and 2). For the amide with a nitro group at the *para* position, the conversion was only 25% after 24 h (Table 1.22, Entry 3). Aliphatic and cyclohexyl amides gave much poorer conversions even with an increased catalyst loading and longer reaction time (Table 1.22, Entry 4 and 5). A tertiary amide also worked under these reaction conditions with a very high conversion (Table 1.22, Entry 6).

Table 1.22. Hydrogenation of activated amides using catalyst **1.61**.[a]



Entry	Substrate	mol%	Time (h)	Conv. (%)	product		ref
					alcohol	Amine	
1		2	12	99	99	99	85
2		2	12	99	99	99	85
3		2	24	25	25	25	85
4		5	36	35	36	34	85
5		5	36	23	23	22	85

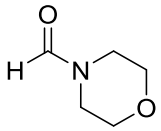
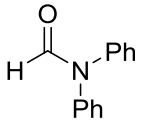
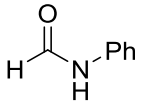
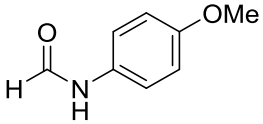
6		5	36	99	99	99	[85]

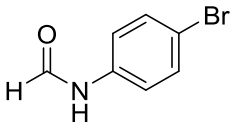
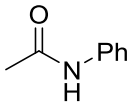
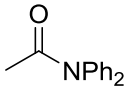
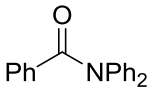
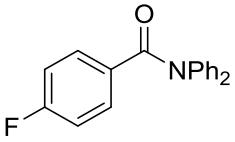
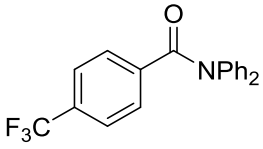
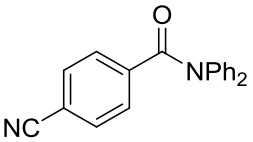
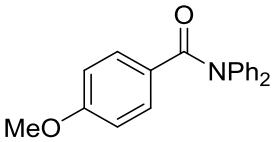
[(a)]Conditions: **1.61** (2-5 mol%), KHMDS (3 equiv. to catalyst), 1,4-dioxane, 140 °C, H_2 (60 bar),12-36 h. Conversion of the amide and yield of amine were calculated by GC using mesitylene as internal standard and TFE yield is based on ^{19}F NMR.

Langer and co-workers developed another PNP-Fe catalyst, **1.62**, in 2016.[86] *N*-phenylbenzamide and 2,2,2-trifluoro-*N*-phenylacetamide can be quantitatively converted to the corresponding alcohols and amines using 2 mol% catalyst loading of **1.62** in THF, 50 bar of hydrogen at 70-100 °C for 24 hours. *N*-substituted-γ-lactams can be converted to the corresponding amino alcohols under these conditions in moderate yields. However, δ-lactams cannot be converted at all.

Sanford[87] and Bernskoetter[88] broadened the substrate scope for amide hydrogenation by using iron catalysts, **1.63** and **1.64**, which worked for formamide, secondary and tertiary amides (Table 1.23). Substrates with electron withdrawing groups gave better results compare to the ones with electron donating groups for both formamides (Table 1.23, Entry 7-10) and tertiary amides (Table 1.23, Entry 14-16 and 18). Nitrile group was also hydrogenated using catalyst **1.63** (Table 1.23, Entry 17).

Table 1.23. Hydrogenation of formamides, secondary and tertiary amides.

Entry	substrate	Cat	Conv. (%)	Yield (%)	TON	ref
1[a]		**1.63**	>99	>99[b]	300	[87]
2[c]		**1.64**	>97	-	1360	[88]
3[a]		**1.63**	>99	99	300	[87]
4[c]		**1.64**	85	-	1190	[88]
5[a]		**1.63**	>99	95	300	[87]
6[c]		**1.64**	>99	-	>1390	[88]
7[a]		**1.63**	69	57	207	[87]
8[c]		**1.64**	>99	-	>1390	[88]

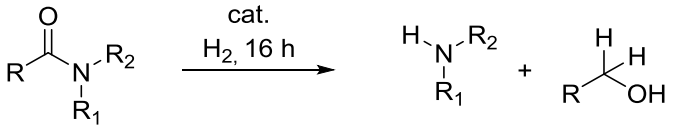
9[a]		**1.63**	>99	96	300	87
10[c]		**1.64**	>99	-	>1390	88
11[d]		**1.63**	>99	88	50	87
12[c]		**1.64**	<5	-	50	88
13[d]		**1.63**	>99	96	50	87
14[e]		**1.63**	>99	99	25	87
15[e]		**1.63**	>99	99	25	87
16[e]		**1.63**	>99	94	25	87
17[e,f]		**1.63**	>99	94	25	87
18[e]		**1.63**	<1	<1	<1	87

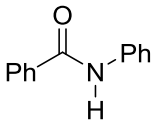
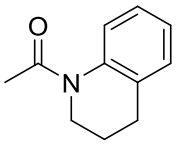
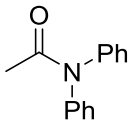
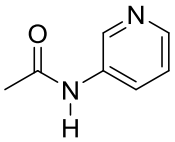
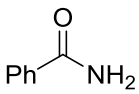
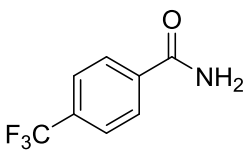
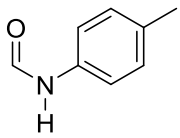
[(a)]Conditions: amide (3 mmol), **1.63** (10 μmol), K_3PO_4 (50 μmol), THF (2 mL), 110 °C, H_2 (20 bar), 3h. Yields are isolated yields of the amine product. Conversions and TONs (based on ROH) were determined by ^{1}H NMR spectroscopy. [(b)]Yield determined by ^{1}H NMR spectroscopy. [(c)]Conditions: amide (7 mmol), **1.64** (0.07 mol%), THF (5 mL), 100 °C, H_2 (50 bar), 4h. Conversions and TONs (based on ROH) were determined by ^{1}H NMR spectroscopy and GC analysis. [(d)]Conditions: amide (0.5 mmol), **1.63** (10 μmol), K_3PO_4 (50 μmol), THF (2 mL), 110 °C, H_2 (30 bar), 3 h. Yields are isolated yields of the amine product. Conversions and TONs (based on ROH) were determined by ^{1}H NMR spectroscopy. [(e)]Same as [(d)], amide (0.25 mmol), **1.63** (10 μmol), K_3PO_4 (50 μmol), THF (2 mL), 130 °C, H_2 (50 bar), 3 h. [(f)]The nitrile functional group was also hydrogenated.

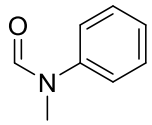
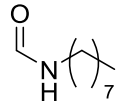
A single example of a manganese catalyst for the hydrogenation of amides was reported by Beller in 2017.[89] Catalyst **1.65** containing imidazolyaminolphosphino ligand (Scheme 1.26) gave high activity and selectivity in the hydrogenation of a large range of

amides including formamides (Table 1.24, Entry 7-9), secondary (Table 1.24, Entry 1 and 4), tertiary (Table 1.24, Entry 2 and 3) and primary aromatic amides (Table 1.24, Entry 5 and 6). However, aliphatic *N*-alkyl amides such as *N*,*N*-dimethyloctanamide or non-activated *N*-alkyl substituted benzamides did not work under this condition. Herbicide diflufenican can also be hydrogenated to the corresponding alcohol and amine under mild conditions for the first time (Scheme 1.27).

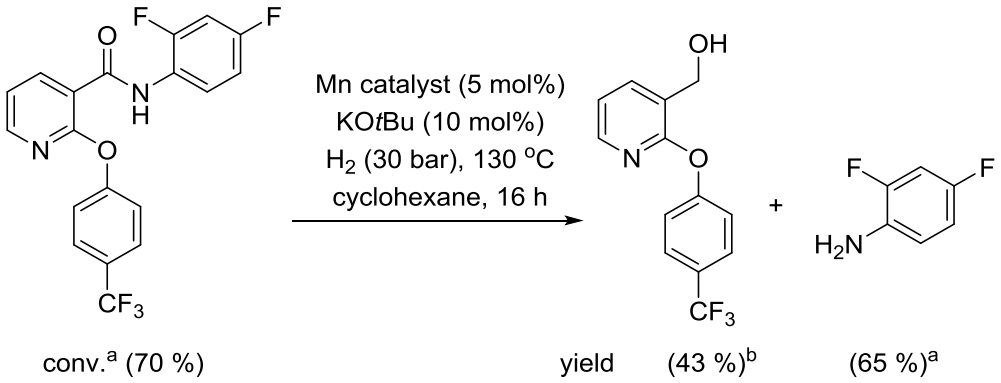
Table 1.24. Hydrogenation of amides using Mn catalyst, **1.65**.[a]



Entry	Amide	Cat. Loading (mol%)	Conversion (%)	Yield of amine (%)	Yield of alcohol (%)	ref
1		2	>99	96	90	89
2		2	94	88	85	89
3		4	85	82	80	89
4[b]		4	>99	>99	90	89
5[c]		5	50	n.d.	40	89
6[d]		5	65	n.d.	60	89
7[e]		2	>99	95	90	89

8[e]		2	90	85	80	[89]
9[e]		2	83	83	80	[89]

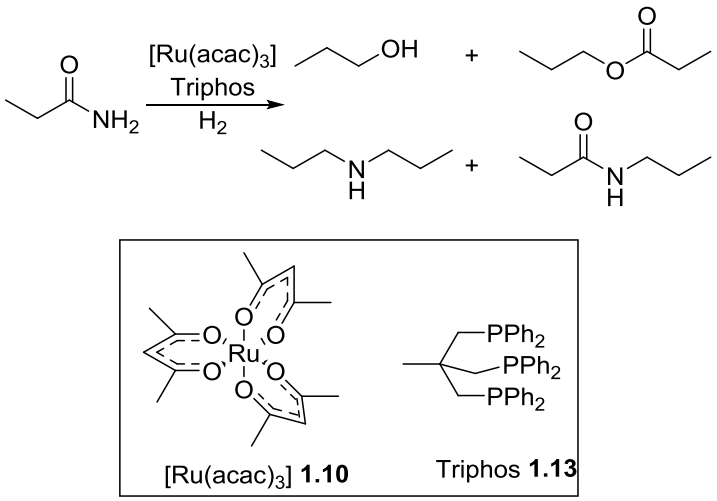
[(a)]Conditions: amide (1 mmol), **1.65** (2-5 mol%), KO^{t}Bu (2.8 mg, 0.025 mmol, 10 mol%), cyclohexane (2 mL), 100 °C, H_2 (30 bar),16 h. Conversion of the amide and yield of the alcohol and amine were calculated by GC using hexadecane as external standard. [(b)]Same as [(a)], cyclohexane/^{t}amylOH (1.5/0.5) mixture is used as solvent, run at 120 °C. [(c)]Amide (0.25 mmol), **1.65** (5 mol%), KO^{t}Bu (3 equiv. to Mn), cyclohexane/^{t}amylOH mixture (1.5/0.5) (2 mL), 140 °C, H_2 (50 bar), 48 h. [(d)]Same as [(c)], 24 h. [(e)]Amide (0.25 mmol).



Scheme 1.27. Selective hydrogenation of diflufenican to the corresponding alcohol and amine catalysed by Mn complex **1.65**. Conditions: diflufenican (98.6 mg, 0.25 mmol), **1.65** (5.92 mg, 0.0125 mmol, 5 mol%), KO*t*Bu (2.8 mg, 0.025 mmol, 10 mol%), cyclohexane (2 mL), 100 °C, H_2 (30 bar),16 h. [(a)]Conversion of the amide and yield of the amine were calculated by GC using hexadecane as external standard. [(b)]The yield was calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as external standard.

1.2.3.2 C-O Cleavage

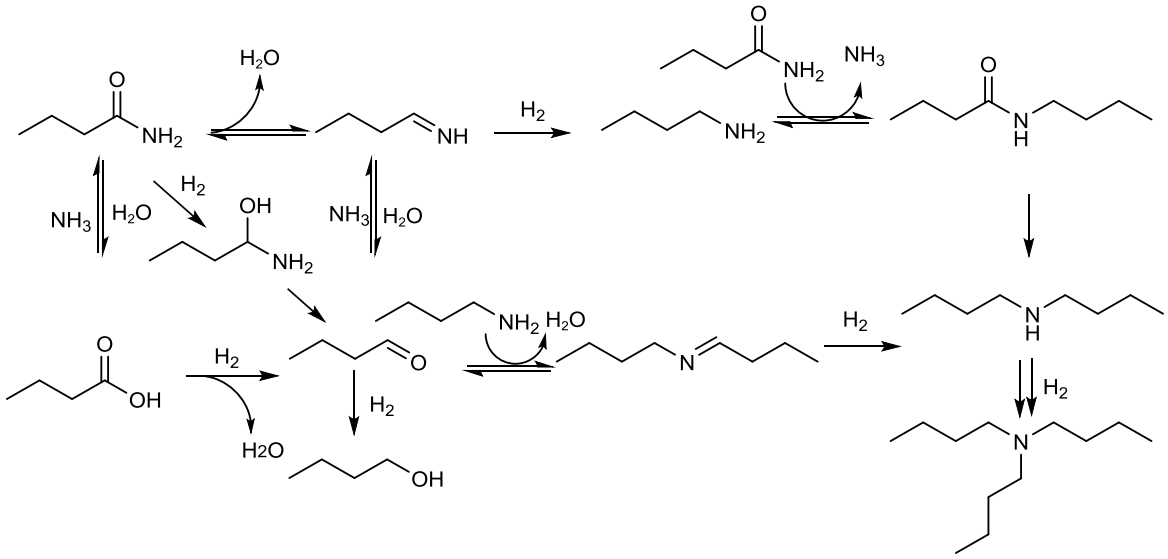
The first homogeneous catalytic hydrogenation of amides was developed by Crabtree and co-workers in 2003.[27] At 164 °C, propanamide was reduced to a mixture of products (dipropylamine, propanol, *N*-propyl propanamide and propyl propanoate, but not the primary amine, propylamine) with [Ru(acac)$_3$], and 1,1,1-tris(diphenylphosphinemethyl)ethane (triphos), **1.13** (Scheme 1.28). This system has been known to be active for carboxylic acid and ester hydrogenation since 1997.[82]



Scheme 1.28. First homogeneous catalytic amide hydrogenation.[82]

Homogeneous hydrogenation of amides to amines through apparent C-O cleavage has been developed by Cole-Hamilton and co-workers[90] following the work of Crabtree and co-workers.[27] They have successfully hydrogenated amides to primary or secondary amines under mild conditions.

When using butanamide as a substrate under [Ru(acac)$_3$], **1.10**/triphos, **1.13**, conditions, none of the desired primary amine was formed, and it gave a mixture of products, including the secondary amine, tertiary amine, secondary ester, secondary amide and alcohol (Table 1.25, Entry 1). A proposed mechanism (Scheme 1.29) can be used to explain the absence of primary amines. Initially formed primary amine may react with the starting primary amide, giving secondary amide; or it can react with an aldehyde, formed by amide hydration and partial hydrogenation of the carboxylic acids, to give imine. Both the secondary amide and imine can then be hydrogenated to the corresponding secondary amine. Repeating of the cycle could give the tertiary amine. The mechanism shown in Scheme 1.29 suggested that, in the presence of ammonia, the three steps (hydrolysis of amide, hydrolysis of imine, and transamidation of primary amide to secondary amide) may be reversed, and this may favour the production of the desired primary amine. The use of aqueous ammonia can increase the selectivity to the primary amine to 85% (Table 1.25, Entry 6 and 7).



Scheme 1.29. Proposed mechanism of butanamide hydrogenation.[90]

Table 1.25. Butanamide hydrogenation with ammonia.[a]

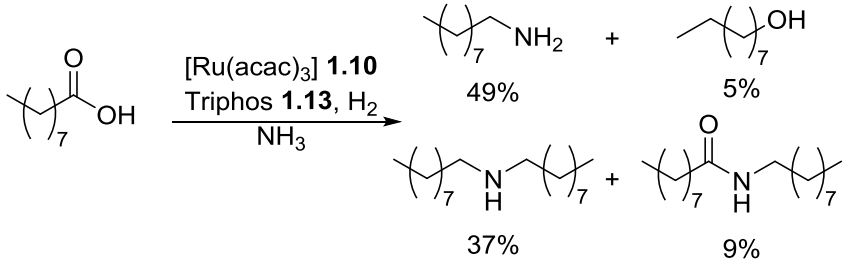
Entry	1[c]	2 [c]	3	4	5	6	7	8	9[d]
H_2O: THF[b]	0.1	0.01	0.1	0.1	-	-	-	-	-
NH_3(aq):THF[b]	-	-	-	-	0.3	0.5	0.7	1	1
NH_3(l):THF[b]	-	-	0.5	1	-	-	-	-	-
1° Amine	0	0	44	36	78	85	85	73	75
Alcohol	Trace	Trace	8	3	12	15	15	25	25
2° Amide	Trace	Trace	10	14	10	0	0	2	0
2° Amine	46	48	38	6	0	0	0	0	0
3°Amine	53	51	0	0	0	0	0	0	0
Conv. (%) ref	100 90	100 90	100 90	59 90	100 90	100 90	100 90	100 90	100 90

[(a)]Conditions: Butanamide (1 g, 11.4 mmol), $[Ru_2(triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), 220 (°C), H_2 (40 bar), THF (10 mL). [(b)]v/v. [(c)] $[Ru(acac)_3]$ (45 mg, 0.1 mmol) and triphos (142 mg, 0.2 mmol) used instead of $[Ru_2(triphos)_2Cl_3]Cl$. [(d)]NH_3 (4 bar).

The use of liquid ammonia gave full conversion with 44% selectivity to the corresponding primary amine (Table 1.25, Entry 3). With a higher concentration of liquid ammonia, the yield was decreased to 59%, while the primary amine selectivity increased to 61% (Table 1.25, Entry 4). Aqueous ammonia could also increase the selectivity to the primary amine to as high as 85% as the ammonia concentration was increased as well (Table 1.25, Entry 5 to 7). When a large excess of aqueous ammonia was used, the concentration of water also increased, which increased the rate of amide and imine hydrolysis, leading to a decrease of primary amine selectivity (Table 1.25,

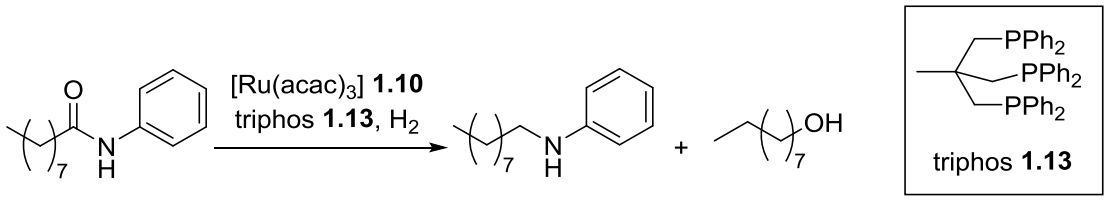
Entry 8). The combined use of aqueous ammonia and ammonia gas did not make a significant difference (Table 1.25, Entry 9).

Nonanoic acid can also be hydrogenated to its primary amine with 49% selectivity using the ruthenium-triphos catalyst in the presence of aqueous ammonia (aqueous ammonia: THF ratio=0.5) (Scheme 1.30).[90]



Scheme 1.30. Hydrogenation of nonanoic acid in the presence of ammonia.[90]

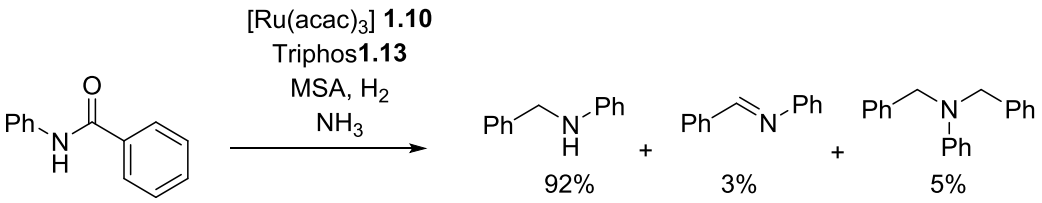
Hydrogenation of *N*-phenylnonanamide using the ruthenium-triphos catalyst in THF at 164 °C (220 °C internal temperature) and 40 bar of H_2 gave 100% conversion and 93% selectivity to the secondary amine in the presence of low water levels (Scheme 1.31). The selectivity is even higher in the absence of water (99%), however, water was thought to be essential to stabilise the catalyst.



Scheme 1.31. Hydrogenation of *N*-phenylnonanamide using ruthenium-triphos catalyst.[90]

An improved procedure was published in 2012 by Cole-Hamilton and co-workers because of the reproducibility issues in the previous report.[91] In this paper, they reported the importance of using an acid. The role of MSA in the reaction was studied using high pressure NMR spectroscopy. MSA is used to generate the active catalytic species, and to control the protonation-deprotonation sequence for high turnover frequency. The nature of the autoclave material is crucial, the reaction works well in Hastelloy™, but hydrogenation of the aromatic rings takes place when using stainless steel. The use of a glass liner in a stainless steel autoclave can reduce this problem and leads to successful

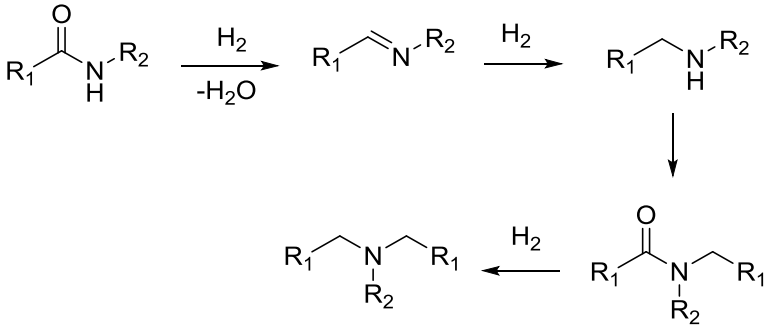
conversion. The reaction of benzanilide with the ruthenium-triphos system in the presence of methanesulfonic acid at 220 ˚C under hydrogen produces *N*-benzylaniline with high selectivities (Scheme 1.32).



Scheme 1.32. Reagents and conditions: amide (5 mmol), [Ru(acac)$_3$] (1.10) (1 mol%), triphos (**1.13**) (2 mol%), THF (10 mL), 220 °C, Hastelloy^{TM} autoclave. H_2 (10 bar at r.t.), MSA (0.5 mol%), 16 h, 100% conversion.[91]

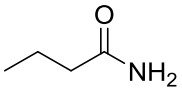
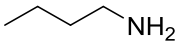
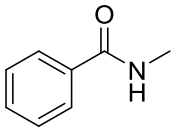
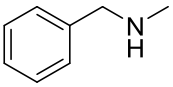
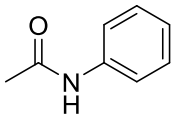
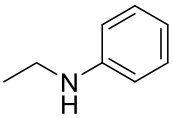
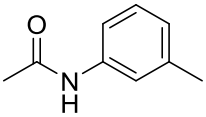
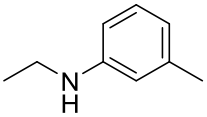
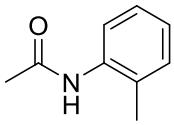
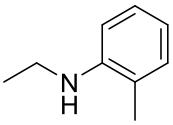
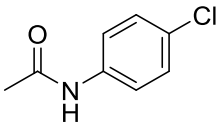
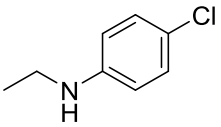
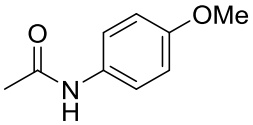
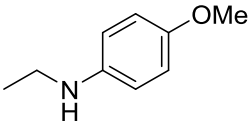
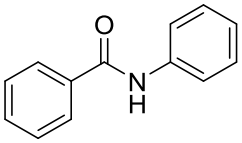
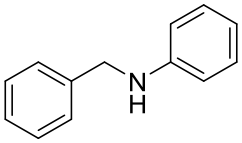
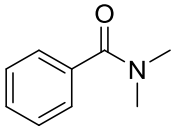
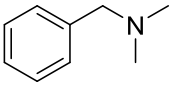
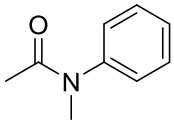
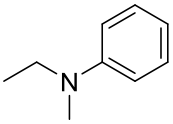
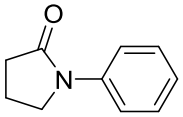
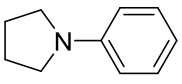
This method has been tested for reproducibility by RWTH Aachen with *N*-phenylacetamide with the optimal conditions shown above. Only 51% conversion was achieved after 16 h at 10 bar of H_2 because of the limited amount of H_2 in the autoclave. Increasing the pressure to 75 bar led to a 100% conversion of the starting material. More than 90% selectivity to the desired amine has been obtained in these reactions.

Dibenzylaniline, aniline, *N*-benzylideneaniline together with the *N*-benzylaniline could be produced using the benzanilide hydrogenation conditions, a proposed reaction scheme is shown in Scheme 1.33 to explain the origin of the products, with an important observation being that small amounts of imine are present in the product mixture. Hydrogenation results of various amides are combined in Table 1.26.



Scheme 1.33. Origin of various products during the hydrogenation of amides.[91]

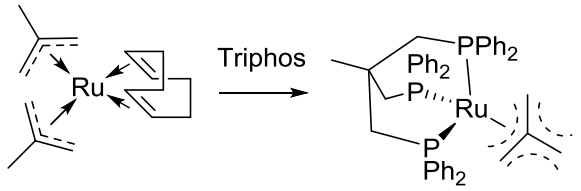
Table 1.26. Substrate scope for amide hydrogenation with [Ru(acac)$_3$], **1.10**/triphos, **1.13**.[a]

Entry	Substrate	Conv.[b](%)	Product	Sel.[b] (%)	ref
1[c]		100		61	91
2		82[d]		<5[d]	91
3		100		92	91
4		100		79	91
5		100		90	91
6		64		28	91
7[e,f]		97		78	91
8[e,f]		100		92	91
9[f]		33[d]		7[d]	91
10		19		63	91
11		19		100	91

[(a)]amide (5 mmol), [Ru(acac)$_3$], **1.10** (1 mol%), triphos, **1.13** (2 mol%), MSA (1.5 mol%), THF (10 mL) and H_2 (10 bar) at 200 °C, 16 h. [(b)]Conversion and selectivity calculated by NMR integration. [(c)]Reaction performed in the presence of aq. NH_3 (10 mL).[(d)]Based on uncalibrated GC-FID integration.[(e)]MSA (1.0 mol%). [(f)]at 220 °C.

Butanamide can be hydrogenated in the presence of aqueous ammonia to the primary butylamine with moderate selectivity (61%). The results for secondary and tertiary amide hydrogenation in Table 1.26 show that good conversions and selectivities are higher if there is a phenyl group on nitrogen (Table 1.26, Entry 3-8). When there is a methyl group on nitrogen, the selectivity was only 5% for the secondary amine (Table 1.26, Entry 2) and 7% for the tertiary amine (Table 1.26, Entry 9). Hydrogenation of lactam has a high selectivity (100%), but with a very poor conversion (19%). This Ru-triphos system can be extended to tertiary amides albeit with reduced yields even with an aromatic ring attached to the nitrogen (Table 1.26, Entry 10).

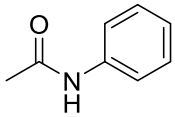
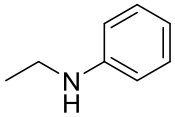
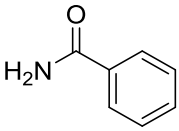
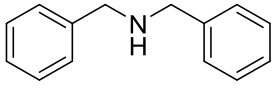
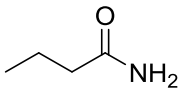
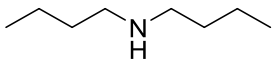
[Ru(triphos)(TMM)], **1.16**, (see Sections 1.2.1 and 1.2.2) which can be synthesised by a one-step reaction with commercially available [Ru(cod)(methallyl)$_2$] and triphos, **1.13**, (Scheme 1.34) is also active for amide hydrogenation (Table 1.27)[29] through either a neutral or cationic path way with high yields.



1.16

Scheme 1.34. Synthesis of catalyst [Ru(triphos)(TMM)], **1.16**.[29]

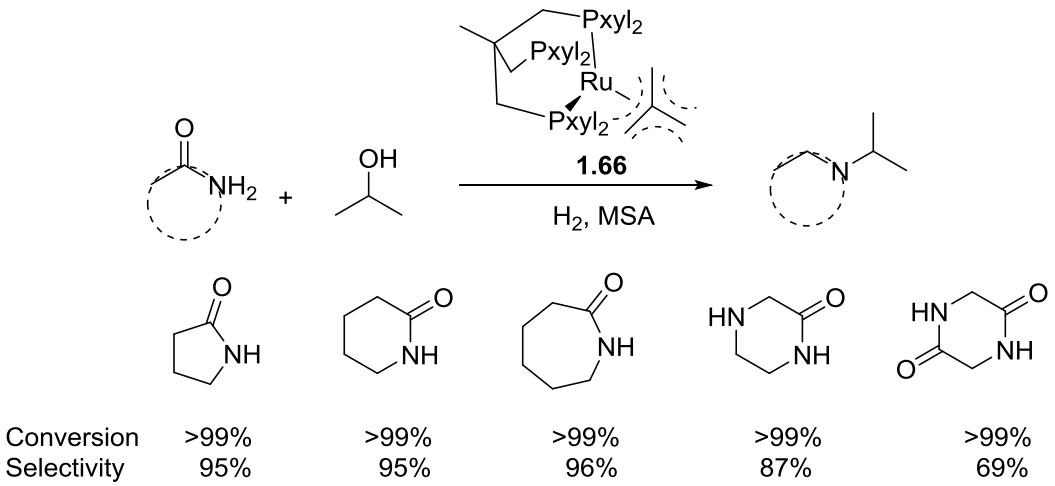
Table 1.27. Hydrogenation of amides with [Ru(triphos)(TMM)], **1.16**.[a]

Entry	Substrate	Conv.[b](%)	Product	Sel.[b](%)	ref
1[c]		99		99	29
2		99		98	29
3		99		99	29

[a]amide (1 mmol), [Ru(triphos)(TMM)], **1.16** (2 mol%), $HNTf_2$ (3 mol%), dioxane (1 mL) and H_2 (50 bar) at 160°C, 16 h. [b]Conversion and selectivity determined by ^1H NMR using mesitylene as internal standard. [c]No acid additive $HNTf_2$.

Hydrogenation of secondary amides with [Ru(triphos)(TMM)], **1.16**, gave the corresponding secondary amines in high conversion and selectivity. (Table 1.27, Entry 1) However, the hydrogenation of aliphatic and aromatic primary amides, only resulted in the selective formation of the secondary amines (Table 1.27, Entry 2 and 3).[29]

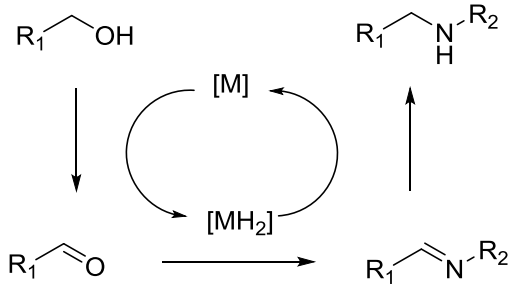
Later on, a newer version of catalyst **1.16**, with 3,5-xylyl groups instead of phenyl groups on the phosphorus [Ru(triphos-xyl)(TMM)], **1.66**, achieved much higher TON's as deactivation through dimerisation is prevented.[92] Lactams were reduced to cyclic tertiary amines in the presence of alcohols with excellent conversions and selectivities (Scheme 1.35) under hydrogen. The molecular hydrogen can be replaced by using an alcohol as a hydrogen transfer reagent with similar results.



Scheme 1.35. Lactam hydrogenation with [Ru(triphos-xyl)(TMM)] (**1.66**).[92] Reaction conditions: Lactam (1 mmol), **1.66** (1 mol%), MSA (1.5 mol%), isopropyl alcohol (2 mL), H_2 (100 bar), 200 °C. Conversion and selectivity determined by ^{1}H and quantitive ^{13}C NMR spectroscopy using mesitylene as an internal standard. *N*,*N*-diisopropylpiperazine is the product when starting with piperazin-2-one and piperazine-2,5-dione.

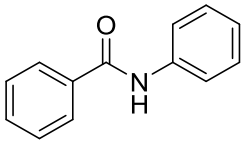
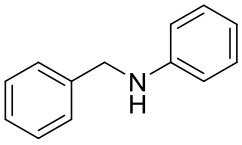
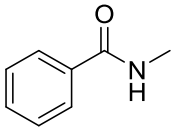
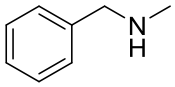
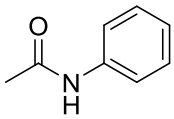
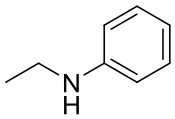
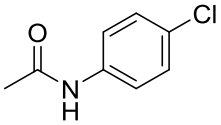
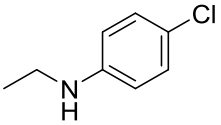
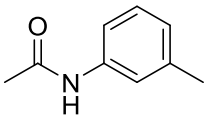
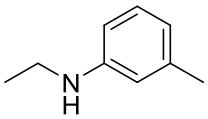
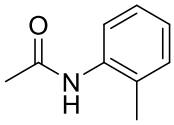
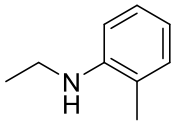
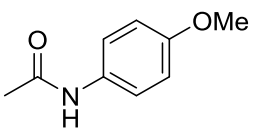
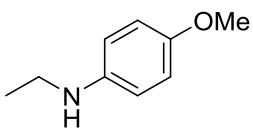
Beller and coworkers further optimised the conditions of the [Ru(acac)$_3$], **1.10**/triphos, **1.13**, hydrogenation of aliphatic and aromatic secondary and tertiary amide.[93] Metal triflates were studied in place of MSA and uniquely, Yb(OTf)$_3$.H_2O improved the yields and selectivities to the desired amines under milder reaction conditions (160 °C). Time dependent and control experiments indicated that alcohols formed initially by hydrolysis of the amide to the carboxylic acid followed by hydrogenation. Amines were then

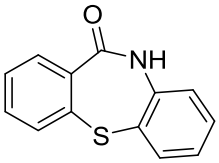
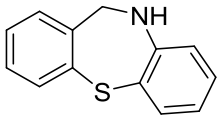
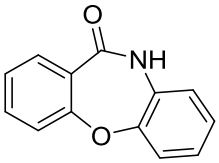
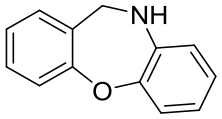
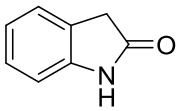
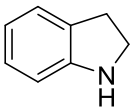
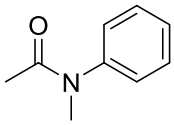
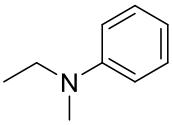
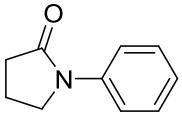
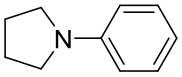
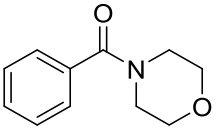
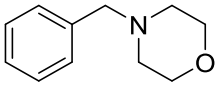
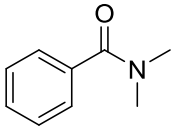
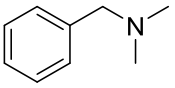
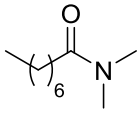
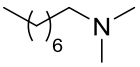
formed from the alcohols by a hydrogen borrowing mechanism (Scheme 1.36). A large substrate scope was demonstrated under these conditions, and the results are summarised in Table 1.28.



Scheme 1.36. Hydrogen borrowing mechanism to form amines from alcohols.[93,94]

Table 1.28. Substrate scope of amide hydrogenation with [Ru(acac)$_3$], **1.10**/triphos, **1.13**/ Yb(OTf)$_3$.H$_2$O.

Entry	Substrate	Conv.[b](%)	Product	Sel.[b] (%)	ref
1		>99		85	93
2[c]		50		28	93
3		>99		80	93
4[d]		>99		80	93
5		>99		88	93
6[e]		>99		80	93
7		>99		95	93

8		>99		100	93
9[c]		95		100	93
10[f]		>99		80	93
11[g]		>99		76	93
12[h]		>99		80	93
13[g]		>99		53	93
14[c]		89		51	93
15[c]		31		36	93

[(a)]amide (0.5 mmol), $[Ru(acac)_3]$, **1.10** (2 mol%), triphos, **1.13** (4 mol%), $Yb(OTf)_3 \cdot H_2O$ (4 mol%), THF (2 mL) and H_2 (5 bar) at 150 °C, 15 h. [(b)]Conversion and selectivity calculated by GC using hexadecane as internal standard. [(c)]$[Ru(acac)_3]$ (6 mol%), triphos (12 mol%), $Yb(OTf)_3 \cdot H_2O$ (12 mol%), THF (2 mL), 15 h. [(d)]$[Ru(acac)_3]$ (4 mol%), triphos (8 mol%), $Yb(OTf)_3 \cdot H_2O$ (8 mol%), THF (2 mL), 15 h. [(e)]$[Ru(acac)_3]$ (4 mol%), triphos (8 mol%), $Yb(OTf)_3 \cdot H_2O$ (8 mol%), 1,4-dioxane (2 mL), 45 h. [(f)]50 bar of H_2. [(g)]$[Ru(acac)_3]$ (6 mol%), triphos (12 mol%), $Yb(OTf)_3 \cdot H_2O$ (12 mol%), 1,4-dioxane (2 mL), 60 h. [(h)]$[Ru(acac)_3]$ (6 mol%), triphos (12 mol%), $Yb(OTf)_3 \cdot H_2O$ (12 mol%), ethylene glycol diethylether (2 mL), 45 h.

The hydrogenation of benzamides was achieved in high conversion and selectivity to the corresponding amine which was in line with the results from Cole-Hamilton and co-workers who also observed apparent C-O cleavage (Table 1.26, Entry 1).[91] Good

conversion and selectivity were obtained when there was an aromatic group attached directly to the nitrogen (Table 1.28, Entry 1, 3-7,11,12). The substituent connected directly to the carbonyl could be either an aliphatic or aromatic group, which does not make much impact on the results, and the yields are not decreased or increased by a significant amount. When an aliphatic group is attached to the nitrogen, the selectivity decreases dramatically with the main products become secondary and tertiary amides (Table 1.28, Entry 2, 14 and 15). For comparison, the selectivity to the corresponding amine was 28% instead of 5% when $Yb(OTf)_3 \cdot H_2O$ was used instead of MSA for the secondary amide (Table 1.26, Entry 1 vs Table 1.28, Entry 2), and 51% instead of 7% for the tertiary amide (Table 1.26, Entry 14 vs Table 1.28, Entry 9). Lactams and their derivatives are also hydrogenated to the corresponding amines in good yields (Table 1.28, Entry 8-10 and 12). Heterocyclic amide hydrogenation proceeded in only 53% selectivity (Table 1.28, Entry 13).

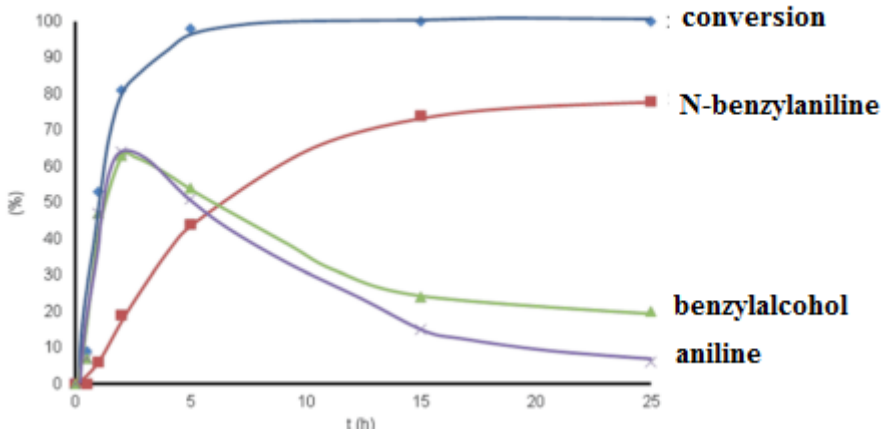


Figure 1.1. Reaction profile of benzanilide hydrogenation. Reproduced with permission from ref [93].

The reaction profile of benzanilide hydrogenation was obtained by analyzing the components in the reaction mixture over time (Figure 1.1). From the profile, benzyl alcohol and aniline were observed as the intermediates. The amount of benzylalcohol and aniline, which are the products of C-N cleavage of the amide, increases in the first 2 h. Their relative amounts start decreasing afterwards, while the amount of *N*-benzylaniline keeps increasing until it reaches its maximum amount after around 16 hours. This profile strongly suggested that the amide hydrogenation starts by C-N

cleavage to the corresponding amines and alcohols, which is followed by the amination of the alcohol to afford the desired amine. It is very probable that all amide hydrogenations using the Ru/triphos system proceed by this method, which may account for the benefical effects of small amounts of water on the reaction. The Ru/triphos system seems, therefore, to offer its unusual reactivity because it catalyses both acid hydrogenation and amination of alcohols.

1.2.3.3 Conclusion

The reduction of esters, carboxylic acids and amides has been well studied. Good conversions and selectivities to the corresponding alcohols and amines are obtained by using various catalysts. The Ru/triphos system is found to be the most versatile catalyst system for these hydrogenations.

The great advantage of homogeneous catalysts over their heterogeneous counterparts is their selectivity when using substrates containing aromatic rings. Most of the heterogeneous catalysts that are capable of reducing carboxylic acid derivatives also catalyse the hydrogenation of aromatic rings.[81] In contrast, catalysts such as those derived from Ru/triphos retain aromatic rings during the hydrogenation of carboxylic acids and their derivatives. Ru/triphos is the key catalytic system that is used in the following hydrogenation studies (Chapter 2 and 3).

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Chapter 2 A new route to the synthesis of linear diamines as polymer precursors: Hydrogenation of dicarboxylic acids and their derivatives in the presence of amines

The work presented in this chapter was partially published in Green Chemistry.[1]

A new and selective route for the synthesis of polymer precursors, primary diamines or N-substituted diamines, from dicarboxylic acids, diesters, diamides and diols using a Ru/ triphos catalyst is reported in this chapter. Excellent conversions and yields are obtained under optimised reaction conditions. The reaction worked very well using 1,4-dioxane as solvent, but the greener solvent, 2-methyl tetrahydrofuran, also gave very similar results. This method provides a potential route to converting waste biomass to value-added materials. The reaction is proposed to go through both amide and aldehyde pathways.

2.1 Introduction

2.1.1 Tall oil as biomass substrates

One of the important principles of green chemistry is to find renewable feedstocks to replace fossil fuels. Tall oil, a waste oil byproduct from paper manufacture, is one of the potential renewable feedstocks. Tall oil is the third most abundant by-product after lignin and hemicellulose produced from wood pulp by using the Kraft process. About 30-50 kg/ton pulp of crude tall oil is produced from the Kraft process.[2] Crude tall oil contains three major components: resin acids, unsaponifiables and fatty acids (Figure 2.1). These components can be separated by fractional distillation.[3] Resin acid contains mainly abietic acid and pimaric acid, and it is usually used by musicians to improve the grip of bows for string instruments. Unsaponifiables which include mostly sterols have no industrial use at the moment.

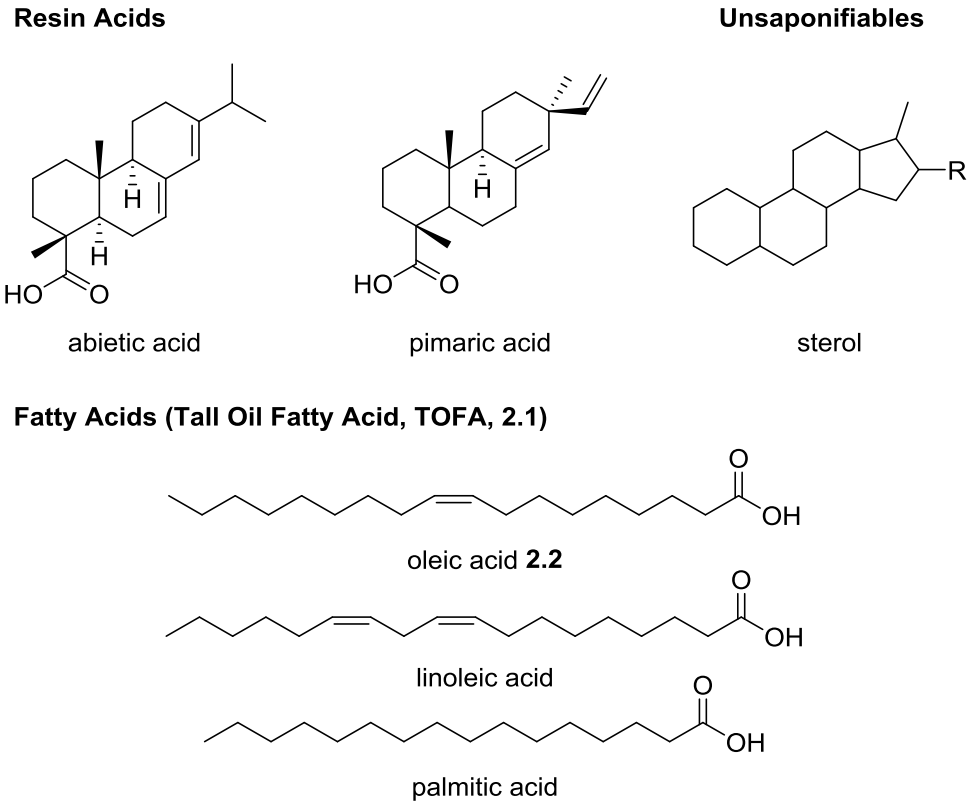


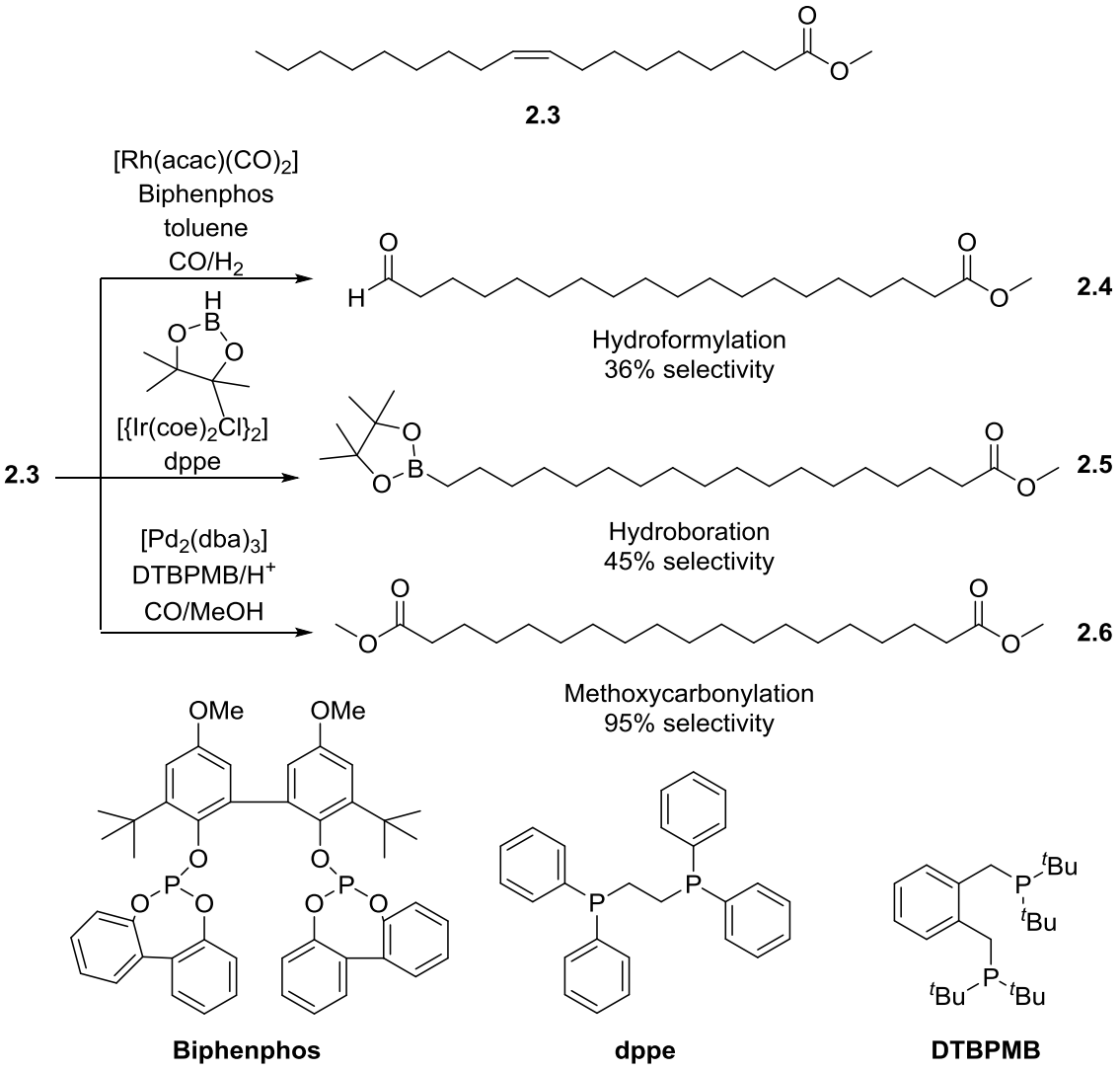
Figure 2.1. Components of crude tall oil.

Tall oil fatty acid (TOFA, **2.1**), which mainly contains oleic acid, **2.2**, linoleic acid and palmitic acid, is traditionally used in coatings, inks, rubbers, and adhesives. It can also be used in emulsifiers, soaps or lubricants. The most economically viable use of TOFA, **2.1**, is to make biodiesel from the ester derivatives of TOFA (fatty acid esters). One of the examples is methyl oleate, **2.3**, which can be produced by methyl esterification of oleic acid, **2.2**, the key component of TOFA. Methyl oleate, **2.3**, has a similar flash point, kinematic viscosity, density and carbon residue as diesel fuel, so methyl oleate, **2.3**, could be a potential alternative to or replacement for fossil fuel based petroleum diesel.[4]

Methyl oleate, **2.3**, can be transformed to various products by using different environmental friendly transition metal catalysts.[5] Methyl 19-oxononadecanoate, **2.4**, is formed by hydroformylation[6] of methyl oleate, **2.3**, with a rhodium catalyst; dioxaborolanyl ester, **2.5**, can be obtained by hydroboration[7] with an iridium catalyst; and 1,19-dimethyl nonadecanedioate, **2.6**, is produced by methoxycarbonylation[8] with the $[Pd_2(dba)_3]$/DTBPMB catalytic system (Scheme 2.1). These esters (**2.4**, **2.5**, **2.6**) can

be used as precursors for the synthesis of polyesters and polyamides to replace fossil fuel based polymers.

1,19-Dimethyl nonadecanedioate, **2.6**, is the substrate we are mostly interested in for the hydrogenation study in this chapter, and the detail of the methoxycarbonylation will be discussed in Section 2.1.3.

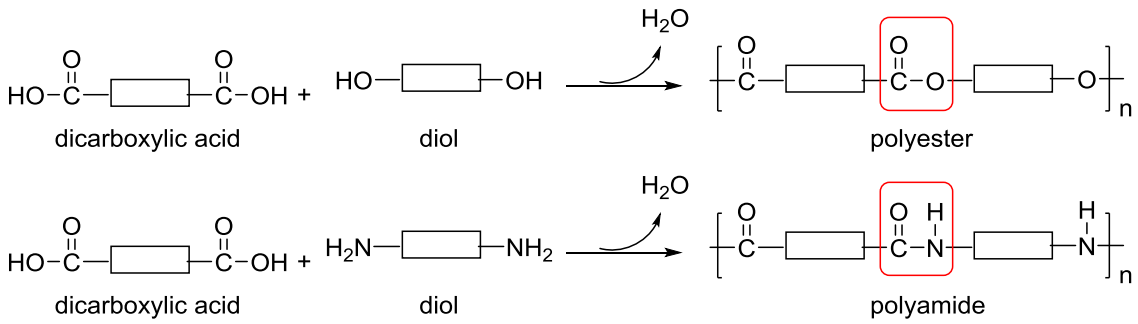


Scheme 2.1. The key transition-metal catalytic reactions of methyl oleate.

2.1.2 Polymers

A polymer is a large molecule or macromolecule composed of many repeating units. There are two types of polymers: natural polymers and synthetic polymers. Natural polymers include DNA, protein, natural rubber and the key components of wood, such as cellulose and lignin. Synthetic rubber, nylon and polyvinyl chloride (PVC) all belong to the synthetic polymers.

Polyesters are polymers which contains ester functional groups in the main chain (Scheme 2.2). The most widely used applications of polyesters are in clothing, goods packaging and plastic drink bottles. Polyamides are macromolecules with repeating units linked by amide bonds (Scheme 2.2). Proteins are naturally occurring polyamides, and nylons, aramids, and sodium poly(aspartate) are artificial polyamides. Polyamides have high durability and strength, and these properties make them very important in the manufacture of textiles, carpets and sportswears.



Scheme 2.2. Synthesis and general structures of polyesters and polyamides.

2.1.2.1 History of polymeric materials

Ancient Mesoamericans were believed to be the first people to use polymers. Rubber balls made from latex from local rubber trees were developed by ancient Mesoamericans before 1600 BC.[9] The term "polymer" was created by Jön Jakob Berzelius in 1833, although Berzelius did very little work which could be considered to be polymer chemistry in the modern sense. The history of polymeric materials can be mainly divided into two ages: the pre-synthetic material age (before 1930) and the synthetic material age (after 1930) (Figure 2.2). In the pre-synthetic material age, only biological polymers such as natural rubber, starch and cellulose were studied. However,

at that time, the nature of those polymeric materials was not understood. Polymers were believed to be aggregations of small molecules until the 1920s when Herman Staudinger enunciated the hypothesis of macromolecule, which defined polymers as long chains of short repeating molecular units linked by covalent bonds, "For such colloidal particles in which the molecule is identical with the primary particles, in other words, where the single atoms of the colloidal molecule are bound together by normal valency activities, we suggest the term Makromolekü."[10] Staudinger also predicted that macromolecules, particularly proteins, would be found to play important roles in living organisms. In about 1930, the macromolecular hypothesis of Herman Staudinger was first accepted, which led to the beginning of a new area: synthetic polymers. The development of synthetic materials such as plastics are based on Staudinger's hypothesis, and Staudinger was awarded the Nobel Prize in Chemistry in 1953 for the concept of macromolecules and his prolonged effort to establish the science of large molecules.

In the 1930s, Wallace Carothers and his group at Dupont in the USA proved the theories of Staudinger, and commercialized poly-(2-chloro-1,3-butadiene) (Neoprene) and polyamides (nylon 6,6: formed by condensation polymerisation between hexanedioic acid and 1,6-diaminohexane).[11] Because of its good chemical stability and flexibility over a wide range of temperatures, neoprene was originally used in consumer goods such as gloves and shoe soles. During World War II, neoprenes were all claimed by the military and removed from the commercial market. More recently, neoprene has a large variety of applications such as laptop sleeves, orthopedic braces and electrical insulators. Nylon 6,6 which has a high mechanical strength, rigidity and heat and chemical resistance can be used in textiles, carpets, ropes, airbags and hoses.

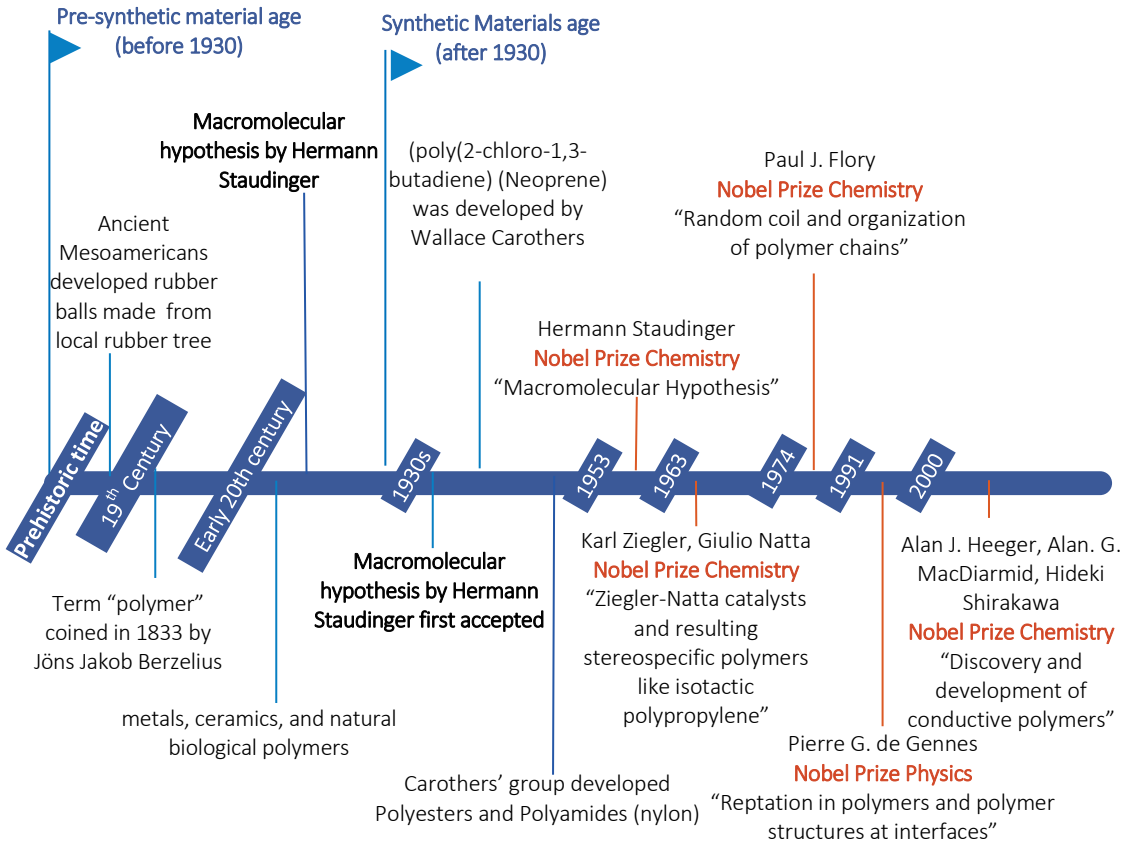


Figure 2.2. History of polymers.

After World War II, the limited supply of natural materials such as silk and rubber demanded an increased production of synthetic substitutes, such as Kevlar and Teflon (PTFE). Kevlar, developed by Stephanie Kwolek, has a tensile strength and resilence down to cryogenic temperatures (-196 ˚C), it can be used as a steel replacement in racing tires, cryogenics and armour.[12] Teflon with extreme non-reactivity, high temperature resistance, dielectric properties and low friction can be used as a coating for non-stick frying pans, plain bearing, gears, slide plates and insulators. The extensive study of polymer chemistry has been rewarded by 5 Nobel Prizes to 8 individuals (Hermann Staudinger, Karl Ziegler, Giulio Natta, Paul J. Flory, Pierre G. de Gennes, Alan J. Heeger, Alan G. MacDiarmid and Hideki Shirakawa), with their achievements described in Figure 2.2. The discoveries in polymer chemistry have had an incalculable impact on the present way of life. Polymeric products are found everywhere around us with almost an endless list, from products used in daily life (eg. water bottles) to niche and specialist application (eg. spacesuits).

2.1.2.2 Synthesis of polymers

Polymers are formed by polymerisation of monomers in a chemical reaction. There are two polymerisation methods: chain-growth polymerisation and step-growth polymerisation (Figure 2.3).

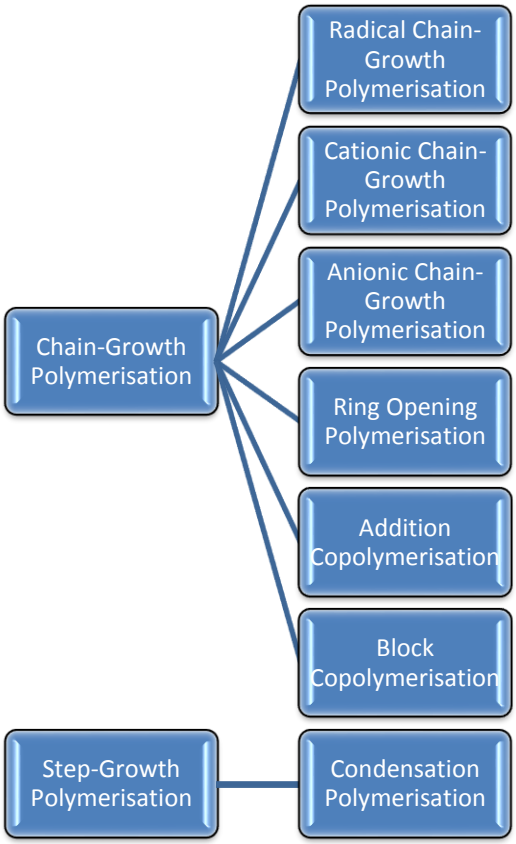


Figure 2.3. Synthetic methods for polymerizsation.

2.1.2.2.1. Chain-growth polymerisation

Chain-growth is one of the polymerisation techniques, which includes radical chain-growth polymerisation, cationic chain-growth polymerisation, anionic chain-growth polymerisation, ring opening polymerisation, addition copolymerisation, and block copolymerisation (Figure 2.3). Unsaturated monomers add onto the active site (eg. a radical, a cationic and an anionic center) of a growing polymer chain one at a time, and the addition of each monomer unit regenerates the active site. Chain-growth polymerisation includes three steps: initiation, propagation and termination. An active

center is created by the initiation step which could involve thermal decomposition, photolysis, redox reactions or persulfate. Monomers react at the active site at the end of the chain during propagation. One example of termination is the combination of two active chain ends (Figure 2.4). The chain becomes inactive after the termination step. Monomers exist throughout the reaction, and the monomer concentration decreases steadily with time as it incorporated into polymers. Polymer is formed throughout the reaction, and a high degree of conversion is obtained with long reaction time. Plastics such as polyethylene, polypropylene, and polyvinyl chloride are all made by chain-growth polymerisation.

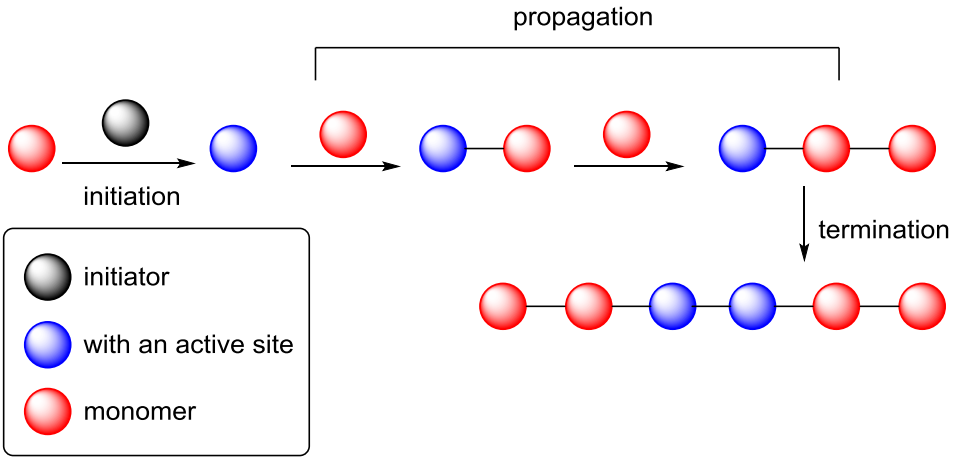


Figure 2.4. Illustration of chain-growth polymerisation.

2.1.2.2.2. Step-growth polymerisation

Step-growth polymerisation is another polymerisation technique, in which bi-functional or multifunctional monomers react with any other molecule firstly to form dimers, then to form oligomers and finally long chain polymers (Figure 2.5). All these intermediate species (dimers and oligomers) have approximately equal reactivity and all react with each other. The reaction proceeds very rapidly at the beginning of the reaction, but the molecular weight increases only slowly, and high molecular weight polymers are only obtained at the end of the process, when long oligomers react with each other. Molecular species of oligomers with different molecular weight exist throughout the reaction, and long reaction time is needed for the synthesis of high molecular weight polymers.

The concept of condensation polymerisation was introduced by Wallace Hume Carothers in 1929,[13] a polymer and a molecule with a low molecular weight (usually water molecule) are obtained after the reaction. Condensation polymerisation is not identical to step-growth polymerisation, but its reaction mechanism corresponds to a step-growth polymerisation. Polyesters, polyamide (nylon) and polyurethanes are all synthesised by step-growth polymerisation. Monomers with three or more functional groups will lead to branches in a polymer, and they will eventually form a cross-linked network. An initiator is not necessary in step-growth polymerisation, and no termination is needed after the reaction. The end groups of the oligomers and polymers are reactive throughout the process.

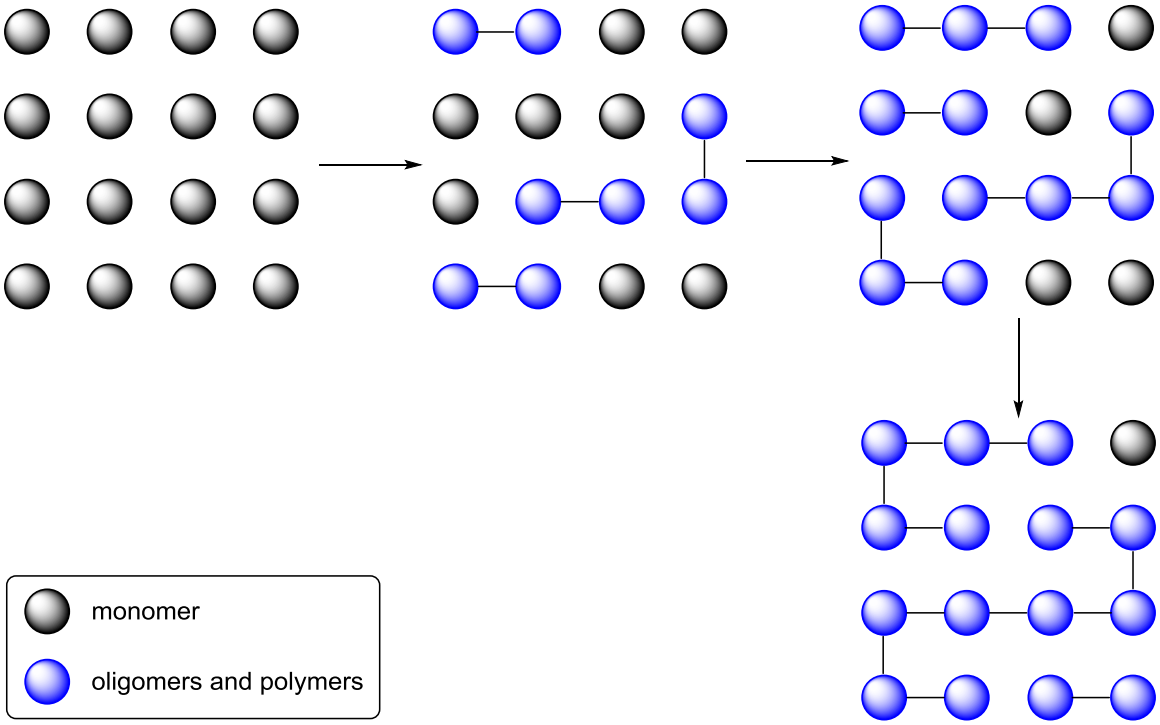


Figure 2.5. General illustration of step-growth polymerisation.

2.1.3 Synthesis of monomers of polyamides: Diesters and dicarboxylic acids from biomass

The essential monomers for the synthesis of polyamides are difunctional carboxylic acids or diesters (Scheme 2.2). Long chain diacids and diesters can be obtained sustainably from non-food biomass, for example, undecylenic acid, which could afford dodecanedioic acid and esters by a carboxylation reactions,[14] can be derived from castor

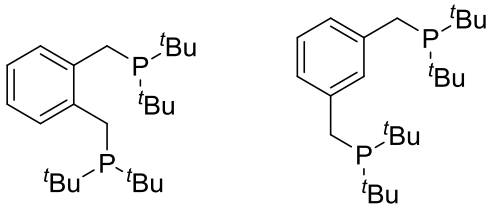
oil.[15] Tall oil fatty acid from waste tall oil contains mainly oleic acid, which can be converted into 1,19-dimethyl nonadecanedioate by isomerising alkoxycarbonylation (methoxycarbonylation),[14] using the catalytic system derived from Pd/1,2-*bis*(di-*tert*-butylphoshinomethyl)benzene/(1,2-DTBPMB)/methane sulfonic acid (MSA) originally developed and commercialized for ethene methoxycarbonylation,[16] but subsequently shown to be highly effective for the production of terminal esters by isomerising methoxycarbonylation of terminal or internal alkenes[17] or of α,ω-diesters from unsaturated esters[8] including methyl oleate,[18–26] high oleic sunflower oil[27–29], algal oils[30] for polymers such as polyamides, polyimides and polyureas.

Methoxycarbonylation is one type of alkoxycarbonylation which converts an unsaturated hydrocarbon to its methyl ester with a metal catalyst, and it was first developed by Reppe in 1953.[31] Complexes such as $[Ru_3(CO)_{12}]$/1-Butyl-3-methylimidazolium chloride,[32] $[Pd(OAc)_2]$/phosphine[33] or Pt/C[34] are all found to be active catalysts for the alkoxycarbonylation reaction. Among the all metal complexes, Pd/phosphine complexes were the most favorable combination, because of their high activity and selectivity under mild conditions.

A study by Mecking and co-workers[35] revealed that sterically congested ligands around the palladium metal center are responsible for both the high selectivity and productivity of isomerising alkoxycarbonylation, because the metal centers with bulky ligands have higher energy differences between the rate-limiting steps (methanolysis of Pd-acyl formed by carbon monoxide insertion) in the synthesis of the linear and the branched products.

The ligand 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (1,2-DTBPMB), **2.7**, was first reported by Shaw in 1976.[36] Later, Spencer investigated the catalytic activity of Pt and Pd complexes of DTBPMB towards the methoxycarbonylation reaction of methyl oleate,[37] showing higher selectivity and activity towards the linear product, 1,19-dimethyl nonadecanedioate, **2.6**. Behr and coworkers studied the impact of the bite angle, β_n, on the activity of methoxycarbonylation.[38] Methoxycarbonylation of methyl oleate using $[Pd_2(dba)_3]$ based catalysts was tested as a model reaction. When 1,2-DTBPMB (β_n=90°) was used as the ligand, high conversion (80%) and high selectivity (81%) for the linear product, **2.6**, was observed. Interestingly, when 1,3-DTBPMB, **2.8**,

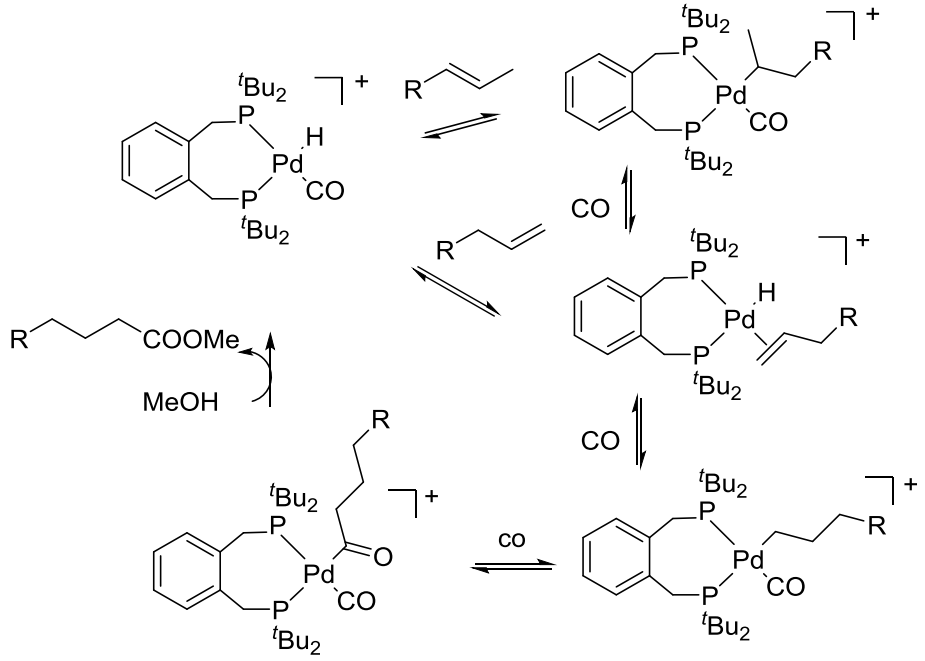
(Figure 2.6) was used, a complete loss of catalytic activity (0% conversion) was observed. Behr's study suggests that phosphine bite angles, β_n, within metal-DTBPMB complex play a significant role towards the catalytic activity in methoxycarbonylation reaction, and the enlargement of bite angle leads to a total loss of catalytic activity.



2.7 **2.8**

Figure 2.6. Structure of 1,2-DTBPMB, **2.7**, and 1,3-DTBPMB, **2.8**.

Mechanistic studies[17] of methoxycarbonylation reactions using deuterated substrates suggest that the reaction perhaps occur *via* a hydride mechanism as shown in Scheme 2.3. Direct methoxycarbonylation of 1-octene occurs at the beginning, however, alkene isomerisation competes with this reaction, and the linear product can be formed by the isomerisation of the internal alkenes in a slower second phase of the reaction.



Scheme 2.3. Proposed hydride mechanism for methoxycarbonylation reaction.

2.1.4 Synthesis of monomers of polyamides: *N*-alkylation of amines with carboxylic acids and derivatives

The other important monomers for the synthesis of polyamides are diamines (Scheme 2.2). Amines are an important group of chemicals and chemical intermediates for a wide range of applications such as the manufacture of drugs, azo-dyes and nylons. Amines are industrially synthesised by alkylation of ammonia with alcohols.[39] The same amines can be obtained by the reaction between haloalkanes and ammonia or the corresponding amine, however, the degree of alkylation is hard to control.[40] Amines can also be obtained by reduction of nitriles,[41] alkylazides[42], amides[43] and nitro compounds,[44] catalytically or stoichiometrically. Reductive amination of aldehydes[45] and ketones[46] can also produce amines, however, it requires more steps for the synthesis of the starting materials, and carboxylic acids and esters are more easily obtained from nature.

N-alkylation of amines with alcohols has been studied by different groups using different metal catalysts.[47–53] However, there are few examples for the *N*-alkylation of amines with carboxylic acids and esters which could save the step of alcohol synthesis. In 2007, Cole-Hamilton and co-workers developed the first catalytic method for *N*-alkylation using molecular hydrogen as reductant. Nonanoic acid was converted to nonylamine in 50% yield using a ruthenium catalyst and 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) as a ligand.[54] This study has been followed up later with an extended substrate scope using a Lewis acid promoter.[55] Karstedt's catalyst was also found to be active for this *N*-alkylation reaction with carboxylic acids. However stoichiometric amounts of various silanes were used as the hydride source. Reactions only preceded well with carboxylic acids as the reagents, while, starting with esters gave only 5% yield of the desired amine.[56] Ruthenium,[57] iridium,[58] and boron[59] catalysts were also studied by different groups together with silanes as the H donor, these previous studies are summarised in Figure 2.7.

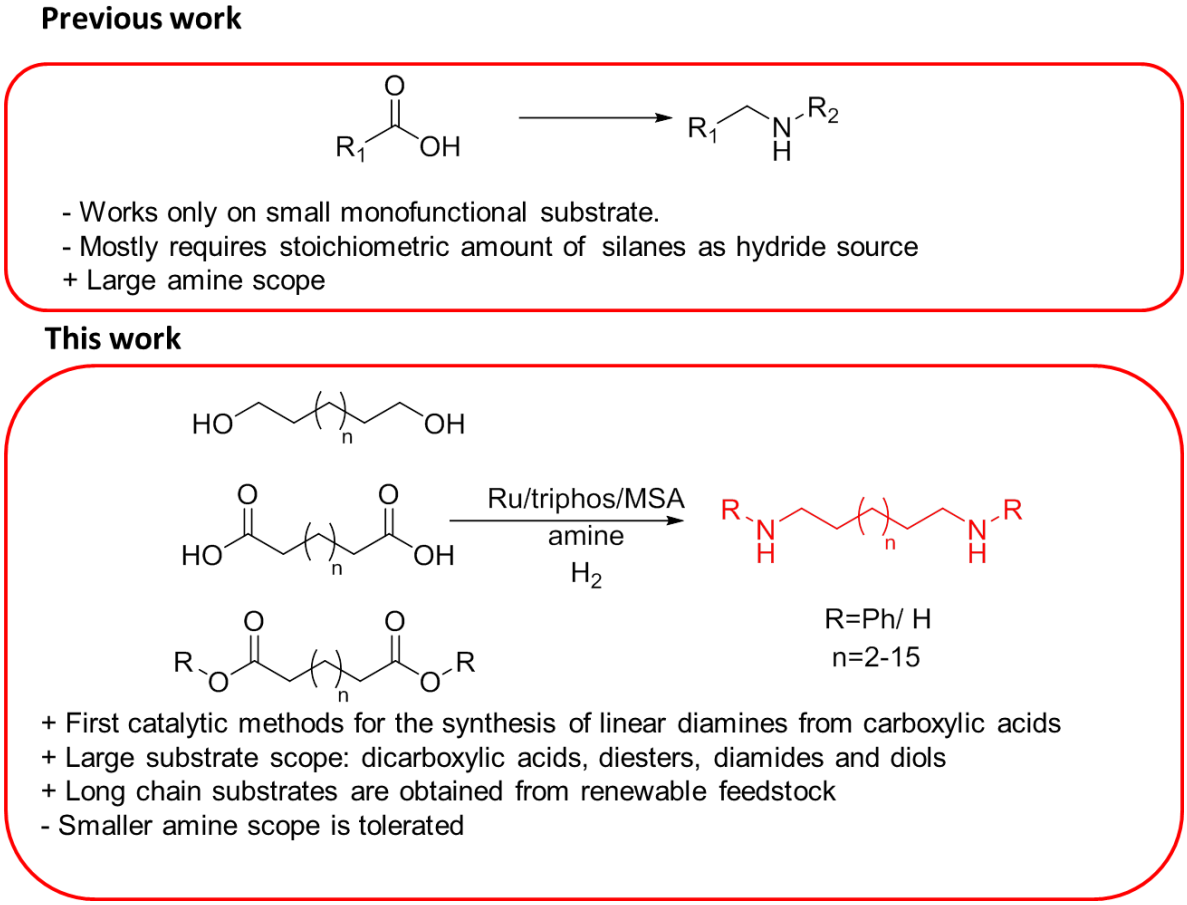


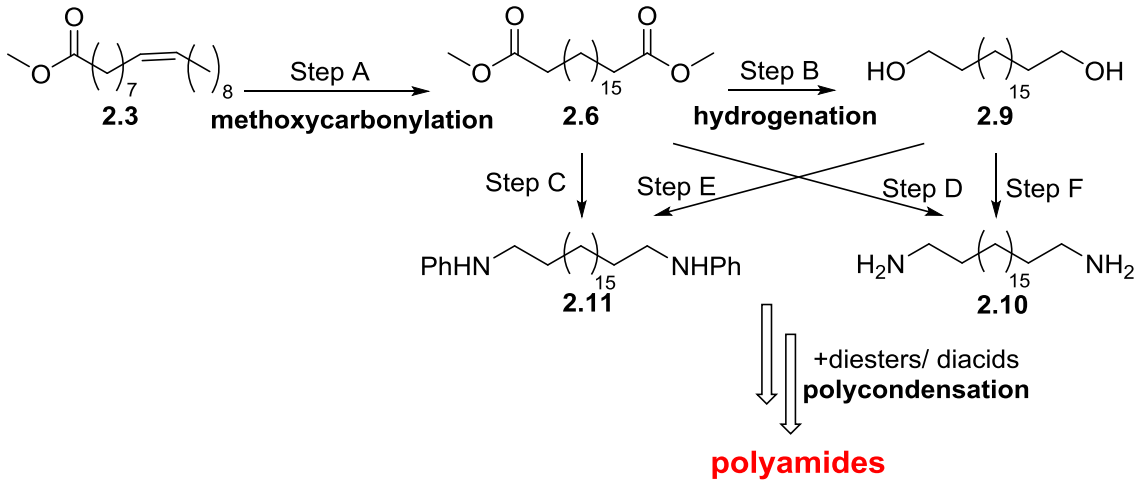
Figure 2.7. Brief summary of the current status of the formation of diamines from diacids and their derivatives compared with the work reported here.

To our knowledge, there are no reported catalytic methods for the synthesis of linear diamines from linear difunctionalised carboxylic acids and their derivatives such as diesters or diamides, although in Chapter 3 of this thesis we show that *N*-heterocycles can be obtained from diesters with 4-8 C atoms in the chain.[60] In some cases, linear diamines were formed as byproducts when excess amine was employed, but these reactions were not optimised.

Herein, a methodology to convert dicarboxylic acids, diesters and diamides to the desired diamines in the presence of the corresponding anilines or ammonia using a ruthenium catalyst (Figure 2.7) is reported. Value-added materials can be produced from waste bio-feedstocks which makes this method attractive.

2.2 Results and discussion

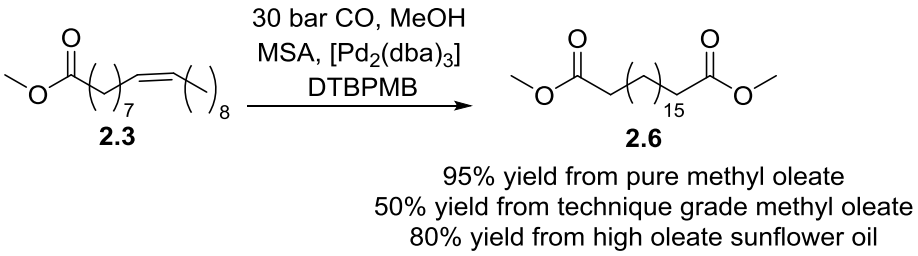
The plan of this project was to make primary and secondary diamines from methyl oleate which could be obtained from tall oil fatty acid (TOFA) by esterification. Dimethyl 1,19-nonadecanedioate, **2.6**, can be synthesised from methyl oleate, **2.3**, by an isomerising methoxycarbonylation reaction using a palladium catalyst. Dimethyl 1,19-nonadecanedioate, **2.6**, can be hydrogenated to diol, **2.9**, or to diamines **2.10** and **2.11** in a tandem process in the presence of amine sources. Finally, a condensation reaction can take place to form the corresponding polymers; polyester, polyamide and *N*-phenylpolyamide respectively (Scheme 2.4).



Scheme 2.4. Schematic for the synthesis of polyesters and polyamides.

2.2.1 Preparation of dimethyl 1,19-nonadecanedioate

Step A in Scheme 2.4 was carried out by a methoxycarbonylation reaction.[61] The product, 1, 19-Dimethyl nonadecanedioate, **2.6**, was obtained in 95% yield as a snowy white powder from pure methyl oleate. Technique grade methyl oleate (~60%) could also produce the expected 1,19-dimethyl ester in 50% yield. Whilst, starting from sunflower oil (38% oleic acid), 80% yield was obtained, calculated on the basis of the oleate content (Scheme 2.5). Those results are consistent with the literature results previously reported in our group.[61]



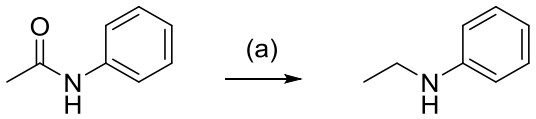
Scheme 2.5. Methoxycarbonylation of methyl oleate, **2.3**.

2.2.2 Optimisation of conditions for ester hydrogenation in the presence of an amine

The synthesis of diol, **2.9**, from methyl oleate, **2.3**, *via* intermediate dimethyl 1,19-nonadecanedioate, **2.6**, (Scheme 2.4, Step A and B), was achieved with a yield comparable to previous work carried out by Cole-Hamilton and co-workers.[14,61] The present study focuses on the synthesis of primary and secondary diamines from the diester (Step C and D in Scheme 2.4). For the synthesis of the diamines from the diester, hydrogenation with an amine source using the [Ru(acac)$_3$], **2.12** /triphos, **2.13**, system[43] in distilled THF solvent was employed. The [Ru(acac)$_3$]/triphos system[43] was found to be effective for the challenging hydrogenation of amides, based on this we decided to employ it for our purposes. Surprisingly, the [Ru(acac)$_3$]/triphos system was not successful in the hydrogenation of diester with an amine source to produce diamine in the present study. To verify whether the old batch of catalyst and ligand were influencing the reactions, amide hydrogenation reactions were carried out by using different batches of commercially available and purified ruthenium metal catalyst [Ru(acac)$_3$], **2.12**, triphos ligand, **2.13**, and MSA, however, none of those trials influenced the results significantly. Solvent does usually have a strong effect on the reactions, and in order to investigate different sources of THF in amide hydrogenation reactions, acetanilide, **2.14**, was used as a benchmark substrate. Acetanilide, **2.14**, was selected because it has very simple structure and high conversion and selectivity (100% conversion, 92% yield).[43] The obtained results varied dramatically when conducting the reaction with different THF sources. When THF from solvent purifier (Grubbs solvent system, filter through an alumina column packed with a catalyst) was used (Table 1, Entry 1), full conversion was obtained for the hydrogenation of acetanilide, **2.14**, with 89% yield of the corresponding *N*-ethylaniline, **2.15**. However, when distilled THF

(over sodium/benzophenone) was used, *N*-ethylaniline, **2.15**, was obtained in only 7% yield (Table 2.1, Entry 2).

Table 2.1. Hydrogenation of acetanilide.[a]

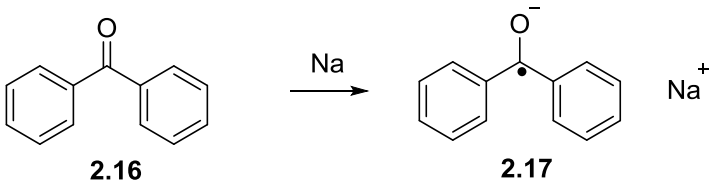


2.14 **2.15**

Entry	Solvent	Water equiv.to [Ru(acac)$_3$]	Conv. (%)	Yield (%)
1	solvent purifier	0.8	100	89
2	Distilled THF	0.2	72	7
3	DistilledTHF + 10 % H_2O[b]	1100	82	29
4	distilled THF+ 1% H_2O[b]	110	98	80
5	Undistilled THF	0.72	100	60
6[c]	Distilled THF+ molecular sieve	0.24	100	70

[(a)][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1.5 mol%), solvent (10 mL), substrate (5 mmol), 10 bar of H_2, 16 h, 200 °C. The conversions and yields are calculated by NMR with 1,4-dinitrobenzene as internal standard. Water content was measured using Karl Fischer titrations. [(b)]Percentage of water is based on the volume% of THF. [(c)]Molecular sieves dried under vacuum at 150 °C for 3 days. 18% tertiary amine obtained as side product.

Sodium/benzophenone were used for the THF distillation. Sodium metal reduces benzophenone, **2.16**, to the diphenylketyl radical, **2.17**, which is an efficient oxygen and water scavenging agent. The diphenylketyl radical, **2.17**, has a dark blue colour, and the colour of the solvent mixture will turn blue when the solvent is dry and free of oxygen because of the ketyl species. This reaction is illustrated in Scheme 2.6.[62] The side products formed from phenyl radicals after distillation are summarised in Figure 2.8. In theory, the low concentration of these compounds should not cause any problems because, in most cases, their volatility at the boiling point of THF is very low.



Scheme 2.6. Formation of active ketyl radical with sodium metal.

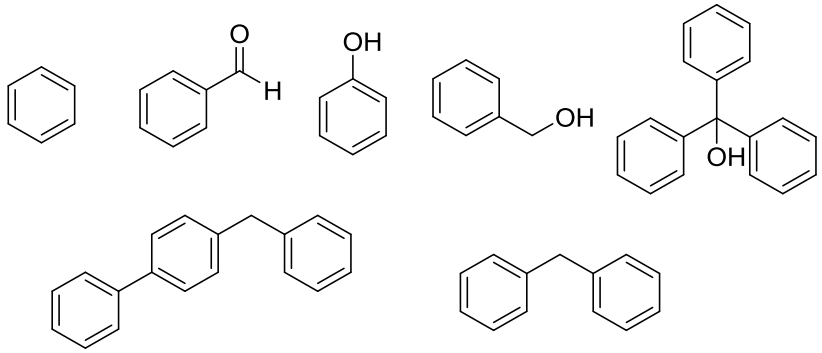


Figure 2.8. Side products form from phenyl radicals.[62]

The purity of both THF sources (from the still and the solvent purifier) was examined to ensure that the side products from benzophenone (Figure 2.8) were not transported into the distillate. NMR, GC-FID and GC-MS showed no obvious organic impurities. Any organic impurities present would be below the detection limits of the methods used, in the case of GC-FID this would be less than 1 ppm, an organic impurity at this level should not have a significant impact on the reaction.

The other difference between the two THF sources might be the water content, although THF produced from both sources is supposed to be dry. Therefore, a Karl Fischer Titration was carried out to find out the exact water level in both of them. Karl Fischer Titration (with the machine shown in Figure 2.9) is a classic titration method to measure water content in all types of substance. The Karl Fischer titration is based on the oxidation of sulfur dioxide by iodine in methanolic hydroxide solution (Equation 2.1 and Equation 2.2).[63] The water contents of THF obtained from different sources are shown in Table 2.2.

$$CH_3OH + SO_2 + RN \rightarrow [RNH]SO_3CH_3$$ Equation 2.1

$$H_2O + I_2 + SO_2 + CH_3OH + 3RN \rightarrow [RNH]SO_4CH_3 + 2[RNH]\ (RN=\text{imidazole})$$

Equation 2.2

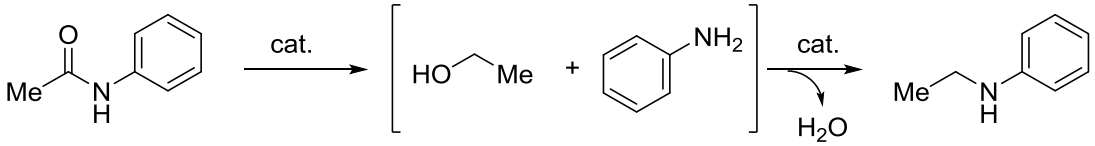
Table 2.2. Water contents of different solvent sources.

Entry	Solvents	Source	Water content/ ppm	H_2O equiv. to $[Ru(acac)_3]$
1	THF	Still (Sodium/ benzophenone)	*19.29*	0.2
2	THF	Solvent purifier	*72.09*	0.8
3	THF	undistilled	*64.80*	0.72
4	THF	Still+ molecular sieves	*22.18*	0.24
5	1,4-dioxane	undistilled	*115.81*	1.29

Figure 2.9. Karl Fischer kit for water level measurement.

There is a 52.8 ppm difference of water content in THF from the still and the solvent purifier (Table 2.2, Entry 1 and 2). This big difference suggests that a small amount of water may be necessary for this reaction. To find out if water content is the only problem for the different results, the same hydrogenation reaction was tested with distilled THF with 110 equiv. of water compare to ruthenium catalyst (Table 2.1, Entry 4), the selectivity increased significantly to 78%, which supported our theory. But when 1100 equiv. of water compare to ruthenium catalyst was used (Table 2.2, Entry 3), the selectivity decreased to 24%, although it is still higher than using the distilled THF

alone (7%). These results suggested that a small amount of water is required for this hydrogenation reaction, while too much water is detrimental. The reason for this is still not clear, but in literature,[64] it has been seen that the [$Ru(acac)_3$] and triphos system is more stable in the presence of water. Furthermore, when $Yb(OTf)_3.H_2O$ is used in place of MSA, it has been shown that the reaction proceeds by first forming the alcohol, which is than transformed into the amine (Scheme 2.7).[65] Formation of the alcohol requires water so this may be the reason that water is required in the MSA reactions as well. Only a small amount of water is required because water is also a product of the second step of the reaction so it is regenerated.



Scheme 2.7. Hydrogenation using $Yb(OTf)_3.H_2O$.

The conversion and selectivity were the highest when 0.8 equiv. of water was used compared to ruthenium catalyst (Table 2.1, Entry 1). When the THF solvent was used directly from a newly opened bottle, which has a water content of 72 ppm (0.7 equiv. compare to ruthenium catalyst), a slight decrease of yield was obtained (60%). More interestingly, when activated molecular sieves were added into the distilled THF for over 3 days, 70% yield of the desired amine was obtained (Table 2.1, Entry 4). Karl Fisher test shows 22.18 ppm of water in the distilled THF with molecular sieves. Very strangely, with the similar water content as the distilled THF, the results for the hydrogenation varied a lot (60% vs 7% yield). In the literature, with the same drying method for THF (distilled over sodium/benzophenone, then dried over activated molecular sieves for 3 days), the water content was proved to be 4.1 ppm.[66] In this case (THF dried over molecular sieves), the side product, *N*,*N*-diethylaniline, was also obtained in 18% yield, while under other conditions, <3% of *N*,*N*-diethylaniline was obtained. Although the reason for the contradictory observations was not fully understood, it is safe to say distilled solvent was not adequate for this hydrogenation reaction in our case.

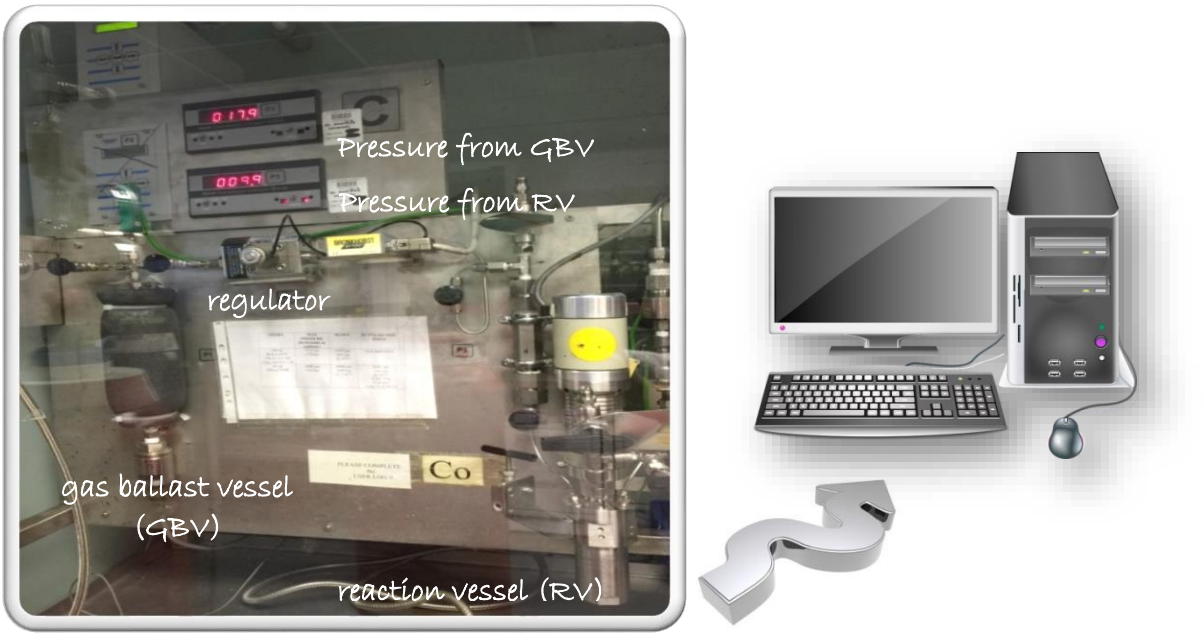


Figure 2.10. Autoclave used to monitor the hydrogen uptake during the reaction.

The hydrogenation of acetanilide, **2.14**, was also studied using a more complicated system (Figure 2.10) which can monitor the uptake of hydrogen gas during the hydrogenation reaction. The reaction mixture was stirred using a mechanical stirrer in the little reaction vessel. The hydrogen gas is stored in the gas ballast vessel, and the valves between the reactor and the ballast were all opened, and the regulator was set to 10 bar. This means that the whole system will be maintained at 10 bar of hydrogen. When the reaction consumed hydrogen, in order to keep the pressure at 10 bar, the gas from the ballast flows automatically towards the reactor, and the pressure of the ballast vessel is monitored every minute, which gives the exact hydrogen consumption during the reaction. The pressure drop in the ballast vessel during a typical reaction is illustrated in Figure 2.11. From the graph, the hydrogen pressure dropped by 0.85 bar in 1000 min. The discontinuities in the pressure drop simply reflect that a finite pressure drop below the set pressure of 10 bar must occur before the valve opens to allow gas to pass from the ballast vessel to the reactor. At 1000 minutes, the reaction was stopped and quantified by using quantitative ^{1}H NMR.

The volume and temperature of the gas ballast vessel were 150 mL and around 19 °C, respectively. The total pressure drop was 0.85 bar, starting with 40.37 bar and reduce to 39.52 bar at the end of the reaction. According to the ideal gas law, assuming the

hydrogen is acting as an ideal gas (Equation 2.3), the reaction results in loss of almost 5 mmol of hydrogen. In the reaction, 5 mmol of acetanilide was used, and each molecule of acetanilide required two molecules hydrogen for the synthesis of the corresponding amine. Therefore, from gas consumption, only half of the substrates were converted. From quantitive ^{1}H NMR, 50% of the amide was converted to the amine which matched with the results calculated by the hydrogen gas consumption.

$$PV=nRT \Rightarrow \Delta n=\Delta PV/RT= (85000Pascal*0.00015\ m^3)/(8.314*292K)=5.3\ mmol$$

Equation 2.3. Ideal gas law, and actual calculation for the gas loss in this reaction.

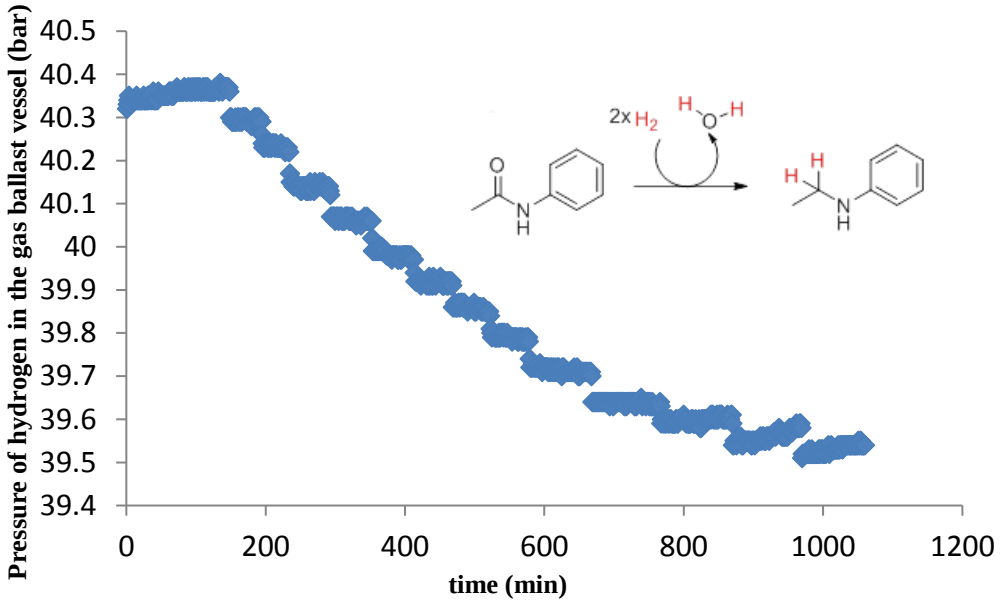
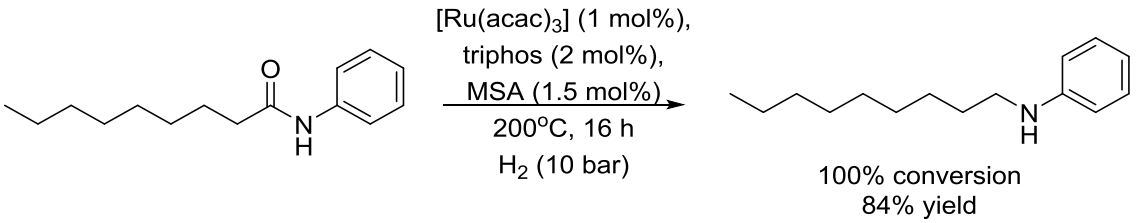
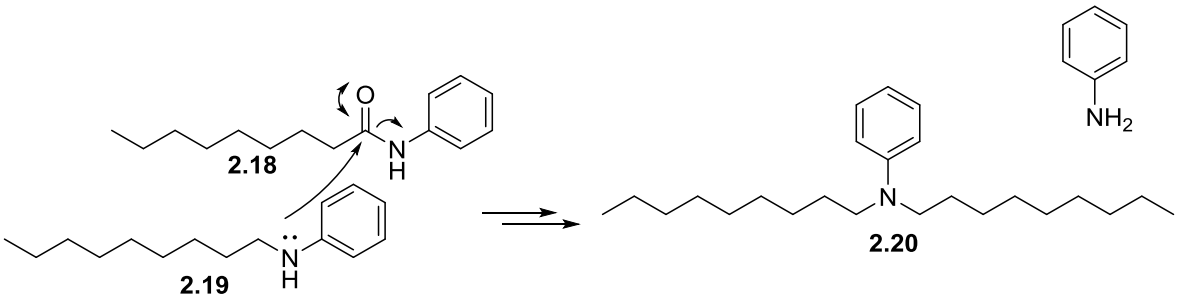


Figure 2.11. Monitor of hydrogen gas loss for the hydrogenation of acetanilide. *Reagents and conditions*: Acetanilide (5 mmol), [Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1.5 mol%), 1.5 bar of H_2, 200 °C.

The hydrogenation of the small amide, acetanilide, **2.14**, was successfully achieved. *N*-phenylnonanamide, **2.18**, which contains a longer side chain was then conducted under the same conditions in dried but not distilled THF. In this case, the amide, **2.18**, was fully converted, and with 84% selectivity to the desired amine, **2.19**, (Scheme 2.8). The mass spectrum indicates tertiary amine, *N*,*N*-dinonylaniline, **2.20**, formation as a side product and the corresponding production of aniline (Scheme 2.9).



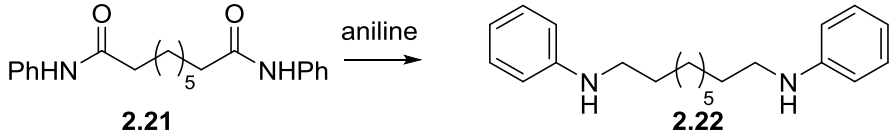
Scheme 2.8. Hydrogenation of *N*-phenylnonanamide **2.18**.



Scheme 2.9. Mechanism of the synthesis of side product *N*,*N*-dinonylaniline.

These reaction conditions were then applied to the difunctional substrates. Hydrogenation of N_1,N_9-diphenylnonanediamide, **2.21**, was carried out first under similar conditions as the hydrogenation of acetanilide, **2.14**. Only 34% conversion was obtained after 20 hours (Table 2.3, Entry 1). However, when increasing the reaction temperature to 220 °C, 94% conversion was obtained, although the yield of the desired product **2.22** was lower than anticipated with mono-hydrogenated amide as the major side product (Table 2.3, Entry 2). This type of amide hydrogenation will be discussed in detail later in this chapter. But clearly, higher temperature is preferred for the study of difunctionalised substrates. Since the temperature was increased to 220 °C, the solvent for this reaction was changed to 1,4-dioxane as it has a higher boiling point and is more stable at high temperature. 1,4-Dioxane from the bottle was only degassed by argon before use.

Table 2.3. Hydrogenation of *N*-phenyl nonanediamide, **2.21**, at different temperatures.[a]



Entry	T	Conv. (%)	Yield (%)
1	200	34	15

2	220	94	32

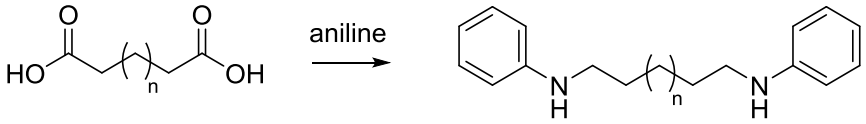
[a][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1.5 mol%), THF (15 mL), substrate (2.5 mmol), H_2 (10 bar), 220 °C, 20 h, conversions and yields were calculated based on quantitive NMR using 1,4-dinitrobenzene as internal standard.

2.2.3 Carboxylic acids and esters as substrates

After optimising the conditions, the focus was moved to the synthesis of diamines from dicarboxylic acids and their derivatives. The initial studies were focused on the synthesis of *N*-substituted diamines as they could be used as precursors for *N*-substituted polymers.[67] Polyamides containing aromatic groups are known to be highly stable and to be fire retardants,[68,69] therefore, *N*-phenyl polyamides have the potential to be highly stable materials. So far, *N, N'-diphenyl diamines* are only known to be produced from dibromoalkanes stoichiometrically[70] or from amination of linear diols using Pt-Sn/r-Al_2O_3 in xylenes.[71]

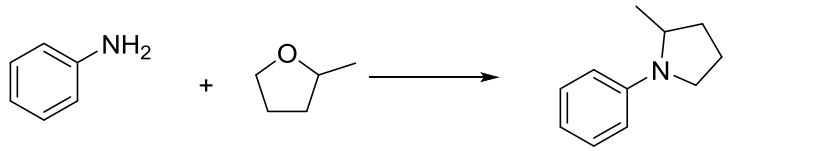
Previous reports using molecular hydrogen as the reductant only managed to convert small monofunctional carboxylic acids to their corresponding amines using molecular hydrogen.[43,54,55,72,73] Here, the first method to produce diamines from dicarboxylic acids and their derivatives in the presence of an amine source is reported; it works efficient even for the very long chain fatty acids. *N, N'*-diphenyl diamines can be obtained from the hydrogenation of carboxylic acids in the presence of aniline using ruthenium(III) acetylacetonate, **2.12**, ([Ru(acac)$_3$]) and 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos), **2.13**, in excellent yields (Table 2.4, Entry 1-4). Difunctional carboxylic acids with different chain length: 8C, **2.23**, 10C, **2.24**, 12C, **2.25**, and 19C, **2.26**, could be tolerated under the reaction conditions. Replacing aniline with water leads to diol (Table 2.4, Entry 5). When using 1.5 equivalents of aniline with dodecanedioic acid, 52% yield of the diamine was obtained (Table 2.4, Entry 6), the cyclic product, which is formed for substrate with chain lengths up to 7[60] was not observed. When 2-methyltetrahydrofuran (2-MeTHF) was used as solvent, very similar results were obtained to those obtained using 1,4-dioxane (Table 2.4, Entry 7 vs Table 2.4, Entry 3). But in this case, 2-methyl-1-phenylpyrrolidine, **2.27**, from the reaction of 2-MeTHF with aniline was also obtained as a side product (6% relative to aniline) (Scheme 2.10).

Table 2.4. Hydrogenation of carboxylic acids and their derivatives in the presence of aniline.[a]



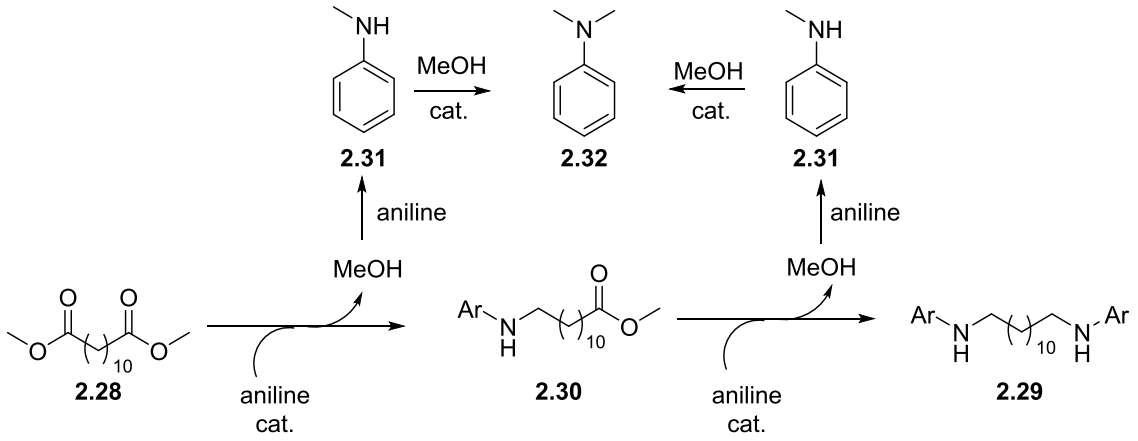
Entry	Chain length	Conv. (%)	Yield [b](%)
1	8 (**2.23**)	100	91
2	10 (**2.24**)	100	97
3	12 (**2.25**)	100	98
4	19 (**2.26**)	100	93
5[c]	12 (**2.25**)	97	95
6[d]	12 (**2.25**)	100	52
7[e]	12 (**2.25**)	100	97

[(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), aniline (3 equiv.), H_2 (10 bar), 220 °C, 42 h. [(b)]NMR yield using 1,4-dinitrobenzene as internal standard. [(c)]omitting aniline, [Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1 mol%), dioxane (15 mL), substrate (2.5 mmol), H_2O (10 mL), H_2 (10 bar), 220 °C, 20 h, major product is 1,12-dodecanediol. [(d)]As [(a)], aniline (1.5 equiv.) [(e)]As [(a)], 2-MeTHF (15 mL) was used as solvent.



Scheme 2.10. Side reaction between aniline and 2-methyl THF.

As esters are also widespread in nature, esters were tested as substrates as well. Reactions starting from dicarboxylic esters could also produce *N, N'*-diphenyl diamines in the presence of aniline. However, when reacting dimethyl dodecanedioate, **2.28**, with aniline under the same reaction conditions as the reaction starting from carboxylic acids, the diamine, **2.29**, was only obtained in 60% yield after 42 hours. (Table 2.5, Entry 1). In this case, methyl 12-(phenylamino)dodecanoate **2.30** was also observed in 30% yield. *N*-methyl aniline, **2.31**, and *N*,*N*-dimethylamine, **2.32**, were produced by methylation of aniline (Scheme 2.11). The methyl groups were derived from methanol which was a byproduct from the methyl ester hydrogenation.



Scheme 2.11. Side *N*-alkylation reaction between the alcohol produced from ester hydrogenation, in this case methanol and aniline.

The availability of aniline is reduced because of the side reactions between methanol and aniline, which leads to an insufficient aniline stock for the reaction with the ester. Higher equivalents of aniline were therefore introduced (increase from 3 equivalent to 5 equivalent compare to the substrates), after 42 hours methyl 12-(phenylamino)dodecanoate, **2.30**, was still observed by GCMS (Figure 2.12). Further increase of the reaction time to 70 hours led to full conversion, and the desired diamine, **2.29**, was obtained in 94% yield without the production of ester amine **2.30** (Figure 2.12) (Table 2.5, Entry 2).

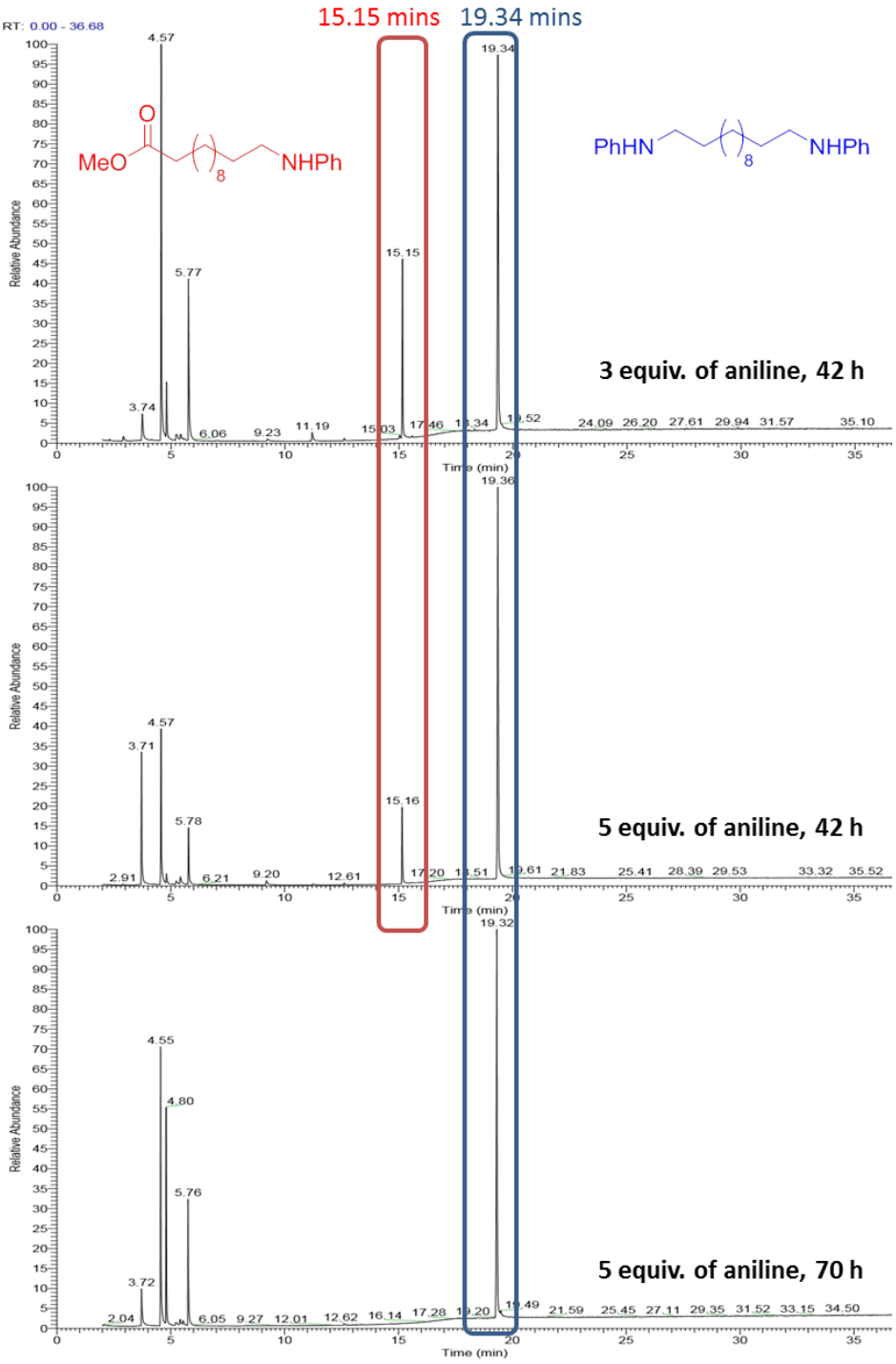


Figure 2.12. GC-MS analysis of the reactions between 1,12-dimethyl dodecanedioate and aniline under different conditions.

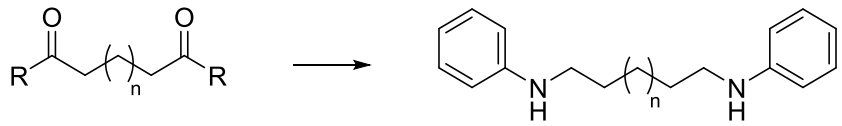
Replacing the methyl ester by diphenyl dodecanedioate, **2.33**, led to similar results, and gave the desired product **2.29** in 95% yield (Table 2.5, Entry 4) with only 3 equivalents of aniline. In this case, phenol is obtained as the byproduct. No alkylation between phenol and aniline was observed because phenyl does not contain α-hydrogen atoms so

the hydrogen borrowing mechanism *via* an aldehyde, required for alkylation of aniline by phenol, cannot take place.[60]

Hydrogenation of diethyl ester, **2.34**, gave the product in 76% yield (Table 2.5, Entry 3) with ethyl 12-(phenylamino)dodecanoate, **2.35**, as the side product. 1,19-Dimethyl nonadecanedioate, **2.6**, obtained from waste tall oil[61], can also be used as substrate for the production of N_1,N_{19}-diphenylnonadecane-1,19-diamine, **2.36**, in 96% yield (Table 2.5, Entry 5).

Extending the substrate scope, diamide, **2.37**, could also be hydrogenated to the corresponding diamine, **2.29**, in a 56% yield after 42 hours (Table 2.5, Entry 6). Monohydrogenated amide, **2.38**, was also obtained in 37% yield. Increasing the reaction time to 70 hours, the yield of the desired diamine, **2.29**, was increased to 98% (Table 2.5, Entry 7).

Table 2.5. Hydrogenation of dicarboxylic acid derivatives in the presence of aniline.[a]

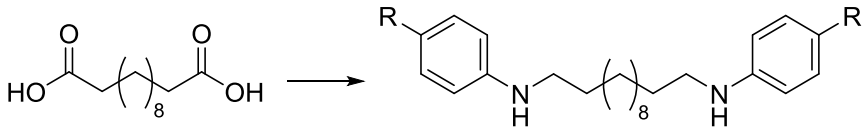


Entry	n	R	Equiv. aniline	Conv. (%)	Product	Yield (%)
1[b]	8	OMe **2.28**	3	100	**2.29**	60
2	8	OMe **2.28**	5	100	**2.29**	94
3	8	OEt **2.34**	5	100	**2.29**	76
4	8	OPh **2.33**	3	100	**2.29**	95
5	15	OMe **2.6**	5	100	**2.36**	96 (91)
6[b]	8	NPh **2.37**	3	95	**2.29**	56
7	8	NPh **2.37**	3	100	**2.29**	98
8[c]	8	NPh **2.37**	0	81	**2.29**	41

[(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), aniline (0-5 equiv.), H_2 (10 bar), 220 °C, 70 h; The conversion and yield are calculated by NMR with 1,4-dinitrobenzene as internal standard, isolated yields in parenthesis. [(b)] As footnote [(a)], 42 h. [(c)]As footnote [(b)] without added aniline. Other products include **2.38** (15%) aniline and other products.

Different amines were also tested on the hydrogenation of dodecanedioic acid, **2.25**, with aniline derivatives (Table 2.6). An electron donating methoxy group in the 4-position gave very similar results to those from the reaction with aniline, the corresponding diamine **2.39** was obtained in 97% yield by ^{1}H NMR analysis (Table 2.6, Entry 1), which is similar to the result obtained with aniline (98%) (Table 2.4, Entry 3). Weakly electron withdrawing 4-fluoro substitution gave slightly poorer results compared to the corresponding diamine **2.40** (80%) (Table 2.6, Entry 2). However, stronger electron withdrawing groups (such as trifluoromethyl and nitro) did not produce the expected diamine (Table 2.6, Entry 3 and 4).

Table 2.6. Other amines Aniline derivatives.[a]

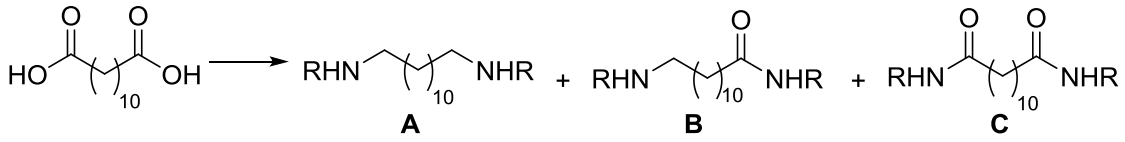


Entry	R	Conv.[b] (%)	Product	Yield [b](%)
1	OMe	100	**2.39**	97
2	F	100	**2.40**	80
3	CF_3	100	-	0
4	NO_2	100	-	0

[(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), aniline (3 equiv.), H_2 (10 bar), 220 °C, 42 h. [(b)]NMR yield using 1,4-dinitrobenzene as internal standard.

The reaction works very well with aniline and some aniline derivatives (Table 2.4, Table 2.5 and Table 2.6). However, other amines such as aliphatic, benzylic and olefinic amines are less successful, and the results are shown in Table 2.7.

Table 2.7. Reaction with different substrates and amines.[a]



Entry	Amine	Conv. (%)	Product		
			Yield A (%)	Yield B (%)	Yield C (%)
1	Isopropylamine **2.41**	100	18[b] (**2.43**)	47[b] (**2.44**)	28 (**2.45**)
2	*n*-Butylamine **2.42**	100	0 (**2.46**)	0	58 (**2.47**)
3	diisopropylamine **2.48**	100	0	0	0
4	Diphenylamine **2.49**	100	0	-	-
5	*N*-methyl aniline **2.31**	100	n.d. (**2.50**)	n.d.	n.d.
6	Benzylamine **2.51**	100	0 (**2.52**)	n.d. (**2.54**)	42 (**2.53**)
7	4-nitrobenzylamine **2.55**	100	0 (**2.56**)	0	polymer
8	Dibenzylamine **2.57**	100	0 (**2.58**)	n.d.	-
9	*N*-Boc-benzylamine **2.59**	100	0 (**2.60**)	0	0
10	Allylamine **2.62**	100	0 (**2.64**)	0	0
11	Benzylamide **2.63**	n.d.	0 (**2.65**)	0	0

[(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), amines (3 equiv.), H_2 (10 bar), 220 °C, 42 h. [(b)]Yields calculated by ^{1}H NMR with 1,4-dinitrobenzene as internal standard.

Aliphatic amines (eg. isopropylamine, **2.41**, *n*-butylamine, **2.42**) were tested first. When isopropylamine, **2.41**, was used as the amine source, the reaction mixture was obtained as a white solid in a yellow solution, The white solid could be solubilised in DCM and the solution was analysed by GCMS. The desired diamine, **2.43**, monohydrogenated amide amine, **2.44**, and diamides, **2.45**, were all observed from the spectra. Recrystallisation with EtOAc afforded the diamide, **2.45**, as a pale yellow solid in 28%

yield. Quantitive ^{1}H NMR of the concentrated mother liquors showed 18% yield of the diamine, **2.43**, and 47% yield of the monohydrogenated product, **2.44** (Table 2.7, Entry 1).

When *n*-butylamine, **2.42**, was used as the amine source with dodecanedioic acid, **2.25**, the expected N_1,N_{12}-dibutyldodecane-1,12-diamine, **2.46**, was not obtained by NMR or MS analysis. Instead, the amide product N_1,N_{12}-dibutyldodecanediamide, **2.47**, was obtained in 58% yield (Table 2.7, Entry 2).

Attempts at the synthesis of tertiary amines were also carried out. Diisopropylamine, **2.48**, and diphenylamine, **2.49**, led to no formation of the desired diamines (Table 2.7, Entry 3-4). When *N*-methyl aniline, **2.31**, was tested (Table 2.7, Entry 5), the desired N_1,N_{12}-dimethyl-N_1,N_{12}-diphenyldodecane-1,12-diamine, **2.50**, was obtained as a mixture of other products illustrated in Figure 2.13, analysed by GCMS or MS in both positive and negative modes. Isolation of **2.50** was not successful with flash column chromatography over either silica or alumina with different solvent gradients.

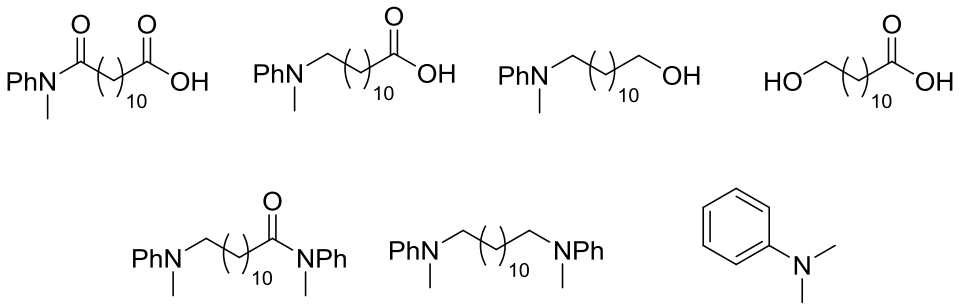
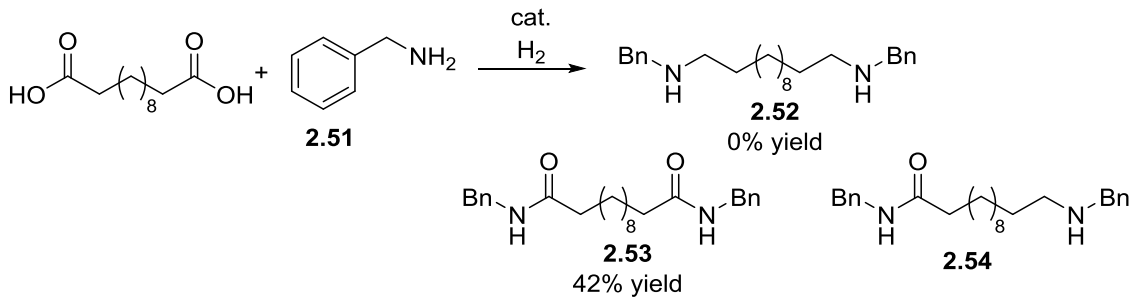


Figure 2.13. Side products in the reaction mixture from dicarboxylic acid and *N*-methyl aniline.

Protecting groups were also introduced for the synthesis of linear diamines. If protected linear diamines could be formed successfully, deprotection could then afford the primary linear diamines as the precursors for the synthesis of nylons.

When benzylamine **2.51** was used, the desired hydrogenated product, benzyldiamine **2.52**, was not detected after the reaction by NMR, GCMS or MS (Table 2.7, Entry 6). However, diamide **2.53** which is a side product from the nucleophilic substitution between benzylamine and the carboxylic acid was obtained in 42% yield as a white solid. The other side products obtained were the mono-hydrogenated product, *N*-benzyl-12-(benzylamino)dodecanamide **2.54** (Scheme 2.12).



Scheme 2.12. The reaction between carboxylic acid and benzylamine.

The big difference between aniline and benzylamine reactions could be related to their electronic properties. Benzylamine is more electron rich compared to aniline, so benzylamine with an electron withdrawing group (4-nitrobenzene, **2.55**) was introduced (Table 2.7, Entry 7). Strangely, a black polymer was obtained in this case, and the expected diamine, N_1, N_{12}-bis(4-nitrobenzyl)dodecane-1,12-diamine, **2.56**, was not obtained.

When reacting dicarboxylic acid with dibenzylamine, **2.57** (Table 2.7, Entry 8), the expected diamine **2.58** was not formed again. Other products were analysed by MS, GCMS and are summarised in Figure 2.14.

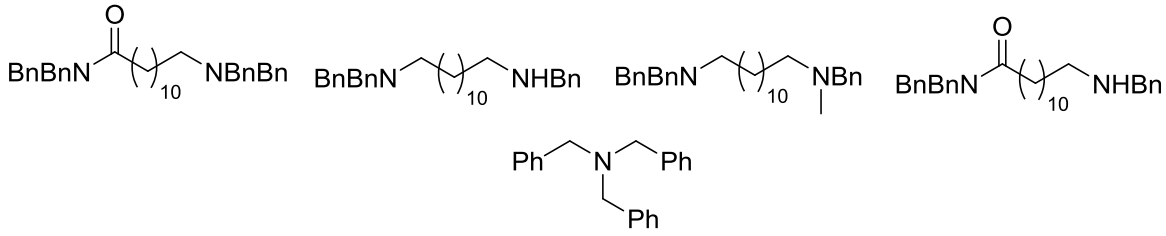


Figure 2.14. Products from the hydrogenation of dodecanedioic acid in the presence of dibenzylamine.

When the diacid reacted with *N*-Boc-benzyl amine, **2.59**, the corresponding *N*-Boc-diamine, **2.60**, was not formed (Table 2.7, Entry 9). Instead, dibenzyl diamide, **2.61**, and monohydrogenated product were produced (Figure 2.15), which means that the Boc group was not stable under the reaction conditions.

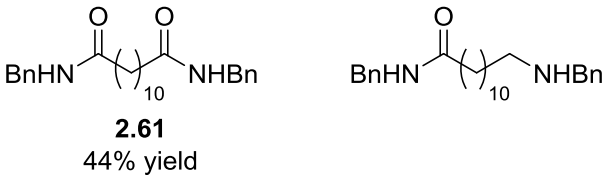


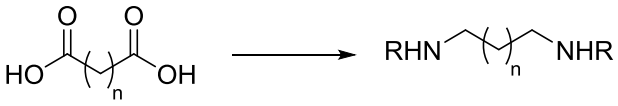
Figure 2.15. Products in the reaction mixture between dicarboxylic acid and *N*-Boc-benzylamine.

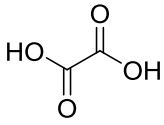
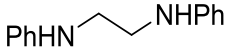
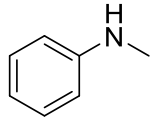
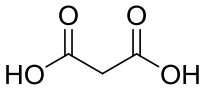
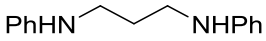
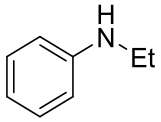
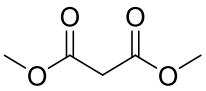
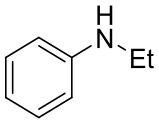
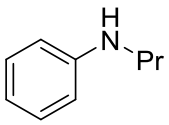
Reactions with allylamine, **2.62,** and benzylamide, **2.63,** were also studied, and the desired diamines **2.64** and **2.65** were not produced (Table 2.7, Entries 10 and 11).

It is also interesting to find out if this reaction could be used for shorter chain dicarboxylic acids, since shorter chain diamines are known to be important ligands or intermediates for ligands, such as NHCs. Therefore, reaction of oxalic acid, **2.66**, and malonic acid, **2.67**, were carried out with aniline.

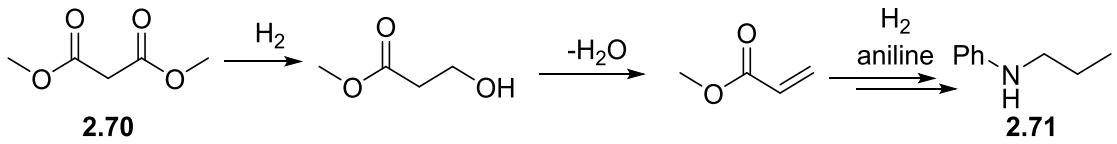
After the reaction, the expected *N, N'*-diphenyl diamines, **2.68** and **2.69** were not obtained, *N*-methyl aniline, **2.31**, and *N*-ethyl aniline, **2.15**, were obtained from oxalic acid, **2.66**, and malonic acid, **2.67**, correspondingly. Oxalic acid, **2.66**, decomposed to carbon dioxide and formic acid, and malonic acid, **2.67,** decomposed to carbon dioxide and acetic acid under the reaction conditions. Formic acid and acetic acid were subsequently converted to *N*-methyl aniline, **2.31**, and *N*-ethyl aniline, **2.15**. Oxalic acid, **2.66**, was converted to 23% of *N*-methyl aniline, **2.31** (Table 2.8, Entry 1), and malonic acid, **2.67**, was converted to *N*-ethyl aniline, **2.15**, in 70% yield (Table 2.8, Entry 2). In order to increase the stability of the shorter chain carboxylic acids, their ester derivatives were tested, as they have higher boiling point (181 °C for dimethyl malonate *vs* 135°C for malonic acid). Reaction with dimethyl malonate, **2.70**, gave a mixture of *N*-ethyl aniline, **2.15**, and *N*-propyl aniline, **2.71** (Table 2.8, Entry 3). The side product, *N*-ethyl aniline, **2.15**, is also formed from decomposition of the ester as observed in the case of the carboxylic acid. The *N*-propyl aniline, **2.71**, may be obtained by hydrogenation of one end to alcohol, followed by dehydration to a conjugated monoester. Hydrogenation of both the double bond and the ester with aniline would afford *N*-propylaniline, **2.71** (Scheme 2.13).

Table 2.8. Reaction of difunctional substrates with a shorter chain length.[a]



Entry	Substrate	Amine	Conv. (%)	Product
1	 **2.66**	aniline	100	 **2.68** 0%  **2.31** 23%
2	 **2.67**	aniline	100	 **2.69** 0%  **2.15** 70%
3[b]	 **2.70**	aniline	100	 **2.15** 36%  **2.71** 63%

[(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), aniline (3 equiv.), H_2 (10 bar), 220 °C, 42 h. [(b)]aniline (5 equiv.).



Scheme 2.13. Proposed mechamism for the production of *N*-propylaniline from dimethyl malonate.

2.2.4 Diols as substrates

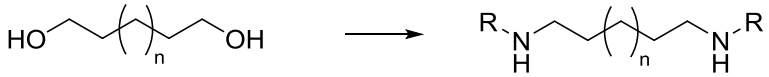
Partly to obtain a better understanding of the reactions when using aniline and partly to try to synthesise di-primary amines in a two step process from dicarboxylic acid derivatives, diols were also studied as substrates. Diols can be synthesised from dicarboxylic acids by hydrogenation using a variety of catalysts including Ru/triphos,[61] which is also an efficient system for the amination of alcohols *via* a hydrogen borrowing mechanism.[65] For example, 1-octanol is known to be aminated to the corresponding octylamine using ammonia gas with the Ru/triphos system.[52] Long chain diamines have also been prepared by amination of diols using liquid ammonia catalysed by the Ru/triphos system in yields up to 68%.[74]

It is known that alcohols are intermediates in the formation of amines by the hydrogenation of amides using the Ru/triphos system promoted by the Lewis acid, $Yb(OTf)_3.3H_2O$,[65] but alcohol intermediates were not detected in the Ru/triphos catalysed hydrogenation of short chain dicarboxylic acid derivatives in the presence of aniline to give *N*-phenyl heterocycles.[60]

Reactions were firstly carried out in the presence of hydrogen to give comparable conditions to those used for diacids or esters. This allowed determination of whether the diol is a viable intermediate in the reactions starting from dicarboxylic acid derivatives.

Amination of C_{12}, **2.72**, and C_{19} diols, **2.9**, with aniline gave excellent yields of the diamine (Table 2.9, Entry 1 and 2). Reaction with other amines such as benzylamine afforded the N_1,N_{12}-dibenzyldodecane-1,12-diamine, **2.52**, in 86% yield (Table 2.9, Entry 3). The benzyldiamine, **2.52**, can itself be used as a precursor or can be deprotected to the primary diamine. Other amines such as isopropylamine, **2.41**, also produced the desired product, **2.43**, in a reasonable yield (Table 2.9, Entry 5). Control experiments showed, however, that hydrogen gas is necessary for these reactions. Much lower yields were obtained in the absence of hydrogen (Table 2.9, Entry 5-8 compared with Entry 3 and 1) when reacting diol with benzylamine or aniline.

Table 2.9. Amination of diols in the presence of an amine.[a]



Entry	n	Substrate	R	Conv. (%)	Product	Yield (%)
1	8	**2.72**	Ph	100	**2.29**	98
2	15	**2.9**	Ph	100	**2.36**	98
3	8	**2.72**	Bn	100	**2.52**	86
4	8	**2.72**	^{i}Pr	100	**2.43**	62
5[b]	8	**2.72**	Bn	100	**2.52**	33
6[c]	8	**2.72**	Bn	100	**2.52**	31
7[b]	8	**2.72**	Ph	100	**2.29**	45
8[c]	8	**2.72**	Ph	100	**2.29**	72

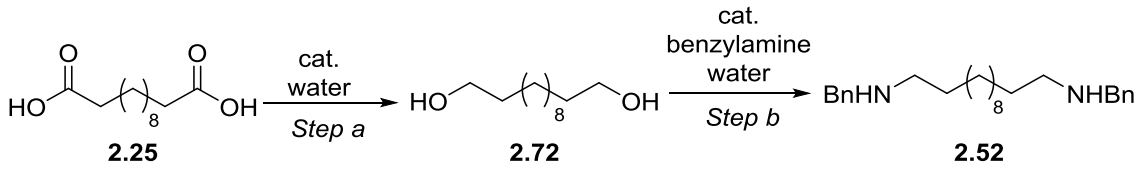
[(a)][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), amine (3 equiv.), H_2 (10 bar), 220 °C, 20 h. [(b)]Same as [(a)], Ar (1 bar) instead of H_2. [(c)]Same as [(a)], Ar (10 bar) instead of H_2.

The benzyldiamine, **2.52**, which could be deprotected for the synthesis of primary diamine, was successfully obtained from diol, **2.72**, in presence of benzylamine, **2.51**, (Table 2.9, Entry 3), but not from dicarboxylic acid, **2.25**, in presence of benzylamine, **2.51**. In addition the diol could be successfully obtained from the dicarboxylic acid by the same catalytic reaction in the presence of water (Table 2.4, Entry 5). Attempts to combine those two steps were carried out aiming to make it into a one-pot reaction.

As aforementioned, dicarboxylic acid was successfully hydrogenated to the diol in the presence of 10 mL of water (Table 2.4, Entry 5). However, if the same amount of water (10 mL) was added to the reaction when reacting benzylamine with diol, no expected product **2.52** was obtained (Table 2.10, Entry 1). The mass spectral analysis of the crude mixture showed a mixture of diamide, monoamide and amine alcohol, as shown in Figure 2.16. Separation of these products was carried out by flash column chromatography over basified silica, reversed phase silica and basic alumnia with different solvents gradients. However, these products have very similar R_f values, which made them difficult to separate. Due to the mixture of products, the structural confirmation of the products cannot be confirmed by NMR spectroscopy. The proposed structures are based on GCMS analysis. Benzylalcohol, **2.73**, which was produced in a reaction between benzylamine, **2.51**, and water, was observed in a large quantity.

Since water was detrimental for *Step b*, but essential for *Step a*, a smaller amount of water (1 mL) was added into the reaction mixture, which increased the yield of the desired product **2.52** to 68% yield with only 92% conversion for *Step b* (Table 2.10, Entry 2). However, when 1 mL of water was used instead of 10 mL for *Step a*, only starting material was recovered, and difunctional carboxylic acid could not be hydrogenated to the alcohol. Hence the observed results suggest that water is essential for the first step, but not for the second step. The tandem reaction was not successful with these experimental conditions.

Table 2.10. Attempted reaction for the tandem reaction for the synthesis of *N. N'*-dibenzyldiamine.



Entry	Step	Amine	Water (mL)	Yield (%)
1	*b*	Benzylamine	10	0
2	*b*	Benzylamine	1	68
3	*a*	---	10	95
4	*a*	---	1	0

[a][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), H_2O (1 or 10 mL), H_2 (10 bar), 220 °C, 20 h. [b][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), benzylamine (3 equiv.), H_2O (1 or 10 mL), H_2 (10 bar), 220 °C, 20 h.

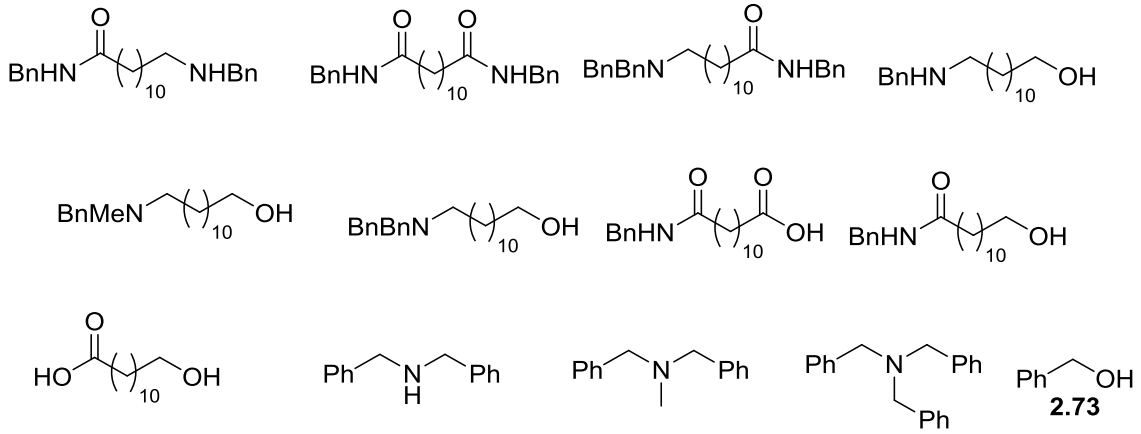
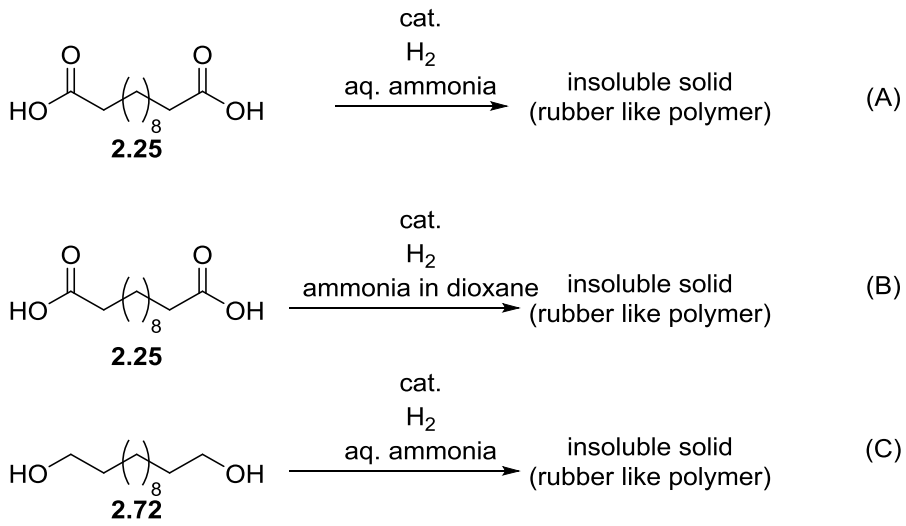


Figure 2.16. Products from Table 2.10, Entry 1.

2.2.5 Synthesis of primary diamines

So far, secondary diamines have been successfully obtained, and they are of potential interest for the synthesis of *N*-substituted polyamides. However, nylons are usually synthesised from primary diamines, and therefore, the direct synthesis of primary diamines was studied. With the conditions used for the synthesis of *N*-substituted diamines ([Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), dicarboxylic acid substrates (2.5 mmol), aqueous ammonia (10 mL), H_2 (10 bar),

220 °C, 42 h), rubber like material was obtained instead of the desired primary diamines (Scheme 2.14, Reaction A). Replacing aqueous ammonia with ammonia in 1,4-dioxane (Scheme 2.14, Reaction B), or replacing the dicarboxylic acid with diol (Scheme 2.14, Reaction C), polymer-like materials were still obtained. These rubber-like materials could not be analysed by solid state mass spectrometry with matrix, as they could not be ground into powders. Different solvents system (such as DCM, MeOH, DMSO and 1,2,4-trichlorobenzene at room temperature or high temperatures), and acids (concentrated sulfuric acid and hydrochloric acid) were all tested to dissolve the solid, but unfortunately, none of them worked. Infrared and elemental analysis were carried out to identify these materials. Infrared spectra of each of the materials had large areas of overlap, and thus were inconclusive. While the elemental analysis gave some little differences as shown in Scheme 2.14. Assuming only carbon, hydrogen, nitrogen and oxygen elements are present in the material, the empirical formula are calculated and shown in Scheme 2.14. The elemental analysis of both samples starting from dicarboxylic acid, **2.25**, (Reaction A and B in Scheme 2.14) appeared to have very similar %proportions of elements and consequently similar empirical formula. The ratio of nitrogen to oxygen is around 1:1 in these two cases, which suggested that nitrogen and oxygen both come from the amide group. The insoluble materials from Reaction A and B are therefore deduced to be polyamides. The same method was carried out to analyse the solid from Reaction C, which has diol, **2.72**, as substrate. The empirical formula in this case has the nitrogen to oxygen ratio around 2:1, which suggests that in addition to the amide groups, there are other nitrogen containing functional groups in the polymer. The solid from Reaction C is therefore deduced to have both amine and amide groups.



	Elemental analysis of the product				
Reaction	**%C**	**%H**	**%N**	**%O**	**Empirical formula**
A	74.98	12.10	6.40	**6.52**	$C_{15}H_{30}NO$
B	74.46	12.75	6.28	**6.51**	$C_{15}H_{31}NO$
C	75.46	14.28	6.87	**3.39**	$C_{30}H_{66}N_2O$

Scheme 2.14. Elemental analysis of the synthesised insoluble material starting with ammonia. %O and empirical formula are calculated by assuming only C, H, N and O elements exist in the material.

Since the differences in the elemental analysis is insignificant (around 1% difference in %C, and 2% in %H), to eliminate the possibility of technical or human errors, a ninhydrin test was carried out. The ninhydrin test is a good way to detect the presence of amines, as it reacts with amines to produce Ruhemann's purple as a deep blue or purple colour. As demonstrated in Figure 2.17, the solid from Reaction A (reaction between dicarboxylic acid **2.25** and aqueous ammonia) did not change colour after spraying with ninhydrin. However, the compound from Reaction C (reaction between diol, **2.72**, and aqueous ammonia), the colour changed to very dark blue with ninhydrin spray evidencing the existence of amine groups (Figure 2.17). The ninhydrin tests supported the results obtained from elemental analysis.

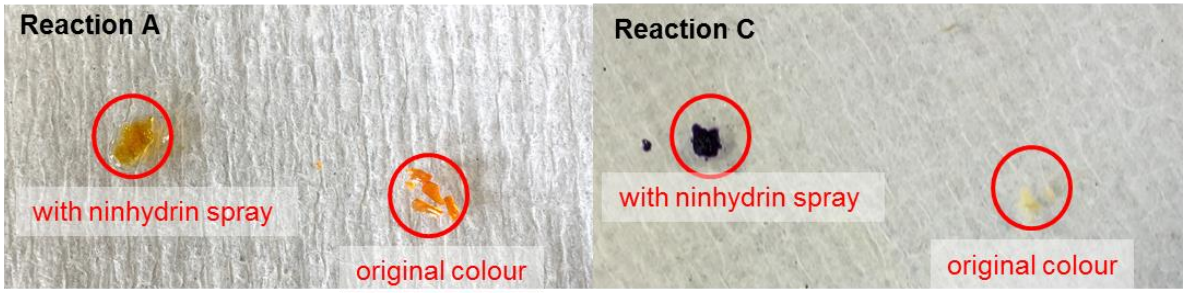
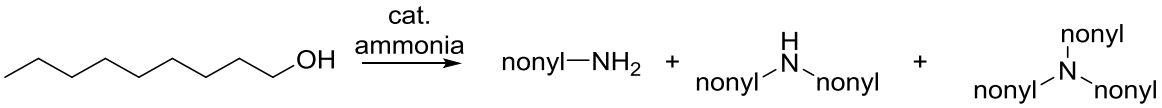


Figure 2.17. Ninhydrin spray on polymers

Because of the formation of polymers, a test reaction was carried out using monofunctional alcohol. *n*-Nonanol, **2.74**, was converted in the presence of aqueous ammonia (Table 2.11). Secondary amine, **2.75**, and tertiary amine, **2.76**, were also formed together with the expected primary amine, **2.77**. Changing the aqueous ammonia to liquid ammonia led to a much lower conversion and selectivity of the primary amine (Table 2.11, Entry 2 *vs* Entry 1). The combination of liquid ammonia plus water slightly increased the conversion and selectivity to 1-nonylamine, **2.77**, compared to the reaction with only liquid ammonia (Table 2.11, Entry 3 *vs* Entry 2). In this case, *n*-nonanol reacted with ammonia first to afford 1-nonylamine, **2.77**, which is more nucleophilic than ammonia. Therefore, the second amination between **2.77** and **2.74** was favored to form the secondary amine, **2.75**. Subsequently, the tertiary amine, **2.76**, was obtained by amination between **2.75** and **2.74**.

Table 2.11. Test reaction with *n*-nonanol with aqueous ammonia and liquid ammonia.[a]



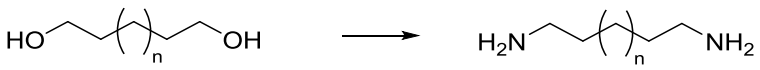
2.74 **2.77** **2.75** **2.76**

Entry	ammonia	Conv. (%)	Sel. 2.77 (%)	Sel. 2.75 (%)	Sel. 2.76 (%)
1	aq.ammonia	80	55	12	33
2	liquid ammonia	6	16	9	2
3[b]	liquid ammonia+water	26	26	49	25

[(a)][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1 mol%), 1,4-dioxane (5 mL), substrate (2.5 mmol), aq. ammonia (2.5 mL), H_2 (10 bar), 220 °C, 16 h. Conversion and selectivity calculated by uncalibrated GC-FID. [(b)]H_2O (1 mL).

The formation of secondary and tertiary nonylamines occurs because the produced alkylamines are better nucleophiles than ammonia so, in the case of a difunctional substrate, polymers are more likely to be formed. The general way to avoid polymerisation was to decrease the concentration of substrates, we then revisited the reaction with difunctional substrates. It turned out that after diluting the reaction mixture from 0.17 mmol/mL to 0.025 mmol/mL, the polymerisation was prevented. Instead, primary diamines could be successfully synthesised starting with diols. Herein, primary diamines were successfully obtained using aqueous ammonia. Reaction of 1,12-dodecanediol, **2.72**, with aqueous ammonia gave 86% conversion and 84% yield to the desired primary, **2.78** (Table 2.12, Entry 1). This is a significant improvement on the literature which has 68% yield of the same product and requires liquid ammonia, which is more difficult to handle, as the amine source.[74] Slightly increasing the concentration of ammonia by using ammonia in 1,4-dioxane (0.5 M) instead of using 1,4-dioxane alone (aqueous ammonia was added in both cases) as the solvent gave a very similar result (86% yield of **2.78**) (Table 2.12, Entry 2). Increasing the reaction time did not improve the conversion (Table 2.12, Entry 3), possibly because of the equilibrium between diol and diamine in the presence of water. When the reaction temperature was lowered to 165 °C, the conversion was slightly decreased (from 86% to 72%) after 20 hours (Table 2.12, Entry 5). 1,6-Hexane diamine, **2.79**, is a very important precursor for the synthesis of nylon 6,6, and it can also be produced using this method in good yield 64% (Table 2.12, Entry 4), with ε-caprolactam as a side product (15%). Nylon 19 precursor, 1,19-nonadecanediamine, **2.10**, was also obtained in this way in a good yield (76%, Table 2.12, Entry 6).

Table 2.12. Amination of diols in the presence of aqueous ammonia.[a]



Entry	n	Conv. (%)	Product	Yield (%)
1	8	86	**2.78**	84
2[b]	8	88	**2.78**	86
3[c]	8	88	**2.78**	87
4	2	93	**2.79**	64
5[d]	8	72	**2.78**	71
6	15	92	**2.10**	76

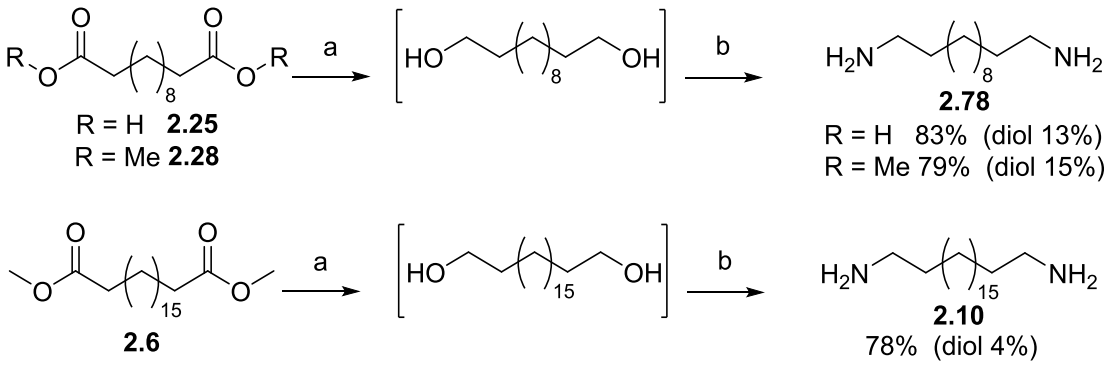
[(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol %), 1,4-dioxane (20 mL), substrate (1.25 mmol), aq. ammonia (35%, 30 mL), H_2 (10 bar), 220 °C, 20 h. [(b)]ammonia in 1,4-dioxane (0.5M, 20 mL) instead of 1,4-dioxane. [(c)]42 h. [(d)]165°C.

With these optimised conditions, direct syntheses from carboxylic acids, esters and diamides were carried out. Disappointingly, none of these reactions gave the desired primary diamine.

2.2.6 Sequential reactions

Since carboxylic acid derivatives can be hydrogenated to diols using Ru/triphos/MSA and since it has been shown above that diols can be transformed into diaminoalkanes by reaction with aqueous ammonia with the same catalytic system, attempted transformations of dicarboxylic acid derivatives to primary diamines by a two step reaction in one pot was carried out. This would remove the problem of intermolecular amide formation between molecules of the form $RO_2C(CH_2)_nNH_2$ to give polymers, which complicate a one pot synthesis.

The hydrogenation of 1,12-decanedoic acid, **2.25**, or its dimethyl ester, **2.28**, was carried out in the presence of water using the Ru/triphos/MSA system. At the end of the reaction, the reactor was depressurised and opened, Aqueous ammonia and extra 1,4-dioxane were added. The autoclave was closed, repressurised with hydrogen and heated. Analysis of the product showed that 1,12-diaminodeodecane, **2.78**, was formed in 83 or 79% yield respectively, the main contaminant being diol (Scheme 2.15). With the same method, 1,19-dimethyl nonadecanedioate, **2.6**, can also be successfully converted to 1,19-nonadecanediamine, **2.10**, in an one-pot reaction (78% yield, Scheme 2.15).



Scheme 2.15**.** One pot synthesis of primary diamines. [(a)][Ru(acac)$_3$] (2 mol%), triphos (4 mol %), MSA (2 mol%), 1,4-dioxane (7.5 mL), substrate (1.25 mmol), distilled water (5 mL), H_2 (10 bar), 220 °C, 20 h. [(b)] 1,4-dioxane (12.5 mL), aq. ammonia (35%, 30 mL), 220 °C, 20 h.

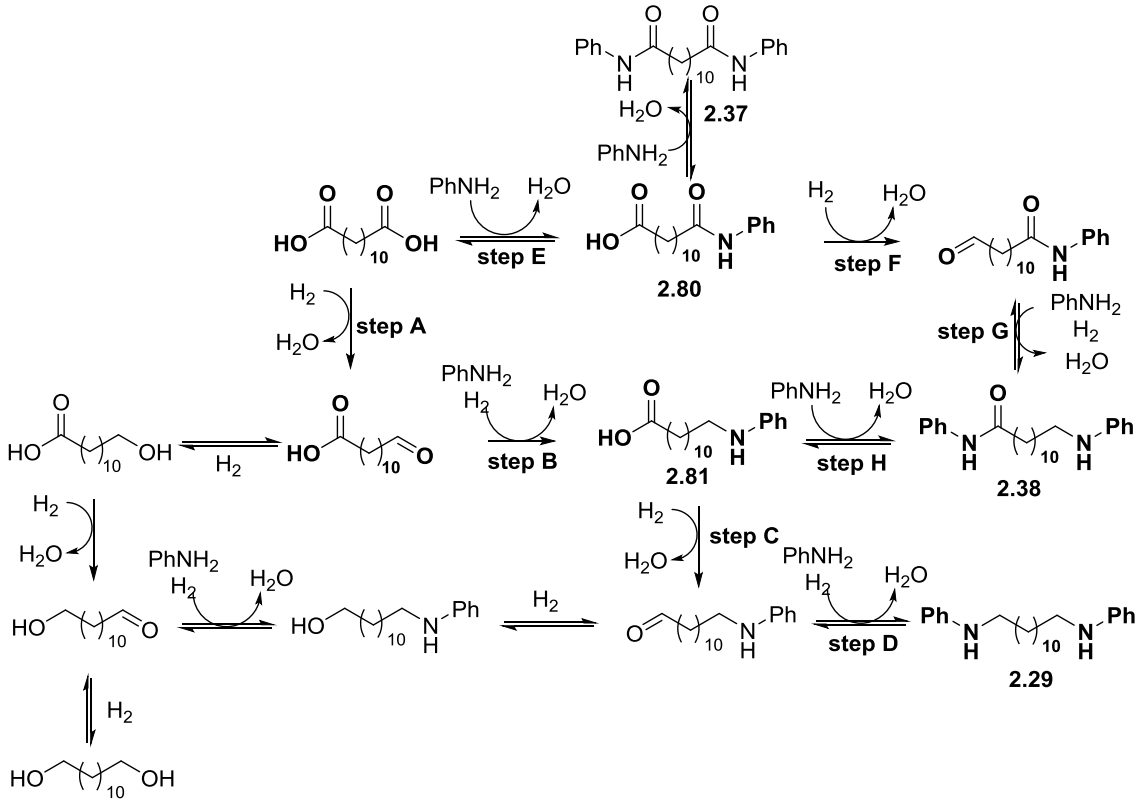
2.2.7 Proposed reaction pathway

Summarising the reactions above, polyamide precursors, primary and secondary diamines can be produced in high yields by hydrogenation of dicarboxylic acids, diesters, diols or diamides in the presence of aniline, aniline derivatives or aqueous ammonia (diols only or a 2-step reaction from di acids or diesters). Dodecanedioic acid, **2.25**, is used as a model to discuss the results.

When hydrogenating dodecanedioic acid, **2.25**, in the presence of aniline, acid amide, **2.80**, diamide, **2.37**, amide amine, **2.38**, and acid amine, **2.81**, were all observed after 20 hours, but not any intermediates containing an alcohol group at one or both ends. After 42 hours, full conversion to the *N,N'*-phenyl diamine, **2.29**, was observed. Hydrogenation of diamide, **2.37**, under the same catalytic conditions (42 h) gave 95% conversion and 56% yield to the desired diamine, **2.29**, the main other product being the aminoamide, **2.38** (37% yield) (Table 2.5, Entry 6). Increasing the reaction time to 70 hours, the substrate was fully converted with 98% yield to the desired diamine, **2.29**. Although these observations suggest that diamide **2.37** may be an intermediate for this reaction, there must also be other faster routes which do not involve the diamide because the diacid is fully converted in 42 h whilst the diamide is not.

Hydrogenation of diamide, **2.37**, in the absence of aniline produces free aniline, which suggests that the partially hydrogenated amide undergoes some C-N bond cleavage to give aldehyde. In addition, it has been shown that for simple amines when using Lewis rather than Brønsted acid promoters, alcohols are intermediates. We propose that the low energy pathways will follow Steps A-D or E-H then C, Scheme 2.16. Three of the compounds observed after shorter reaction times (**2.38**, **2.80** and **2.81**) are contained within these two alternative pathways. The diamide, **2.37**, is not within either pathway, consistent with its being observed after short reaction times, being formed by amidation of **2.80**, being hydrogenated to give **2.29** but not reacting as fast as the diacid. However, control reactions omitting aniline produce diol with high selectivity under the same reaction conditions as used for amine formation (Table 2.4, Entry 5). Starting with diol, **2.72**, and aniline under the same conditions gave 98% yield of the desired diamine, **2.29**, after 20 hours (Table 2.9, Entry 1). Thus, we cannot exclude pathways including

alcohols, since the rapid rate of alcohol consumption would mean that the standing concentration of alcohol intermediates would be very small.



Scheme 2.16. Proposed reaction pathway for: the hydrogenation of 1,12-dodecanedioic acid in the presence of aniline to give **2.29**. Steps A-D and/or E-H, C, D, intermediates are bold), numbered compounds have been identified as being formed during the reaction; the reductive amination of 1,12-dodecanediol with aniline to give **2.29** (bottom) and the hydrogenation of 1,12-dodecanedoic acid to 1,12-dodecanediol (left hand side). The sequential reaction using ammonia proceeds through the hydrogenation to 1,12-dodecanediol followed by reductive amination.

2.3 Conclusions

The hydrogenation of dicarboxylic acids and their esters in the presence of amines provides a new methodology for the synthesis of α,ω-diamines. Reaction of dicarboxylic acids and their derivatives with aniline in the presence of $[Ru(acac)_3]$ and 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) gave good to excellent yields of the *N, N'-diphenyl diamines* with 8 to 19 carbon chains. Although primary diamines could not be obtained in a similar way using aqueous ammonia in place of aniline, they were formed from the reaction between diols and aqueous ammonia in very good yield and selectivity. They could also be formed in good yield by a sequential one pot reaction involving hydrogenation of the diacid or diester to the diol, addition of aqueous

ammonia and further reaction to the diamine using the same catalyst. Renewable feedstocks can hence be converted to important precursors to polyamides.

2.4 Experimental

2.4.1 General method

All the commercially available reagents were used without further purification unless specified. 1,4-Dinitrobenzene, 4-nitroaniline, benzylamine, 1,12-dodecanedioic acid, 1,12-dodecanediol, 1,10-decanedioic acid, 1,7-heptanedioic acid and 1,4-dioxane were purchased from Alfa Aesar; dodecane, *tris*(2,4-pentanedionato)ruthenium(III) ([$Ru(acac)_3$]), 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) and *N*-methylaniline were purchased from Sigma Aldrich; tris(dibenzylideneacetone)dipalladium(0) ([$Pd_2(dba)_3$]) and 4-fluoroaniline were purchased from Fluorochem. Aniline was distilled over zinc powder and KOH under vacuum. Air sensitive or moisture sensitive reactions were carried out under argon in a fume hood using standard Schlenk techniques with oven-dried glassware. Flash column chromatography was performed manually using silica gel (pore size 60 Å, 70-230 mesh particle size, 40-63 μm particle size). Analytical TLC was performed on pre-coated polyester sheets of silica (60 F254 nm) and visualised by short-wave UV light at 254 nm. Permanganate TLC stain was used for compounds with no UV visible chromophore. Ninhydrin stain was also used for primary and secondary amines, giving a dark purple spot for primary amines, and a yellow/orange spot for secondary amines. Mass spectra were recorded on a Micromass LCT with a TOF mass spectrometer coupled to a Waters 2795 HPLC and a Waters 2996 detector. NMR spectra were recorded on Bruker Avance II 400 and Bruker Avance II 500 spectrometers, ^{13}C spectra were measured with ^{1}H decoupling. Residual protio peaks from deuterated solvents were used as reference with TMS at 0 ppm. GCMS was carried out using a Thermo Electron Corporation DSQ II for the GC, and Trace GC ULTRA Thermo Electron Corporation mass spectrometer for the MS with a THERMO TR-5 (5% Phenyl Methylpolysiloxane) column. Method: 50-300 °C, ramp rate 15 °C/min, hold for 20 mins.

2.4.2 Synthesis of esters from carboxylic acids

General procedure 1:[75] To a solution of carboxylic acid (20 g, 1.0 equiv.) in alcohol (50 mL) was slowly added concentrated sulfuric acid (0.3 equiv.). The resulting mixture was stirred at reflux for 2 h until TLC analysis indicated complete consumption of the starting material. The excess alcohol was removed under vacuum to give the crude product, which was poured into crushed ice and then extracted with dichloromethane (DCM, 5 × 50 mL). The organic layers were washed with 5% aq. $NaHCO_3$ solution (50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure.

2.4.3 Synthesis of primary or secondary amides from carboxylic acid

General procedure 2:[76] Oxalyl chloride (4.6 mL, 53 mmol, 4 equiv.) was added dropwise into a suspension of carboxylic acid (13 mmol) in anhydrous DCM (65 mL) in a Schlenk flask. The reaction mixture was stirred overnight under Ar. The reaction mixture was concentrated under reduced pressure to afford the carboxylic acid chloride. For the synthesis of primary amides, anhydrous THF (30 mL) was then added into the flask and the solution of the carboxylic acid chloride was slowly added to aqueous ammonia (6 mL, 53 mmol, 4 equiv.) at 0 °C. A white solid appeared immediately after addition, and the reaction mixture was stirred for 2 h at room temperature. The white solid was filtered and washed with THF (50 mL) to afford the primary amide. For the synthesis of secondary amides, distilled aniline (2.4 mL, 26 mmol, 2 equiv.) in pyridine (16 mL) was prepared under Ar. Acid chloride was then added into the solution of aniline in pyridine dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into distilled water (100 mL). Filtration and drying afforded the crude product.

2.4.4 Hydrogenation of dicarboxylic acids and their derivatives in the presence of an amine source

General procedure 3:[43] $[Ru(acac)_3]$ (0.010-0.020 g, 0.025-0.05 mmol, 1-2 mol%), triphos (0.031-0.062 g, 0.05-0.1 mmol, 2-4 mol%) and substrate (2.5 mmol) were weighed in air and introduced into a 250 mL Hastelloy autoclave fitted with a stirrer bar. The autoclave was sealed and purged by three vacuum/Ar cycles. Methanesulfonic acid (1.62-3.24 μL, 0.025-0.05 mmol, 1-2 mol%) in degassed 1,4-dioxane or 2-methyl tetrahydrofuran (15 mL) was introduced into the autoclave through a septum using a

syringe. Amine (3-5 equiv.) was also introduced into the autoclave. The autoclave was sealed again, connected to the high pressure system, and purged six times with 10 bar of H_2. The autoclave was charged with 10 bar of H_2, and heated to 220 °C for the required amount of time. The autoclave was cooled, vented and opened. The crude mixtures were analysed using GC-MS, GC-FID, NMR spectroscopy, or mass spectrometry, examples of spectra are shown below. Quantitative calculations were based on the analysis of ^{1}H NMR spectra with 1,4-dinitrobenzene as an internal standard.

2.4.5 Reduction of dicarboxylic acids and diesters using $LiAlH_4$

General procedure 4:[77] Dicarboxylic acid (30 mmol) or the diester in anhydrous THF (100 mL) was added slowly into a solution of lithium aluminium hydride (92 mmol, 3 equiv.) in anhydrous THF (250 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. Excess lithium aluminium hydride was quenched with ethyl acetate. Saturated potassium sodium tartrate solution (Rochelle solution) was slowly added to the reaction mixture. The mixture was stirred for 3 hours and the two layers were separated using a separating funnel. The organic layer was dried over magnesium sulfate. Filtration and concentration under reduced pressure afforded the product.

2.4.6 Amination of diols

General procedure 5: For the synthesis of *N*-substituted diamines

[$Ru(acac)_3$] (0.010 g, 0.025 mmol, 1 mol%), triphos (0.031 g, 0.05 mmol, 2 mol%) and substrate (2.5 mmol) were weighed in air and introduced into a 250 mL Hastelloy autoclave fitted with a stirrer bar. The autoclave was sealed and purged by three vacuum/Ar cycles. Methanesulfonic acid (1.62 μL, 0.025 mmol, 1 mol%) in degassed 1,4-dioxane (15 mL) was introduced into the autoclave through a septum using a syringe. For the synthesis of *N*-substituted diamines, amine (3 equiv.) was also introduced into the autoclave. The autoclave was sealed again. Depending on the reaction conditions, the autoclave was charged with Ar (1 bar or 10 bar), or H_2 (10 bar), and heated to 220 °C for 20 h. The autoclave was cooled, vented and opened. The crude mixtures were analysed using GC-MS, GC-FID, NMR spectroscopy, or mass spectrometry, examples of spectra are shown below. Quantitative calculations were based on the analysis of ^{1}H NMR spectra with 1,4-dinitrobenzene as an internal standard.

General procedure 6: For the synthesis of primary diamines

[$Ru(acac)_3$] (0.010 g, 0.025 mmol, 2 mol%), triphos (0.031 g, 0.05 mmol, 4 mol%) and substrate (1.25 mmol) were weighed in air and introduced into a 250 mL Hastelloy autoclave fitted with a stirrer bar. The autoclave was sealed and purged by three vacuum/Ar cycles. Methanesulfonic acid (1.62 μL, 0.025 mmol, 2 mol%) in degassed 1,4-dioxane (20 mL) or ammonia in 1,4-dioxane (0.5 M, 20 mL) was introduced into the autoclave through a septum using a syringe. Aqueous ammonia (35%, 30 mL) was added into the autoclave. The autoclave was sealed again, connected to the high pressure system, and purged six times with 10 bar of H_2. The autoclave was charged with 10 bar of H_2, and heated to 220 °C or 165 °C for the required amount of time. The autoclave was cooled, vented and opened. The crude mixtures were analysed using GC-MS, GC-FID, NMR spectroscopy, or mass spectrometry, examples of spectra are shown below. Quantitative calculations were based on the analysis of ^{1}H NMR spectra with 1,4-dinitrobenzene as an internal standard if the product was soluble in deuterated chloroform or methanol, if not, isolated yields were obtained.

2.4.7 Sequential reactions

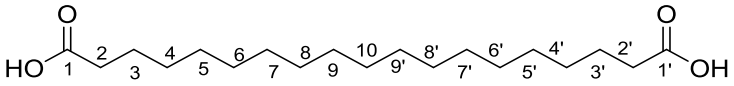
[$Ru(acac)_3$] (0.010 g, 0.025 mmol, 2 mol%), triphos (0.031 g, 0.05 mmol, 4 mol%) and substrate (1.25 mmol) were weighed in air and introduced into a 250 mL Hastelloy autoclave fitted with a stirrer bar. The autoclave was sealed and purged by three vacuum/Ar cycles. Methanesulfonic acid (1.62 μL, 0.025 mmol, 2 mol%) in degassed 1,4-dioxane (7.5 mL) and degassed distilled water (5 mL) were introduced into the autoclave through a septum using a syringe. The autoclave was sealed, and purged 6 times with H_2 (~10 bar). The autoclave was charged with H_2 (10 bar), and heated at 220 °C (internal temperature) for 20 hours. The autoclave was cooled, and hydrogen gas was slowly vented before the autoclave was reconnected to a Schlenk line. Under a flow of Ar, degassed 1,4-dioxane (12.5 mL) and aqueous ammonia (30 mL) were added into the autoclave by a long needle. The autoclave was purged again with H_2 (~10 bar), and charged with 10 bar of H_2. The autoclave was heated at 220 °C for another 20 hours. The autoclave was then cooled, vented and opened. The crude mixtures were concentrated under reduced pressure to yellowish solids. Quantitative calculations were

based on the analysis of ^{1}H NMR spectra with 1,4-dinitrobenzene as an internal standard.

2.4.8 Synthesis and characterization of substrates

2.4.8.1 Dicarboxylic acids

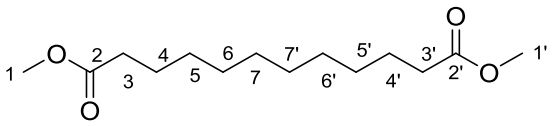
Nonadecanedioic acid, 2.26



Reaction conditions adopted from the literature.[61] 1,19-Dimethyl nonadecanedioate (1.0 g, 2.8 mmol, 1 equiv.) was introduced into a round bottom flask. 1,4-Dioxane (80 mL), distilled water (50 mL) and hydrochloric acid (36% in water, 3 drops) were added and the mixture was heated under reflux overnight. After cooling, the solvent was removed on a rotary evaporator. DCM (100 mL) was added and the heterogeneous mixture was stirred fast before being filtered through a Buchner funnel. The white solid was washed with DCM (50 mL) and dried under reduced pressure to afford the crude material which was then recrystallised from THF and DCM (1:1) to afford 1,19-nonadecanedioic acid as a white powder (0.75 g, 82%); δ_H (400 MHz, d^6-DMSO) 1.23 (26H, s, $H_{4,4'\text{-}9,9',10}$), 1.43-1.51 (4H, m, $H_{3,3'}$), 2.18 (4H, t, *J* = 7.2 Hz, $H_{2,2'}$), 11.96 (2H, s, OH); δ_H (400 MHz, $CDCl_3$/ d^4-MeOD) 1.21-1.36 (26H, s, $H_{4,4'\text{-}9,9',10}$), 1.54-1.63 (4H, m, $H_{3,3'}$), 2.26 (4H, t, *J* = 7.5 Hz, $H_{2,2'}$), 11.96 (2H, s, OH); δ_C (101MHz, $CDCl_3$/ d^4-MeOD) 25.7 ($C_{3,3'}$), 29.8, 30.0, 30.2, 30.3 ($C_{4,4'\text{-}9,9',10}$), 34.8 ($C_{2,2'}$), 177.5 ($C_{1,1'}$). *The spectroscopic properties of this compound were consistent with literature data.*[61]

2.4.8.2 Diesters

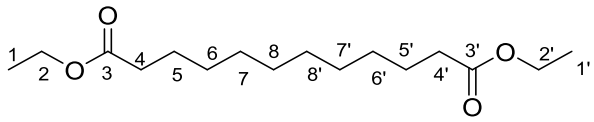
1,12-dimethyl dodecandioate, 2.28



General procedure 1 was applied using dodecanedioic acid (20 g). Dimethyl dodecanedioate was obtained as a white solid (22 g, 98%); δ_H (400 MHz, $CDCl_3$) 1.21-1.36 (12H, s, $H_{5,5'\text{-}7,7'}$), 1.61 (4H, qui, *J* = 7.4 Hz, $H_{4,4'}$), 2.29 (4H, t, *J* = 7.6 Hz, $H_{3,3'}$), 3.66 (6H, s, $H_{1,1'}$); δ_C (101 MHz, $CDCl_3$) 25.1 ($C_{4,4'}$), 29.3, 29.4, 29.5 ($C_{5,5'\text{-}7,7'}$), 34.3

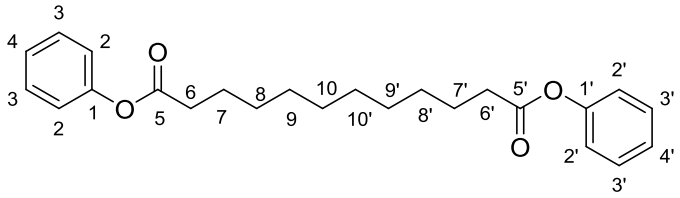
($C_{3,3'}$), 51.6 ($C_{1,1'}$), 174.5 ($C_{2,2'}$). *The spectroscopic properties of this compound were consistent with literature data.*[78]

Diethyl dodecanedioate, 2.34



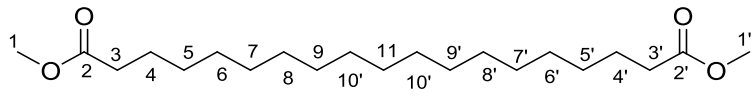
General procedure 1 was applied using 1,12-dodecanedioic acid (10 g) and ethanol. Diethyl 1,12-dodecanedioate was obtained as a colourless oil (12.2 g, 98%); δ_H (400 MHz, $CDCl_3$) 1.20-1.34 (18H, m, $H_{1,1',6,6'-8,8'}$), 1.46-1.71 (4H, m, $H_{5,5'}$), 2.27 (4H, t, J = 7.6 Hz, $H_{4,4'}$), 4.11 (4H, q, J = 7.1 Hz, $H_{2,2'}$); δ_C (101 MHz, $CDCl_3$) 14.4 ($C_{1,1'}$), 25.1 ($C_{5,5'}$), 29.3, 29.4, 29.5 ($C_{6,6'-8,8'}$), 34.5 ($C_{4,4'}$), 60.3 ($C_{2,2'}$), 174.1 ($C_{3,3'}$). Micro Anal. Found: C, 66.93; H, 10.42. Calc'd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. HRMS: (NSI^+) Found: $[M+H]^+$ 287.2215, $C_{16}H_{31}O_4$ requires 287.2217.

Diphenyl dodecanedioate, 2.33



Reaction conditions adopted from the literature.[79] 1,12-Dodecanedioic acid (23.7 g, 103 mmol, 1 equiv.), diphenyl carbonate (44 g, 205.4 mmol, 2 equiv.), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.56 g, 10.3 mmol, 10 mol%) were added into a flask and heated at 160 °C for 24 h. The by-product, phenol, was removed under vacuum. The crude product was filtered through active charcoal and recrystallised from ethyl acetate/ hexane (1:3) to afford diphenyl 1,12-dodecanedioate as a white solid (25 g, 64%). δ_H (400 MHz, $CDCl_3$) 1.31-1.47 (12H, m, $H_{8,8'-10,10'}$), 1.71-1.82 (4H, m, $H_{7,7'}$), 2.56 (4H, t, J = 7.5 Hz, $H_{6,6'}$), 7.03-7.13 (4H, m, $H_{2,2'}$), 7.18-7.26 (2H, m, $H_{4,4'}$), 7.34-7.43 (4H, m, $H_{3,3'}$); δ_C (101 MHz, $CDCl_3$) 25.1 ($C_{7,7'}$), 29.2, 29.4, 29.5 ($C_{8,8'-10,10'}$), 34.5 ($C_{6,6'}$), 121.7 ($C_{2,2'}$), 125.8 ($C_{4,4'}$), 129.5 ($C_{3,3'}$), 150.9 ($C_{1,1'}$), 172.5 ($C_{5,5'}$). mp 59-61°C. Micro Anal. Found: C, 75.29; H, 7.86. Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. HRMS: (NSI^+) Found: $[M+H]^+$ 383.2217, $C_{24}H_{31}O_4$ requires 383.2219.

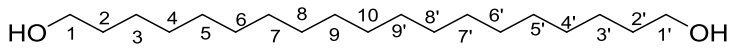
1,19-Dimethylnonadecanedioate, 2.6



Reaction conditions adopted from literature.[61] 1,2-(Bis(ditertbutylphosphinomethyl)-benzene (2.37 g, 6 mmol, 0.2 equiv.) was weighed in a glove box and introduced into a Hastelloy autoclave together with [$Pd_2(dba)_3$] (0.54 g, 0.6 mmol, 0.02 equiv.) under a flow of Ar. The autoclave was sealed and purged with Ar. A mixture of degassed methanol (30 mL), methyl oleate (10 mL) (or sunflower oil, 10 mL) and methanesulfonic acid (0.78 mL, 12 mmol, 0.4 equiv.) was prepared in a Schlenk flask and added to the autoclave by syringe. The autoclave was sealed again, purged with carbon monoxide gas (CO), and the CO pressure was set to 30 bar. The autoclave was heated to 80 °C for 22 h. After cooling, venting and opening, the yellow solid was dissolved in dichloromethane (20 mL) and the yellow solution was filtered through celite. The solvent was removed on a rotary evaporator until a white precipitate appeared. Ice cold methanol was added and the mixture was stirred in an ice bath for 20 min before filtration. The remaining yellow solvent was again evaporated on a rotary evaporator until a precipitate appeared, cooled in an ice bath for 20 min, and filtered. 1,19-Dimethyl nonadecanedioate was obtained as a white powder (methyl oleate: 5.02 g, 95%; sunflower oil: 3.2 g, 80% based on oleate); δ_H (400 MHz, $CDCl_3$) 1.19-1.34 (26H, m, $H_{5,5'\text{-}10,10',11}$), 1.55-1.67 (4H, m, $H_{4,4'}$), 2.29 (4H, t, J = 7.6 Hz, $H_{3,3'}$), 3.66 (6H, s, $H_{1,1'}$); δ_C (101 MHz, $CDCl_3$) 25.1 ($C_{4,4'}$), 29.8 ($C_{5,5'\text{-}10,10',11}$), 34.3 ($C_{3,3'}$), 51.6 ($C_{1,1'}$), 174.5 ($C_{2,2'}$). *The spectroscopic properties of this compound were consistent with literature data.*[14]

2.4.8.3 Diols

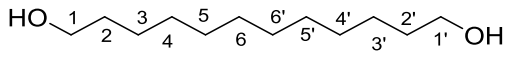
1,19-Nonadecanediol, 2.9



[$Ru(acac)_3$] (4.5 mg, 0.011 mmol, 1 mol%), triphos (14 mg, 0.022 mmol, 2 mol%) and 1,19-dimethyl nonadecanedioate (393 mg, 1.103 mmol) were weighed in air and introduced into a Hastelloy autoclave fitted with a stirrer bar. The autoclave was sealed and purged by three vacuum/ Ar cycles. Degassed 1,4-dioxane (15 mL) and water (10

mL) were introduced into the autoclave through a septum. The autoclave was sealed again, connected to the high pressure system, and purged six times with H_2. The autoclave was charged with 40 bar of H_2, and heated to 220 °C for 16 h. The autoclave was cooled, vented and opened. After opening, the yellow suspension containing a white solid was transferred into a round bottomed flask. The reaction mixture was concentrated under reduced pressure. The solid was recrystallised from THF and DCM. Filtration gave the product as a white solid (265 mg, 80% yield). δ_H (400 MHz, $CDCl_3$/ d^4-MeOD) 1.26 (30H, s, $H_{3,3'\text{-}9,9',10}$), 1.45-1.56 (4H, m, $H_{2,2'}$), 3.55 (4H, t, J = 7.2 Hz, $H_{1,1'}$); δ_C (101 MHz, $CDCl_3$/ d^4-MeOD) 26.3, 30.0, 30.2, 33.0 ($C_{2,2'\text{-}9,9',10}$), 62.7 ($C_{1,1'}$). *The spectroscopic properties of this compound were consistent with literature data.*[14,61]

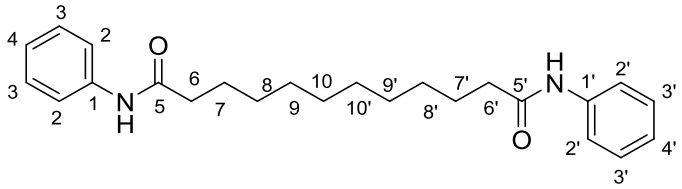
1,12-Dodecanediol, 2.72



General procedure 4 was applied using 1,12-dodecanedioic acid (7.0 g). 1,12-Dodecanediol was obtained as a white solid (5.6 g, 91%). δ_H (500 MHz, $CDCl_3$/ d^4-MeOD) 1.25-1.36 (16H, m, $H_{3,3'\text{-}6,6'}$), 1.47-1.56 (4H, m, $H_{2,2'}$), 3.53 (4H, t, J = 6.7 Hz, $H_{1,1'}$), 4.80 (2H, s, OH); δ_C (126 MHz, $CDCl_3$/ d^4-MeOD) 26.6, 30.3, 30.4 ($C_{3,3'\text{-}6,6'}$), 33.3 ($C_{2,2'}$), 62.8 ($C_{1,1'}$). *The spectroscopic properties of this compound were consistent with literature data.*[80]

2.4.8.4 Diamides

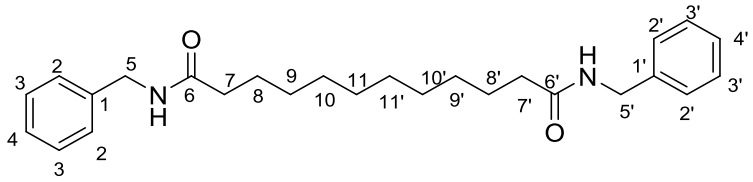
***N*$_1$,*N*$_{12}$-diphenyldodecanediamide, 2.37**



General procedure 2 was applied using 1,12-dodecanedioic acid (10 g). Recrystallisation from hot DCM/MeOH afforded N_1,N_{12}-diphenyldodecanediamide as a white solid (15 g, 90% yield). δ_H (400 MHz, $CDCl_3$/ d^4-MeOD) 1.26-1.36 (12H, m, $H_{8,8'\text{-}10,10'}$), 1.67 (4H, quint, J = 7.4 Hz, $H_{7,7'}$), 2.33 (4H, t, J = 7.5 Hz, $H_{6,6'}$), 7.00-7.10 (2H, m, $H_{4,4'}$), 7.21-7.31 (4H, m, $H_{3,3'}$), 7.47-7.55 (4H, m, $H_{2,2'}$); δ_C (101 MHz, $CDCl_3$/

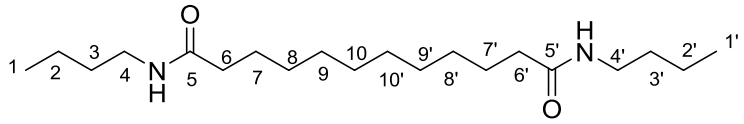
d^4-MeOD) 26.5 ($C_{7,7'}$), 29.9, 30.0, 30.1 ($C_{8,8'\text{-}10,10'}$), 37.7 ($C_{6,6'}$), 120.9 ($C_{2,2'}$), 124.7 ($C_{4,4'}$), 129.4 ($C_{3,3'}$), 139.2 ($C_{1,1'}$), 174.3 ($C_{5,5'}$). Micro Anal. Found: C, 75.61; H, 8.32; N, 7.49. Calc'd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. m.p. 152-154 °C. HRMS: (NSI$^+$) Found: $[M+H]^+$ 381.2534, $C_{24}H_{33}N_2O_2$ requires 381.2537.

N_1,N_{12}-dibenzyldodecanediamide, 2.61



General procedure 3 was applied using 1,12-dodecanedioic acid and benzylamine. The diamide was a side product of this reaction. **2.61** was collected by filtration and washed with DCM (42% yield). δ_H (500 MHz, $CDCl_3$/ d^4-MeOD) 1.21-1.34 (14H, m, $H_{9,9'\text{-}11,11'}$, OH), 1.55-1.66 (4H, m, $H_{8,8'}$), 2.20 (4H, t, J = 7.6 Hz, $H_{7,7'}$), 4.34 (4H, s, $H_{5,5'}$), 7.17-7.32 (10H, m, $H_{2,2'\text{-}4,4'}$); δ_C (101 MHz, $CDCl_3$/ d^4-MeOD) 26.6, 29.8, 29.9, 30.0 ($C_{8,8'\text{-}11,11'}$), 36.8 ($C_{7,7'}$), 43.8 ($C_{5,5'}$), 127.8, 128.1, 129.1 ($C_{2,2'\text{-}4,4'}$), 139.3 ($C_{1,1'}$), 175.6 ($C_{6,6'}$). m.p. 144-146 °C. HRMS: (ESI$^+$) Found: $[M+H]^+$ 409.2842, $C_{26}H_{37}N_2O_2$ requires 409.2855.

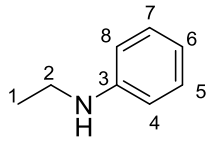
N_1,N_{12}-dibutyldodecanediamide, 2.47



General procedure 3 was applied using 1,12-decanedioic acid and butylamine. N_1,N_{12}-dibutyldodecanediamide was obtained as a side product (58% yield). δ_H (400 MHz, $CDCl_3$) 0.92 (6H, t, J = 7.3 Hz, $H_{1,1'}$), 1.25-1.39 (16H, m, $H_{2,2';\ 8,8'\text{-}10,10'}$), 1.43-1.52 (4H, m, $H_{3,3'}$), 1.56-1.66 (4H, m, $H_{7,7'}$), 2.27 (4H, t, J = 7.6 Hz, $H_{6,6'}$), 3.24 (4H, td, J = 5.7, 7.1 Hz, $H_{4,4'}$), 5.41 (2H, s, NH); δ_C (101 MHz, $CDCl_3$) 13.9 ($C_{1,1'}$), 20.2 ($C_{2,2'}$), 25.9 ($C_{7,7'}$), 29.4 ($C_{8,8'\text{-}10,10'}$), 31.9 ($C_{3,3'}$), 37.1 ($C_{6,6'}$), 39.3 ($C_{4,4'}$), 173.2 ($C_{5,5'}$). HRMS: (NSI$^+$) Found: $[M+H]^+$ 341.3164, $C_{20}H_{41}N_2O_4$ requires 341.3163.

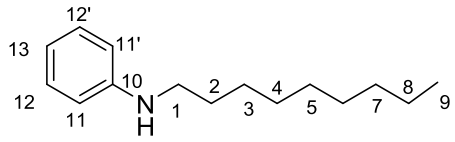
2.4.8.5 Diamines and amines

_N_-ethylaniline, 2.15



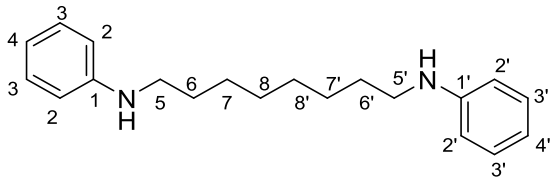
General procedure 3 was applied using acetanilide as substrate. The yield was calculated based on ^{1}H NMR with 1,4-dinitrobenzene as internal standard (82% yield). A purified sample was obtained by flash column chromatography (10% ethyl acetate in petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J*= 7.2 Hz, H_1), 3.17(2H, q, *J*= 7.2 Hz, H_2), 3.33 (1H, br-s, NH), 6.62 (2H, d, *J*= 7.5 Hz, H_4, H_8), 6.71 (1H, t, *J*= 7.5 Hz, H_6), 7.19 (2H, m, H_5, H_7); δ_C (101 MHz, $CDCl_3$) 15.0 (C_1), 38.6 (C_2), 112.9 (C_4, C_8), 117.4 (C_6), 129.4 (C_5, C_7), 148.5 (C_3). *The spectroscopic properties of this compound were consistent with literature data.*[81]

_N_-nonylaniline, 2.77



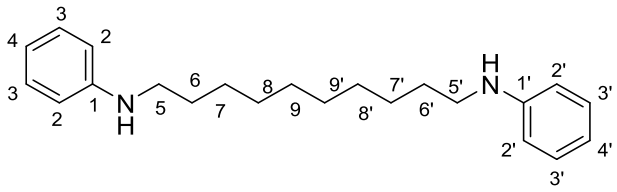
General procedure 3 was applied. The yield was calculated based on ^{1}H NMR with 1,4-dinitrobenzene as an external standard (84% yield). A purified sample was obtained by flash column chromatography (10% ethyl acetate in petroleum ether). δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*= 6.4 Hz, H_9), 1.28 (12H, m, $H_{3\text{-}8}$), 1.62 (2H, app quintet, *J*= 7.6 Hz, H_2), 3.11 (2H, t, *J* = 6.8 Hz, H_1), 6.61 (2H, d, *J* = 7.6 Hz, $H_{11,11'}$), 6.69 (1H, t, *J* = 7.2 Hz, H_{13}), 7.18 (2H, t, *J* = 7.2 Hz, $H_{12,12'}$); δ_C (101 MHz, $CDCl_3$) 14.3 (C_9), 22.8, 27.3 (C_3), 29.4, 29.7 (C_2), 32.0, 44.2 (C_1), 112.8 ($C_{11,11'}$), 117.2 (C_{13}), 129.4 ($C_{12,12'}$), 148.6 (C_{10}). MS: (ESI$^+$ TOF) Found: $[M+H]^+$ 220.27, $C_{15}H_{25}N$ requires 219.1987. *The spectroscopic properties of this compound were consistent with literature data.*[82]

N_1,N_8-diphenyloctane-1,8-diamine



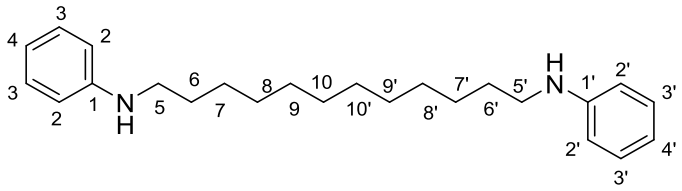
General procedure 3 was applied using 1,8-octanedioic acid and aniline. A sample for analysis was purified by flash column chromatography (10% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.30-1.52 (8H, m, $H_{7,7',8,8'}$), 1.63 (4H, quint, J = 7.5 Hz, $H_{6,6'}$), 3.13 (4H, t, J = 7.1 Hz, $H_{5,5'}$), 3.61 (2H, br s, NH), 6.59-6.66 (4H, m, $H_{2,2'}$), 6.72 (2H, tt, J = 1.1, 7.3 Hz, $H_{4,4'}$), 7.16-7.24 (4H, m, $H_{3,3'}$); δ_C (101 MHz, $CDCl_3$) 27.2, 29.5, 29.7 ($C_{6,6'-8,8'}$), 44.1 ($C_{5,5'}$), 112.8 ($C_{2,2'}$), 117.2 (C_4), 129.3 ($C_{3,3'}$), 148.6 ($C_{1,1'}$). Micro Anal. Found: C, 80.94; H, 9.42; N, 9.25. Calc'd for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45. HRMS: (ESI^+) Found: $[M+H]^+$ 297.2317, $C_{20}H_{29}N_2$ requires 297.2331.

N_1,N_{10}-diphenyldecane-1,10-diamine



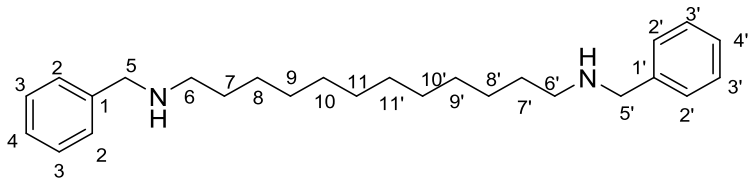
General procedure 3 was applied using 1,10-decanedioic acid and aniline. A sample for analysis was purified by flash column chromatography (10% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.28-1.44 (12H, m, $H_{7,7'-9,9'}$), 1.57-1.67 (4H, m, $H_{6,6'}$), 3.10 (4H, t, J = 7.1 Hz, $H_{5,5'}$), 3.59 (2H, br s, NH), 6.56-6.67 (4H, m, $H_{2,2'}$), 6.69 (2H, tt, J = 1.1, 7.3 Hz, $H_{4,4'}$), 7.12-7.22 (4H, m, $H_{3,3'}$); δ_C (101 MHz, $CDCl_3$) 27.3, 29.6, 29.7 ($C_{6,6'-9,9'}$), 44.1 ($C_{5,5'}$), 112.8 ($C_{2,2'}$), 117.2 (C_4), 129.4 ($C_{3,3'}$), 148.7 ($C_{1,1'}$). Micro Anal. Found: C, 81.61; H, 9.82; N, 8.57. Calc'd for $C_{21}H_{26}N_2O_2$: C, 81.43; H, 9.94; N, 8.63. m.p. 58-59 °C. HRMS: (ESI^+) Found: $[M+H]^+$ 325.2628, $C_{22}H_{33}N_2$ requires 325.2644.

N_1,N_{12}-diphenyldodecane-1,12-diamine, 2.29



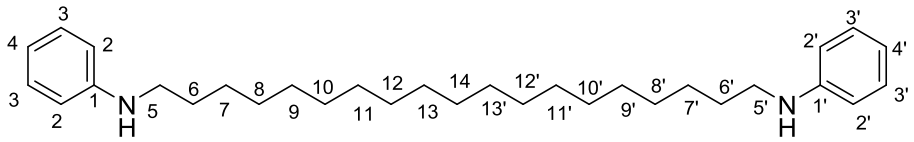
General procedure 3 was applied using 1,12-dodecanedioic acid and aniline. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (10% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.19-1.47 (16H, m, $H_{7,7'\text{-}10,10'}$), 1.52-1.69 (4H, m, $H_{6,6'}$), 3.11 (4H, t, J = 7.1 Hz, $H_{5,5'}$), 3.57 (2H, br s, NH), 6.56-6.64 (4H, m, $H_{2,2'}$), 6.70 (2H, tt, J = 1.1, 7.3 Hz, $H_{4,4'}$), 7.12-7.23 (4H, m, $H_{3,3'}$); δ_C (101 MHz, $CDCl_3$) 27.3, 29.6, 29.7, 29.8 ($C_{6,6'\text{-}10,10'}$), 44.1 ($C_{5,5'}$), 112.8 ($C_{2,2'}$), 117.2 ($C_{4,4'}$), 129.3 ($C_{3,3'}$), 148.7 ($C_{1,1'}$). HRMS: (ESI^+) Found: $[M+H]^+$ 353.2940, $C_{24}H_{37}N_2$ requires 353.2957. *The spectroscopic properties of this compound were consistent with literature data.*[83]

N_1,N_{12}-dibenzyldodecane-1,12-diamine, 2.52



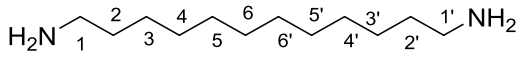
General procedure 5 was applied using 1,12-dodecanediol and benzylamine. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (30% ethyl acetate/ petroleum ether + 1% aqueous ammonia). δ_H (400 MHz, $CDCl_3$) 1.21-1.35 (16H, m, $H_{8,8'\text{-}11,11'}$), 1.51 (4H, quint, J = 7.2 Hz, $H_{7,7'}$), 2.00 (2H, br s, NH), 2.62 (4H, t, J = 7.2 Hz, $H_{6,6'}$), 3.79 (4H, s, $H_{5,5'}$), 7.22-7.28 (2H, m, $H_{4,4'}$), 7.32 (8H, d, J = 4.4 Hz, $H_{2,2',3,3'}$); δ_C (101 MHz, $CDCl_3$) 27.5, 29.7 ($C_{8,8'\text{-}11,11'}$), 30.1 ($C_{7,7'}$), 49.5 ($C_{6,6'}$), 54.1 ($C_{5,5'}$), 127.1 ($C_{4,4'}$), 128.3, 128.5 ($C_{2,2',3,3'}$), 140.3 ($C_{1,1'}$). HRMS: (NSI^+) Found: $[M+H]^+$ 381.3265, $C_{26}H_{41}N_2$ requires 381.3264. *The spectroscopic properties of this compound were similar to those of* **2.52.***2HCl.*[84]

N_1,N_{19}-diphenylnonadecane-1,19-diamine, 2.36



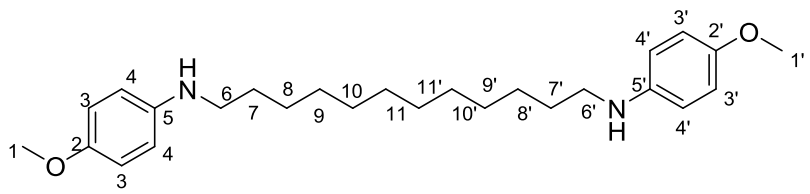
General procedure 3 was applied using 1,19-nonadecanedioic acid and aniline. A sample for analysis was purified by recrystallisation with DCM and Et_2O. The product was obtained as white crystals. δ_H (400 MHz, $CDCl_3$) 1.25-1.45 (30H, m, $H_{7,7'\text{-}13,13',14}$), 1.62 (4H, quint, J = 6.9 Hz, $H_{6,6'}$), 3.11 (4H, t, J = 7.1 Hz, $H_{5,5'}$), 3.60 (2H, br s, NH), 6.57-6.65 (4H, m, $H_{2,2'}$), 6.70 (2H, tt, J = 1.1, 7.3 Hz, $H_{4,4'}$), 7.07-7.23 (4H, m, $H_{3,3'}$); δ_C (101 MHz, $CDCl_3$) 27.3, 29.6, 29.7, 29.8 ($C_{6,6'\text{-}13,13',14}$), 44.1 ($C_{5,5'}$), 112.8 ($C_{2,2'}$), 117.2 ($C_4$), 129.3 ($C_{3,3'}$), 148.7 ($C_{1,1'}$). Micro Anal. Found: C, 82.42; H, 11.33; N, 6.09. Calc'd for $C_{21}H_{26}N_2O_2$: C, 82.60; H, 11.18; N, 6.21. m.p. 66-68 °C. HRMS: (ESI^+) Found: $[M+H]^+$ 451.4034, $C_{31}H_{51}N_2$ requires 451.4052.

1,12-Diaminododecane, 2.78



General procedure 6 was applied using 1,10-decanediol and aqueous ammonia. A sample for analysis was purified by recrystallisation with DCM/MeOH and petroleum ether. δ_H (500 MHz, $CDCl_3$/ d^4-MeOD) 1.19-1.33 (20H, m, $H_{3,3'\text{-}6,6'}$, NH), 1.46 (4H, quint, J = 7.3 Hz, $H_{2,2'}$), 2.65 (4H, t, J = 7.3 Hz, $H_{1,1'}$); δ_C (126 MHz, $CDCl_3$/ d^4-MeOD) 27.2 ($C_{3,3'}$), 29.8, 29.9 ($C_{4,4'\text{-}6,6'}$), 32.4 ($C_{2,2'}$), 41.6 ($C_{1,1'}$). *The spectroscopic properties of this compound were consistent with literature data.*[85]

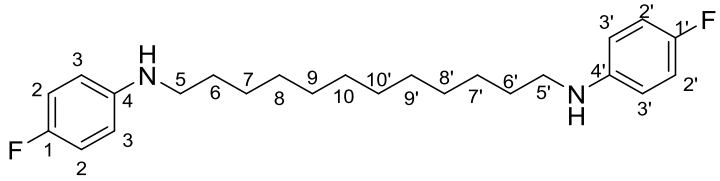
N_1,N_{12}-bis(4-methoxyphenyl)dodecane-1,12-diamine, 2.39



General procedure 3 was applied using 1,12-dodecanedioic acid and 4-methoxyaniline. A sample for analysis was purified by flash column chromatography (30% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.24-1.43 (16H, m, $H_{8,8'\text{-}11,11'}$), 1.60 (4H, quit, J

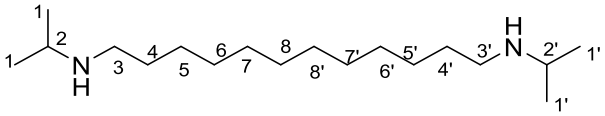
= 7.6 Hz, $H_{7,7'}$), 3.05 (4H, t, *J* = 7.1 Hz, $H_{6,6'}$), 3.75 (6H, s, $H_{1,1'}$), 6.54-6.62 (4H, m, $H_{3,3'}$), 6.74-6.82 (4H, m, $H_{4,4'}$); δ_C (101 MHz, $CDCl_3$) 27.3 ($C_{8,8'}$), 29.6, 29.7, 29.8 ($C_{9,9'-11,11'}$), 45.2 ($C_{6,6'}$), 56.0 ($C_{1,1'}$), 114.2 ($C_{4,4'}$), 115.0 ($C_{3,3'}$), 143.0 ($C_{5,5'}$), 152.1 ($C_{2,2'}$). Micro Anal. Found: C, 75.47; H, 9.55; N, 6.88. Calc'd for $C_{26}H_{40}N_2O_2$: C, 75.68; H, 9.77; N, 6.79. HRMS: (NSI^+) Found: $[M+H]^+$ 413.3156, $C_{26}H_{41}N_2O_2$ requires 413.3163. mp. 80-81 °C.

***N*$_1$,*N*$_{12}$-bis(4-fluorophenyl)dodecane-1,12-diamine, 2.40**



General procedure 3 was applied using 1,12-dodecanedioic acid and 4-fluoro aniline. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (10% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.20-1.45 (16H, m, $H_{7,7'-10,10'}$), 1.60 (4H, quit, *J* = 6.2 Hz, $H_{6,6'}$), 3.05 (4H, t, *J* = 7.1 Hz, $H_{5,5'}$), 6.49-6.57 (4H, m, $H_{3,3'}$), 6.83-6.93 (4H, m, $H_{2,2'}$); δ_C (101 MHz, $CDCl_3$) 27.3, 29.6, 29.7 ($C_{6,6'-11,11'}$), 44.9 ($C_{5,5'}$), 113.6 (d, *J* = 7.4 Hz, $C_{3,3'}$), 115.7 (d, *J* = 7.4 Hz, $C_{2,2'}$), 143.0 ($C_{4,4'}$), 155.8 (d, *J* = 234.4 Hz, $C_{1,1'}$). δ_F (376 MHz, $CDCl_3$) -128.6. Micro Anal. Found: C, 74.33; H, 8.53; N, 7.40. Calc'd for $C_{24}H_{34}F_2N_2$: C, 74.19; H, 8.82; N, 7.21. HRMS: (APCI) Found: $[M+H]^+$ 389.2754, $C_{24}H_{35}F_2N_2$ requires 389.2763. mp. 58-60 °C.

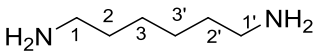
***N*$_1$,*N*$_{12}$-diisopropyldodecane-1,12-diamine, 2.43**



General procedure 5 was applied using 1,12-dodecanediol and isopropylamine. A sample for analysis was purified by preparative TLC (pre-coated glass with basic alumina (60 F254 nm)) (5% MeOH/ DCM). δ_H (400 MHz, $CDCl_3$) 1.04 (12H, d, *J* = 6.6 Hz, $H_{1,1'}$), 1.20-1.32 (16H, m, $H_{5,5'-8,8'}$), 1.40-1.50 (4H, m, $H_{4,4'}$), 2.56 (4H, t, *J* = 7.6 Hz, $H_{3,3'}$), 2.78 (2H, hept, $H_{2,2'}$); δ_C (101 MHz, $CDCl_3$) 23.1 ($C_{1,1'}$), 27.6 ($C_{5,5'}$), 29.7,

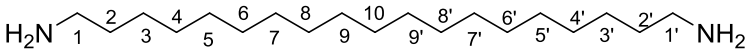
29.8 ($C_{6,6'-8,8'}$), 30.5 ($C_{4,4'}$), 47.8 ($C_{3,3'}$), 50.5 ($C_{2,2'}$). HRMS: (NSI^+) Found: $[M+H]^+$ 285.3265, $C_{18}H_{41}N_2$ requires 285.3264.

Hexane-1,6-diamine, 2.79



General procedure 6 was applied using 1,6-hexanediol and aqueous ammonia. A sample for analysis was purified by sublimation. δ_H (400 MHz, d^4-MeOD) 1.29-1.41 (4H, m, $H_{3,3'}$), 1.43-1.51 (4H, m, $H_{2,2'}$), 2.62 (4H, t, J = 7.2 Hz, $H_{1,1'}$); δ_C (101 MHz, $CDCl_3$) 27.9 ($C_{3,3'}$), 34.0 ($C_{2,2'}$), 42.6 ($C_{1,1'}$). *The spectroscopic properties of this compound were consistent with literature data.*[86]

1,19-nonadecanediamine, 2.10



General procedure 6 was applied using 1,19-nonadecanediol and aqueous ammonia. δ_H (500 MHz, d^6-DMSO) 1.20-1.28 (30H, m, $H_{3,3'-10}$), 1.33-1.47 (4H, m, $H_{2,2'}$), 2.60 (4H, t, J = 7.2 Hz, $H_{1,1'}$); δ_C (126 MHz, d^6-DMSO)* 26.6 ($C_{3,3'}$), 29.4 ($C_{4,4'-10}$), 31.0 ($C_{2,2'}$), 41.0 ($C_{1,1'}$). HRMS: (NSI^+) Found: $[M+H]^+$ 299.3422, $C_{19}H_{43}N_2$ requires 299.3421. *The spectroscopic properties of this compound were consistent with literature data.*[87]

*Peaks observed and assigned based on 2D HSQC NMR spectra, see Figure 2.18

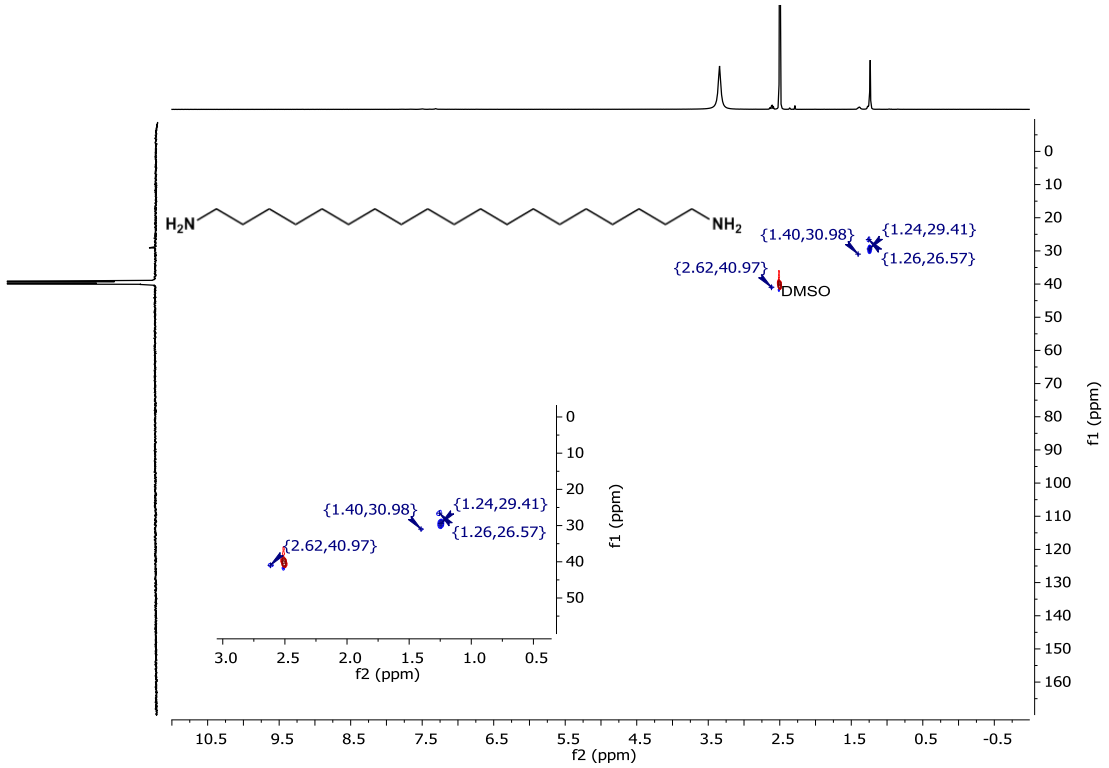


Figure 2.18. HSQC NMR (d^6-DMSO) of 1,19-diaminononadecane, **2.10**.

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Chapter 3 A new route to *N*-phenyl heterocycles from the hydrogenation of diesters in the presence of anilines

The work presented in this chapter was partially published in Chemical Science.[1]

A new route for the one step synthesis of N-heterocycles from readily available starting materials, such as dicarboxylic acids and their esters, in the presence of anilines is studied here. Cyclic amines were obtained in good to excellent yields in the presence of [Ru(acac)$_3$] and 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) at 220 °C. When dimethyl 1,6-hexadienoic acid was reacted with aqueous ammonia, ε-caprolactam was obtained in good yield. A side reaction involving alkylation of the amine by methanol, which is a byproduct of the hydrogenation of the methyl ester, was suppressed by using diesters from longer or branched chain alcohols. Hydrogenation of optically pure diesters gave important insight into the reaction pathway. Reaction of dimethyl (R)-2-methylbutanedioate and dimethyl (S)-2-methylbutanedioate with aniline both afforded racemic 3-methyl-1-phenylpyrrolidine in 78% yield, which suggested the formation of aldehydes as intermediates.

3.1 Introduction

Heterocyclic systems are important building blocks for new materials possessing interesting electronic, mechanical or biological properties.[2] Saturated *N*-heterocycles are highly important motifs in pharmaceuticals products and are notoriously difficult to synthesise.[3]

Important drugs, such as penicillin, **3.1**, saquinavir, **3.2**, which was the first FDA approved protease inhibitor, fluorouracil, **3.3**, which is used in breast cancer treatment, the first official antipsychotic drug, chloropromazine, **3.4**, and morphine, **3.5,** all contain *N*-heterocycles (Figure 3.1).

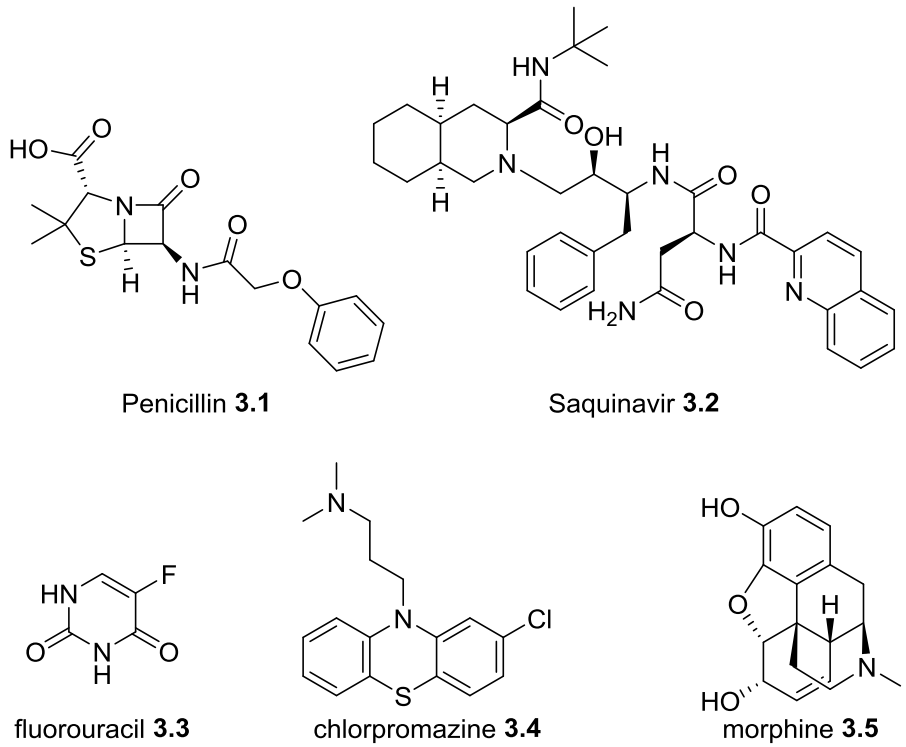


Figure 3.1. Structures of important medicines containing heterocycles.

Azepanes, seven membered heterocycles, are important structures in various medicinal and pharmaceutical products. They have potential in the treatment of cancer,[4] diabetes and viral infections.[5–7] A few examples are shown below (Figure 3.2). Balanol, **3.6**, was reported to have potential for cancer treatment.[4] (3R,4R,6S)-Azepane-3,4,6-triol, **3.7**, a glycosidase inhibitor also contains a 7-membered ring.[8]

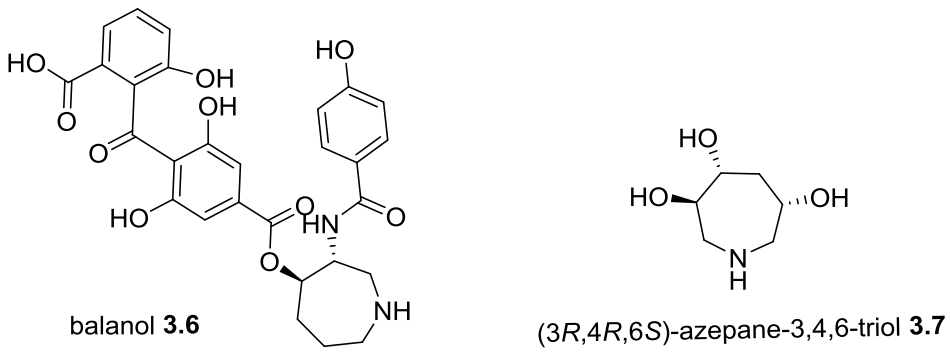
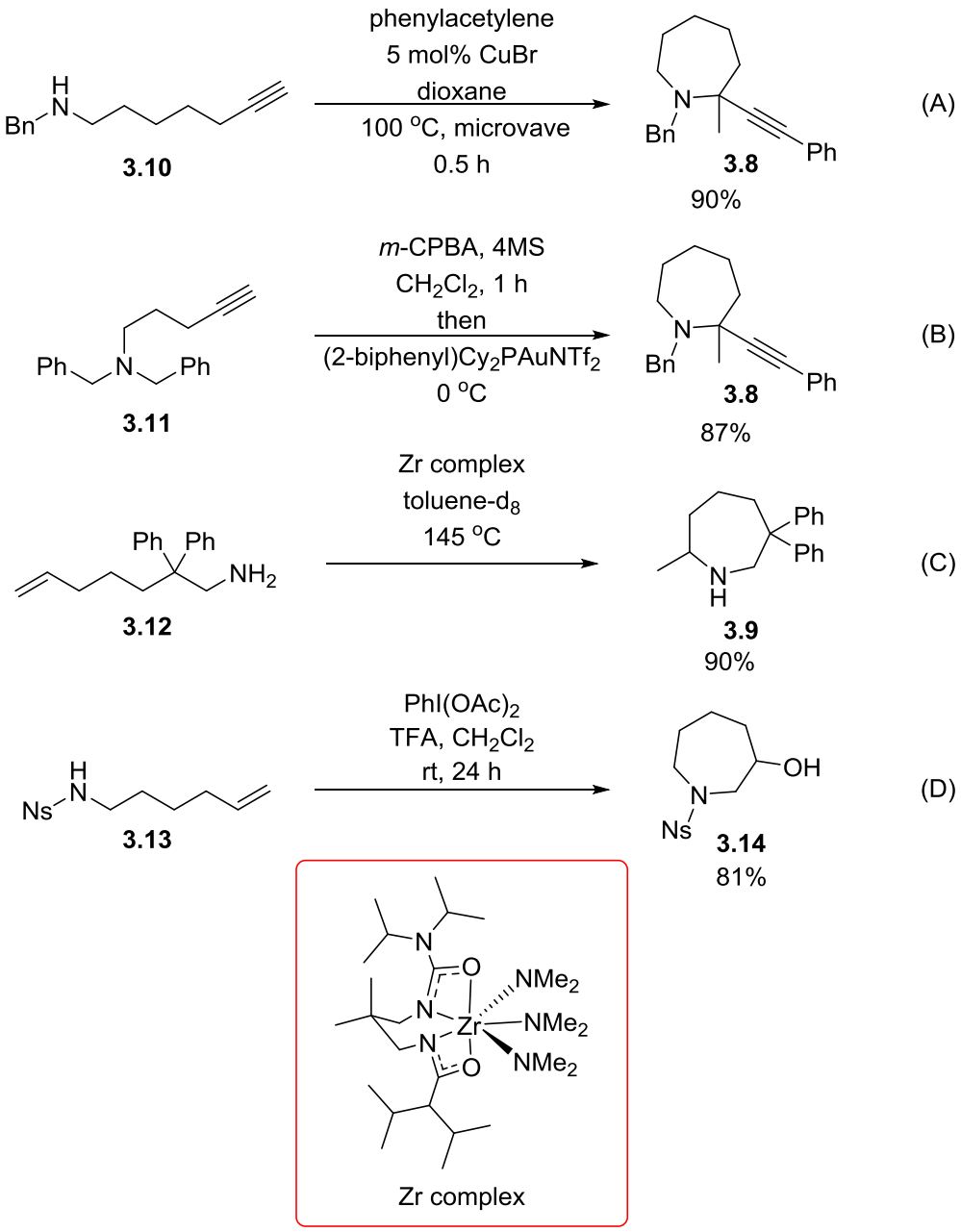


Figure 3.2. Azepane-containing bioactive products.

Common routes for the synthesis of heterocycles involve constructing an amine with a chain terminated by a group with which the amine can cyclise, such as a halide or a double bond (hydroamination), or by transformations of previously formed rings or C-H aminations using azides.[3,9] They can also be synthesised by visible-light photoredox catalysis.[10]

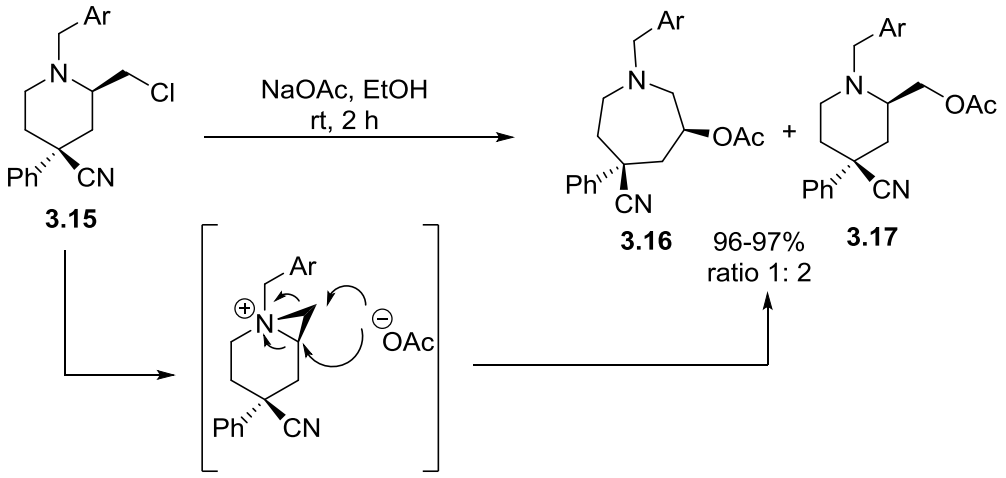
Recently, partial hydrogenation of quinolines has been shown to give tetrahydroquinolines.[11] Hydrogenation of NH lactams can give N-heterocycles,[12] with alkylation of the N atom when the reaction is carried out in alcohols.[13]

Azepane **3.8** and **3.9** can be synthesised *via* copper (I),[14] gold[15] or zirconium[16] catalysed cyclisation from alkenes and alkynes (**3.10**, **3.11** and **3.12**) (Scheme 3.1, Reactions A-C). It is also possible to transform *N*-hexenylsulfonamide, **3.13**, by metal-free intramolecular aminohydroxylation yielding 3-hydroxyhexahydroazepine, **3.14**, with 7-*endo* selectivity (Scheme 3.1, reaction D).[17]



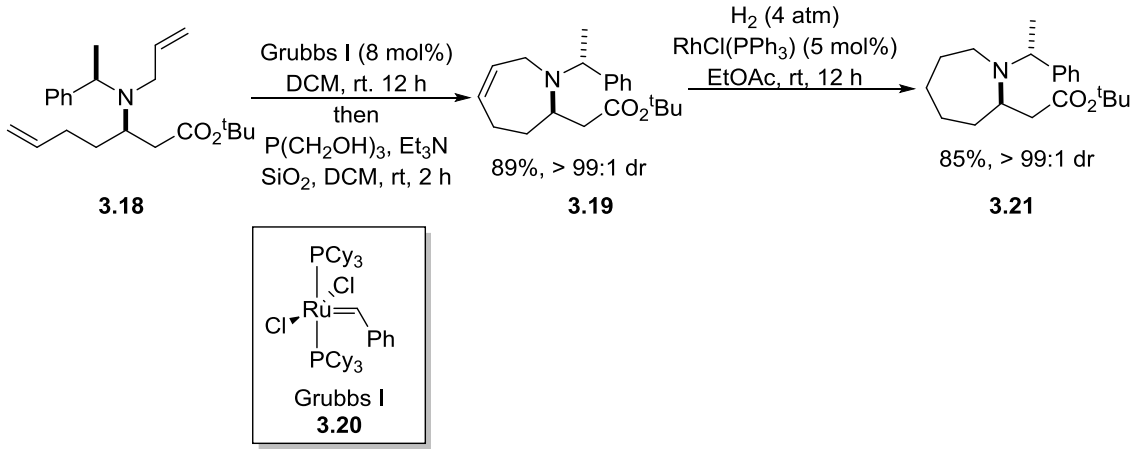
Scheme 3.1. Cyclisation catalysed by copper, gold and zirconium.

The ring expansion of six membered cyclic substrates to form 7-membered rings is also possible. 2-Chloromethylpiperidine, **3.15**, gave a mixture of the ring-expanded hexahydroazepine, **3.16**, and also the directly substituted product, **3.17** (Scheme 3.2).[18]



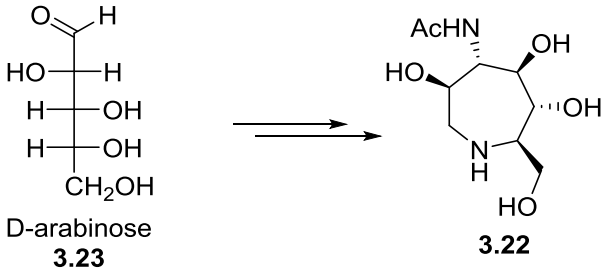
Scheme 3.2. Ring expansion of 2-Chloromethylpiperidine.

Ring closing metathesis (RCM) has been used for the large-scale synthesis of the azepine derivatives of sedum alkaloids from difunctional terminal alkene, **3.18**.[19] The corresponding azepines, **3.19**, were formed in RCM reaction catalysed by Grubbs I, **3.20**, followed by hydrogenation of the unsaturated bond in the ring using Wilkinson's catalyst under hydrogen atmosphere to give the final azepane, **3.21**.



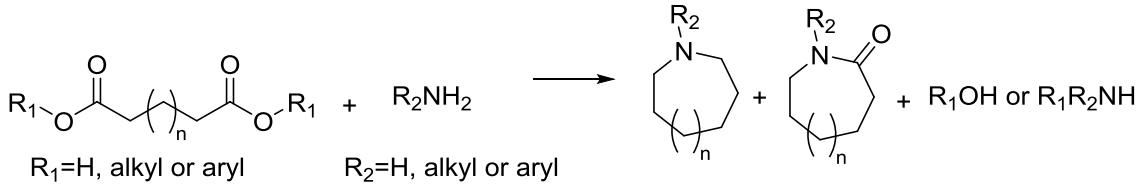
Scheme 3.3. Synthesis of the azepine derivatives of sedum alkaloids.

Azepane azasugars, **3.22**, can be synthesised from D-arabinose, **3.23**:[20] Such products are known to be selective hexosaminidase inhibitors with K_i in the micromolar range.



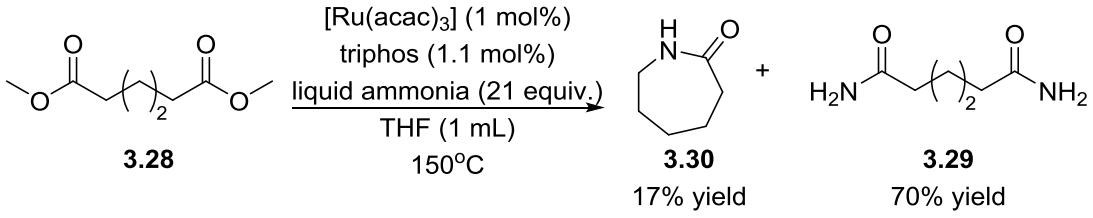
Scheme 3.4. Synthesis of Azepane azasugars from D-arabinose.

A simple route, involving the hydrogenation of dicarboxylic acid derivatives in the presence of an amine, would represent a step change in the synthesis of *N*-heterocycles (Scheme 3.5). The starting linear difunctional carboxylic acids can be obtained from renewable feedstock as described in Chapter 1, and adipic acid can be obtained from glucose.



Scheme 3.5. General scheme for the synthesis of *N*-heterocycles.

The only report of a reaction of this kind gives lactams rather than saturated *N*-heterocycles. The hydrogenation of maleic, **3.24,** or 1,6-hexanedioic acid (adipic acid), **3.25**, in the presence of methylamine and Ru/triphos gave respectively *N*-methypyrrolidone, **3.26**, or *N*-methyl-ε-caprolactam, **3.27**, with 80% or 60% selectivity.[21] Reaction between dimethyl adipate, **3.28**, and liquid ammonia gave 1,6-hexanediamide, **3.29**, as the major product, but ε-caprolactam, **3.30**, was also obtained (17%) (Scheme 3.6).[22]

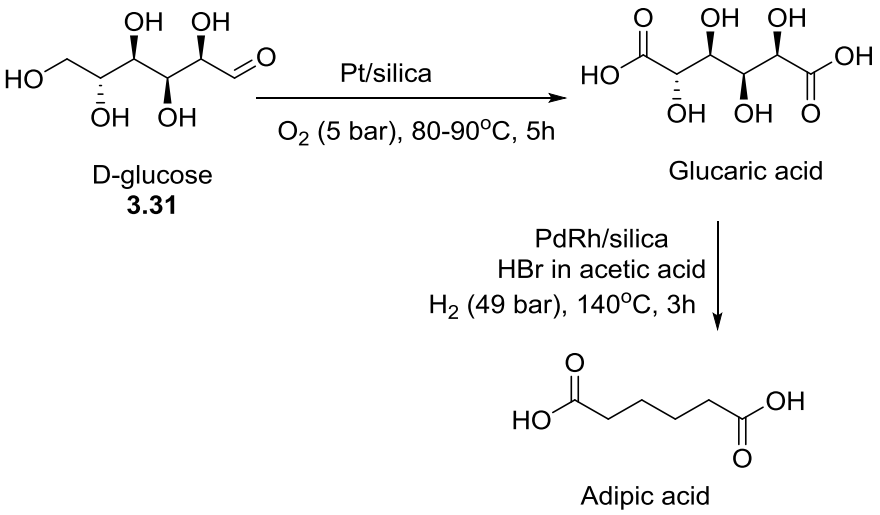


Scheme 3.6. Reaction between dimethyl adipate with liquid ammonia.

Industrially, ε-caprolactam, **3.30**, is produced by the Beckmann rearrangement from cyclohexanone.[23] However, cyclohexanone is only selectively generated by oxidation of cyclohexane with 10-12% conversion per pass.[24] The reaction also involves concentrated sulfuric acid as reagent with ammonium sulfate as the major waste product, which makes this process costly and environmentally unattractive.[25]

3.2 Results and discussion

The initial studies were focused on the reactions using adipate esters for two reasons. The first reason is that, adipate esters can be easily and sustainably obtained either from biomass, such as glucose, **3.31**, by catalytic or enzymatic methods (Scheme 3.7)[26,27] or from alkoxycarbonylation of 1,3-butadiene using palladium catalysts.[28–30]



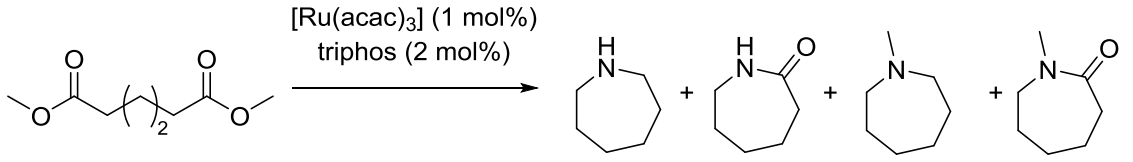
Scheme 3.7. Synthesis of adipic acid from glucose using a catalytic method.[27]

The other reason why we use adipate ester is that, ε-caprolactam, **3.30**, which is a well-known precursor for the synthesis of Nylon-6,[31] can potentially be produced from the adipate ester.

3.2.2 Synthesis of ε-caprolactam with aqueous ammonia

Previously reported[22] examples, for the synthesis of ε-caprolactam, **3.30**, from dimethyl adipate, **3.28**, used liquid ammonia and very low yields were obtained for the desired product (< 18%). Crabtree and co-workers reported that water is required for these types of hydrogenation reactions in order to achieve better yields.[32] Previously in the Cole-Hamilton group[33] and as reported in Chapter 2, it was found that water and small amount of acids are necessary for satisfactory conversions of amides into amines *via* hydrogenation. Therefore, dimethyl adipate, **3.28**, was reacted with aqueous ammonia in the presence of [Ru(acac)$_3$], **3.32** /triphos, **3.33**, and methanesulfonic acid (MSA) (Table 3.1). ε-Caprolactam, **3.30**, was obtained in 60% yield (Table 3.1, Entry 1) after 20 hours, a considerable improvement on the previous report.[22] Azepane, **3.34**, *N*-methyl azepane, **3.35**, and *N*-methyl caprolactam, **3.27**, were also observed. Product **3.35** and **3.27** were formed by methylation of **3.34** or **3.30** caused by methanol, which is the byproduct from the methyl ester hydrogenation. Increasing the reaction time, led to an increased amount of methylated products, **3.35** and **3.27** (Table 3.1, Entry 2).

Table 3.1. Cyclisation of dimethyl adipate in the presence of aqueous ammonia.[a]



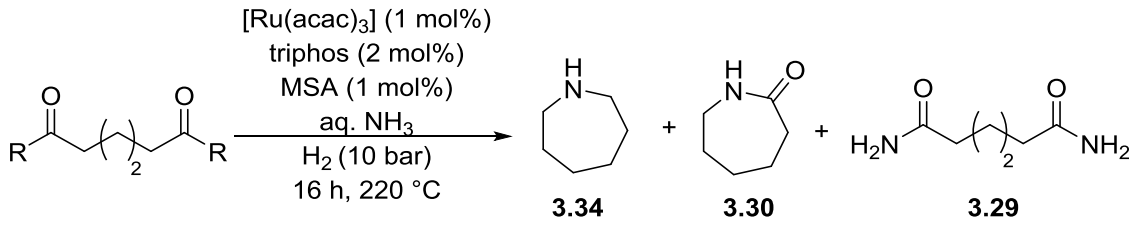
3.28 **3.34** **3.30** **3.35** **3.27**

Entry	t (h)	Conv.(%)	Sel. 3.34 (%)	Sel. 3.30 (%)	Sel. 3.35 (%)	Sel. 3.27 (%)
1	20	100	1	60	16	7.2
2	70	100	5.2	46	19.8	28.5

[(a)][Ru(acac)$_3$], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (1 mol%), 35% aq. NH_3 (5 mL), H_2 (10 bar), 220 °C, selectivity calculated by calibrated GC.

Reactions starting from the adipic acid, **3.25**, were also studied, and the results are shown in Table 3.2.

Table 3.2. Cyclisation of dicarboxylic acid in the presence of aqueous ammonia.[a]



Entry	R	Compound	t (h)	Conv. (%)	Sel. 3.34 (%)	Sel. 3.30 (%)	Sel. 3.29 (%)
1	OH	**3.25**	16	80	n.d.	16.8	14
2	OH	**3.25**	65	100	n.d.	48	0
3	OH	**3.25**	88	100	33	45	0
4[b]	OH	**3.25**	16	>99	n.d.	4	70
5[c]	OH	**3.25**	16	33	n.d.	18	0
6	NH_2	**3.29**	65	100	n.d.	44	-

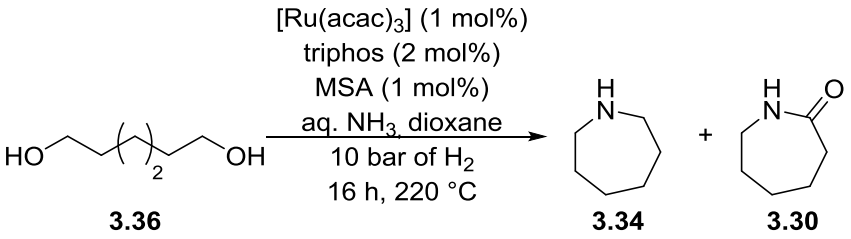
[(a)][Ru(acac)$_3$], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (1 mol%), aq.NH_3 (15 equiv.), H_2 (10 bar), 16 h. [(b)]1 equiv. MSA was added. 1 equiv. of salt was formed. [(c)]aq. NH_3 (1 equiv.)

When reacting adipic acid, **3.25**, with aqueous ammonia for 16 hours, ε-caprolactam, **3.30**, was obtained with a selectivity of 17%, together with the diamide, **3.29** (14% selectivity) (Table 3.2, Entry 1). Increasing the reaction time to 65 hours increased the selectivity of **3.30** to 48% (Table 3.2, Entry 2). However, increasing the reaction time to 88 hours did not make much difference (Table 3.2, Entry 3). When one equivalent of MSA was added, one equivalent of ammonium methanesulfonate salt was obtained as a white solid after the reaction, and the lactam **3.30** was only obtained in 4% selectivity, with 70% selectivity to diamide **3.29** (Table 3.2, Entry 4). When one equivalent of aqueous ammonia was used, the conversion dropped dramatically to 33% and the desired lactam, **3.30**, was obtained with a selectivity of 18% (Table 3.2, Entry 5). When adipic acid, **3.25**, was used as starting material (Table 3.2), similar results were obtained to those reported in Table 3.1 but no *N*-methylated products were observed in this case. Diamide **3.29** could also be converted to the lactam, **3.30**, in a reasonable yield under the reaction conditions reported in Entry 6 (Table 3.2).

For comparison, reactions starting from hexane-1,6-diol, **3.36**, were also studied. When diol, **3.36**, was reacted with aqueous ammonia (Table 3.3, Entry 1), both the lactam,

3.30, and the azepane, **3.34**, were observed. In the absence of hydrogen (Table 3.3, Entry 2), both the conversion and the yield of the ε-caprolactam, **3.30**, decreased dramatically. The formation of ε-caprolactam, **3.30**, suggested an alcohol dehydrogenation pathway proceeding *via* the aldehyde.

Table 3.3. Hydrogenation of hexane-1,6-diol.[a]



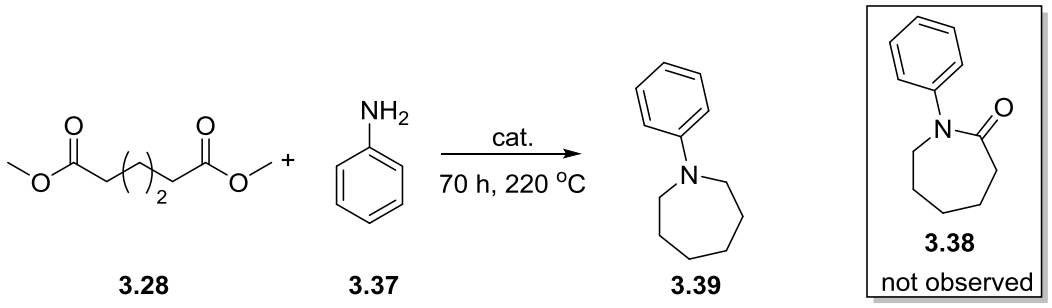
3.36 **3.34** **3.30**

Entry	t (h)	Temperature (°C)	Conversion (%)	Yield of **3.34** (%)	Yield of **3.30** (%)
1	16	220	100	42	28
2[b]	16	220	35.7	n.d.	17

[(a)][Ru(acac)3], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (1 mol%), aq.NH_3 (15 equiv.), 1,4-dioxane (10 mL), H_2 (10 bar), 16 h. [(b)]No hydrogen.

3.2.3 Synthesis of *N*-heterocycles

The reactions with aqueous ammonia were successfully achieved, so the scope of amines was expanded, firstly by using aniline instead of aqueous ammonia to react with esters. Interestingly and surprisingly, when reacting dimethyl adipate, **3.28**, with aniline, **3.37**, the corresponding lactam, *N*-phenyl caprolactam, **3.38**, was not formed at all. *N*-phenyl azepane, **3.39**, was predominately produced instead.

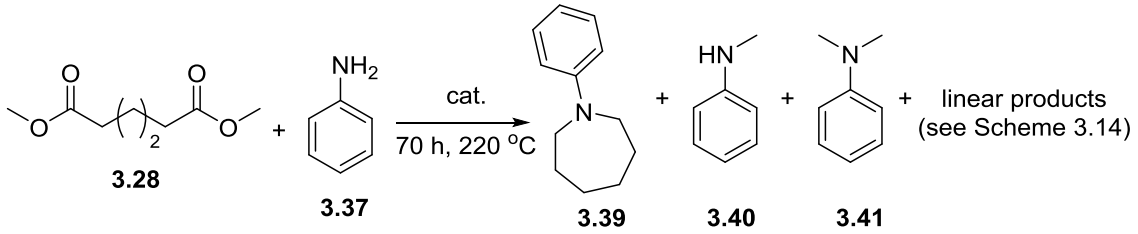


3.28 **3.37** **3.39**

Scheme 3.8. Reaction of dimethyl ester with aniline.

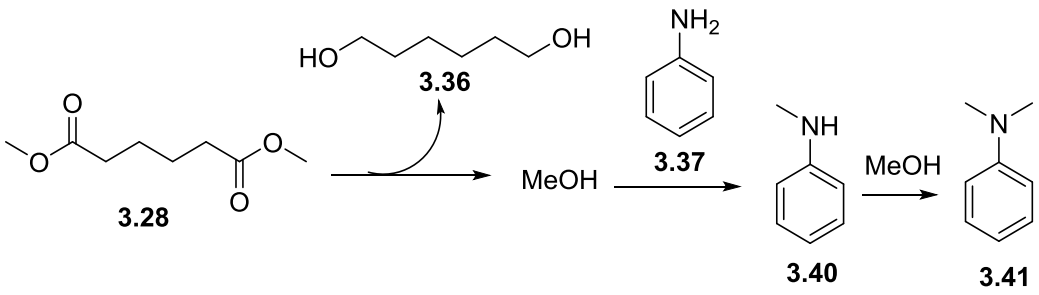
Using one equivalent of aniline (Table 3.4, Entry 1), **3.39** was obtained in 59% selectivity, with 82% conversion. This low conversion was caused by a side reaction between aniline and methanol produced during methyl ester hydrogenation, as observed earlier. Both mono-, **3.40**, and di-substituted *N*-methyl anilines, **3.41**, were produced (Scheme 3.9). The importance of this known side reaction will be discussed later.[34–36] The availability of aniline was therefore reduced. Increasing the quantity of aniline to 1.5 equivalents led to a selectivity of 69% for compound **3.39** and to a higher conversion (91%) (Table 3.4, Entry 2). Further increase of the aniline equivalents, however, did not improve the selectivity of **3.39**. Instead, a significant loss of selectivity was observed (Table 3.4, Entry 5). With 5 equivalent of aniline, the linear products **3.42**, **3.43** and **3.44** were obtained predominantly. The linear diamine, **3.42**, can be further methylated to produce a mixture of monomethylated diamine, **3.43**, and dimethylated diamine, **3.44 (**Scheme 3.14). When increasing the loading of MSA to 5 mol% when using 5 equivalents of aniline, the conversion went to completion, and higher selectivity of the expected cyclic product **3.39** was obtained (Table 3.4, Entry 6 vs Entry 5).

Table 3.4. Hydrogenation of dimethyl adipate with aniline.[a]



Entry	Equiv. aniline	Conv. (%)	Sel. 3.39 (%)
1	1	82	59
2	1.5	91	69
3	2	94	52
4	3	92	54
5	5	87	13
6[b]	5	100	44

[(a)][Ru(acac)$_3$], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (1 mol%), aniline, **3.37** (1-5 equiv.), dimethyl adipate, **3.28** (2.5 mmol), H_2 (10 bar), 70 h, 220 °C. Yields by calibrated GC-FID. [(b)][Ru(acac)$_3$], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (5 mol%), aniline, **3.37** (1-5 equiv.), dimethyl adipate, **3.28** (2.5 mmol), H_2 (10 bar), 70 h, 220 °C. Yields by calibrated GC-FID.



Scheme 3.9. Synthesis of monomethylated, **3.40**, and dimethylated aniline, **3.41**.

The ratio of *N*-methyl aniline, **3.40**, over *N*,*N*-dimethyl aniline, **3.41**, when using different equivalents of aniline for the reaction are illustrated in Figure 3.3. The graph shows that the ratio of (% yield of **3.40** / % yield of **3.41**) increases as the concentration of aniline increases. With a larger quantity of aniline, **3.37**, the methanol byproduct is more likely to react with a different molecule of aniline, **3.37**, to produce a mono-substituted aniline, **3.40**, rather than react with the same molecule of aniline twice yielding the di-substituted aniline, **3.41**.

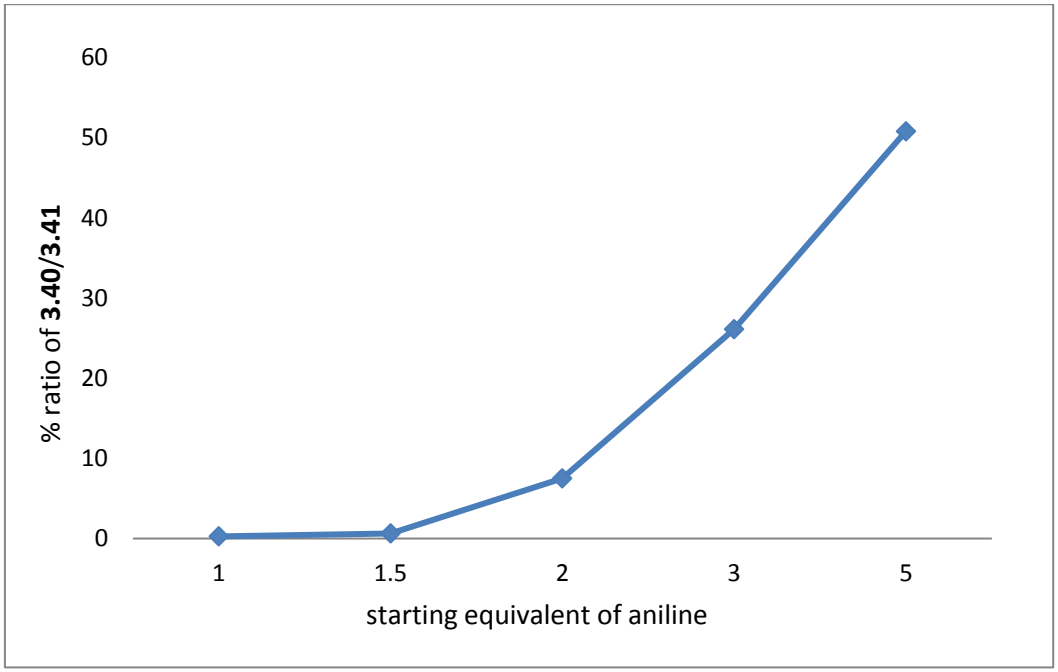


Figure 3.3. The ratio of monomethylated aniline and dimethylated aniline

The time dependence of the reaction was carried out using the optimised conditions (1.5 equivalent of aniline, 220 °C). The autoclave used for monitoring the reaction is shown in Figure 3.4. The sampling tube goes to the bottom of the autoclave, and after certain

time intervals, samples are taken by opening the valve very slowly. Unfortunately, this tube has about 1 mL of dead volume; therefore, around 1 mL of reaction mixture was discarded every time before taking the sample. The samples were analysed by GC analysis with the results illustrated in Figure 3.5.

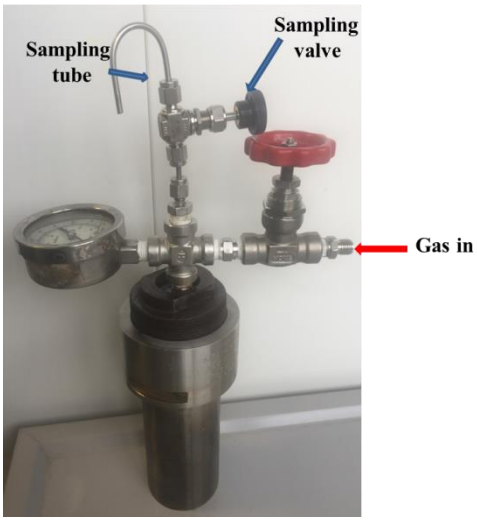


Figure 3.4. Equipment for sampling reactions.

From the graph (Figure 3.5), we can see that both of dimethyl adipate, **3.28**, and aniline, **3.37**, are quickly consumed to give the monoester monoamine, **3.45**, which was slowly converted to the *N*-heterocycle, **3.39**, without any further detectible intermediates. After about 66 h, aniline is used up so **3.39** is no longer produced. The incomplete conversion for this cyclisation reaction was predominantly because of the side reactions between produced methanol and aniline.

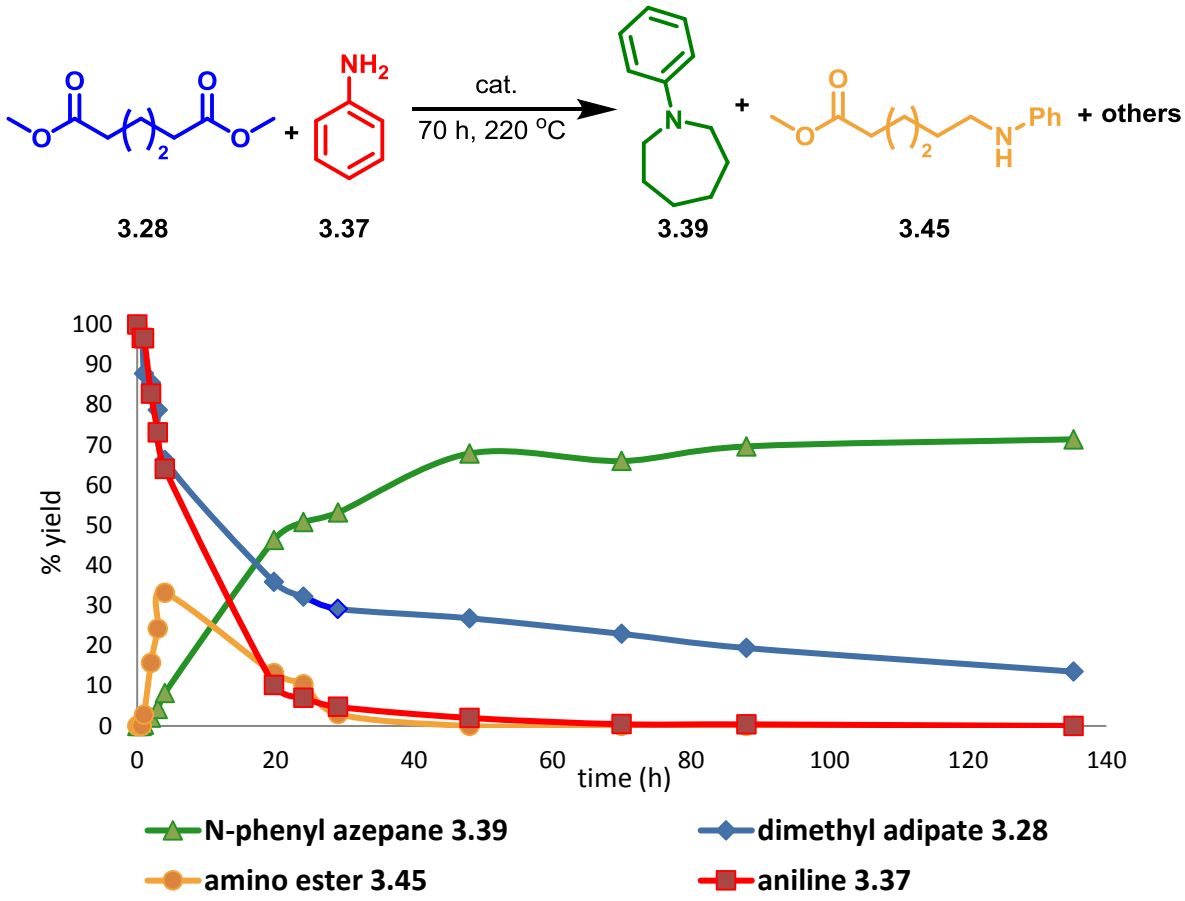
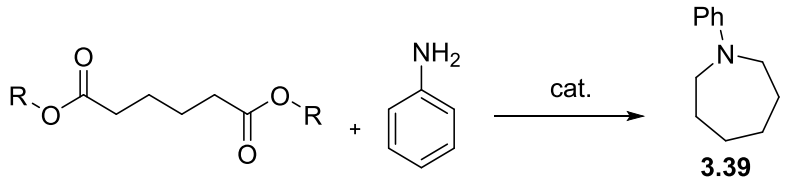


Figure 3.5. Monitoring of the hydrogenation of dimethyl adipate in the presence of aniline against time. Conditions: $[Ru(acac)_3]$ (1 mol%), triphos (2 mol%), MSA (1 mol%), dioxane (45 mL), dimethyl adipate (1 equiv. 7.5 mmol), aniline (1.5 equiv.), H_2 (10 bar), 220 °C.

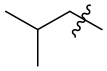
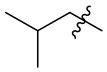
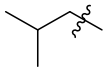
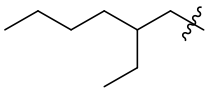
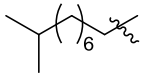
In order to improve the selectivity, different esters of 1,6-hexanoic acid were studied to avoid the production of methanol. Firstly, a bulkier ester, diisobutyl adipate, **3.46**, was subjected to the reaction conditions (Table 3.5, Entry 1). Gratifyingly, the yield of **3.39** was increased to 94% (95% conversion) with 1.5 equivalent of aniline after 70 h, compared to 63% yield when reacting with dimethyl adipate, **3.28** (Table 3.4, Entry 2). Increasing the amount of aniline to 2 equivalents did not significantly influence either the conversion or the yield (Table 3.5, Entry 2). In order to reduce the reaction time, the catalyst loading was increased from 1 mol% to 2 mol% with diisobutyl adipate, **3.46**, as substrate. Monitoring of the reaction over time showed that 80% yield of **3.39** was reached after 24 hours, and it improved to 93% after 42 hours (Figure 3.6) (Table 3.5, Entry 3).

This method can be applied to a wide range of diesters, from aliphatic to aromatic. *N*-phenyl azepane, **3.39**, was successfully obtained in good to excellent yields. Short linear or branched alkyl chains gave higher yields, compared to methyl ester **3.28** (Table 3.5, Entries 3-6), but longer chains (Table 3.5, Entries 7, 9 and 10) or very bulky esters (Table 3.5, Entry 8) led to a slight decrease in yield. It is interesting to mention that when using di-*tert*-butyl adipate, **3.51**, as the substrate (Table 3.5, Entry 8), the *N*-phenylcaprolactam, **3.38**, was also obtained in 10% yield which was not observed in any other cases. Excellent yields of **3.39** was obtained (92%) when using diphenyl 1,6-hexanediaote, **3.54**, as substrate (Table 3.5, Entry 11). However, when dibenzyl diester, **3.55**, was used, the yield decreased to 71% (Table 3.5, Entry 12). The reaction using dicarboxylic acid, **3.25**, as substrate only afford the desired cyclic product **3.39** in 13% yield (Table 3.5, Entry 13), the major product being *N*-phenylcaprolactam (30%).

Table 3.5. Study of different adipate ester substrates.[a]



3.39

Entry	R	Compound	Conv. (%)	Yield (%)
1[b]		**3.46**	95	94
2[c]		**3.46**	96	95
3		**3.46**	99	93
4	Et	**3.47**	98	95
5	^{n}Pr	**3.48**	99	93
6	^{i}Pr	**3.49**	92	88
7	^{n}Bu	**3.50**	97	63
8	^{t}Bu	**3.51**	100	80
9		**3.52**	100	80
10		**3.53**	100	59
11	Ph	**3.54**	100	92
12	$PhCH_2$	**3.55**	100	71

13	H	**3.25**	100	13

[(a)][Ru(acac)$_3$], **3.32** (2 mol%), triphos, **3.33** (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5mmol), aniline (1.5 equiv.), H_2 (10 bar), 220 °C, 42 h. [(b)][Ru(acac)$_3$] (1 mol%), triphos (2 mol%), MSA (1 mol%), 1,4-dioxane (15 mL), substrate (1 equiv., 2.5 mmol), aniline (1.5 equiv.), H_2 (10 bar), 220 °C, 70 h. [(c)]as [(b)] but aniline (2 equiv.). Yields by calibrated GC-FID.

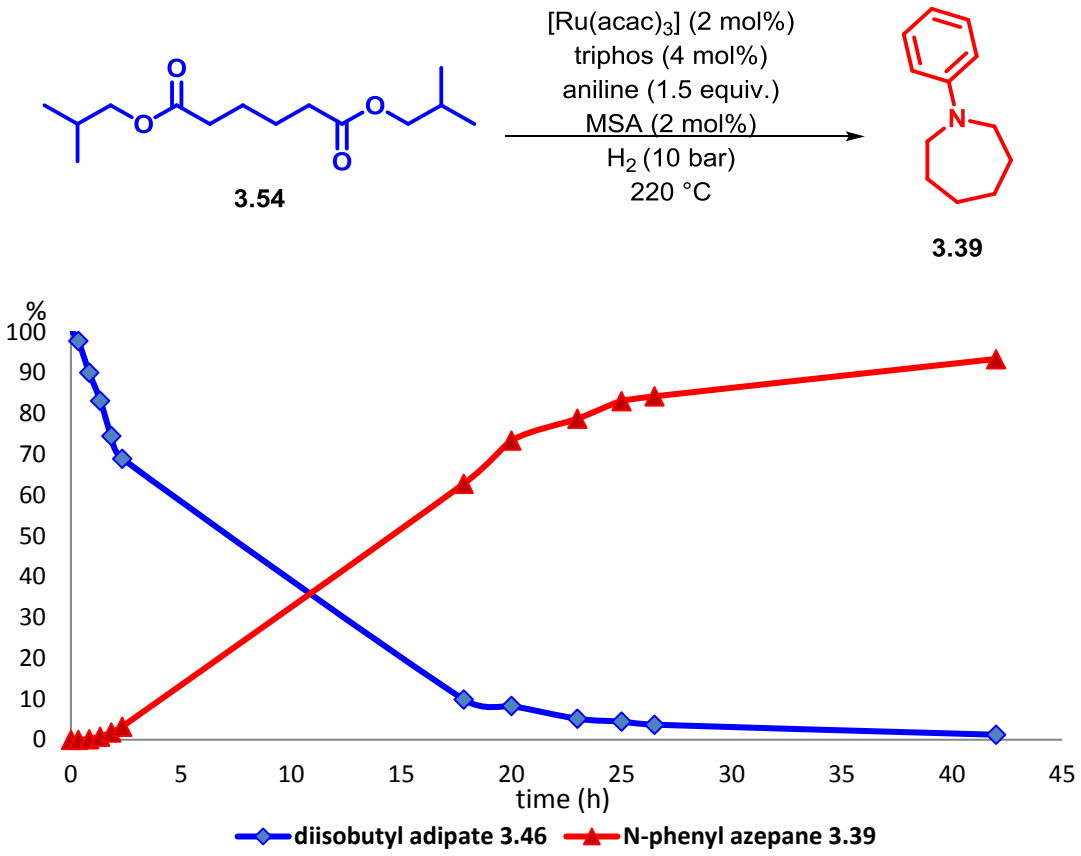


Figure 3.6. Monitoring of the reaction between diisobutyl adipate and aniline (Table 3.5, Entry 3). Yield calculated by calibrated GC-FID.

A representative NMR example for the crude reaction mixture (Table 3.5, Entry 11) is shown in Figure 3.7. From the NMR spectrum, it can be observed that the crude reaction mixture contained mostly the expected *N*-phenyl azepane, **3.39**, together with phenol as side product, and dodecane as internal standard.

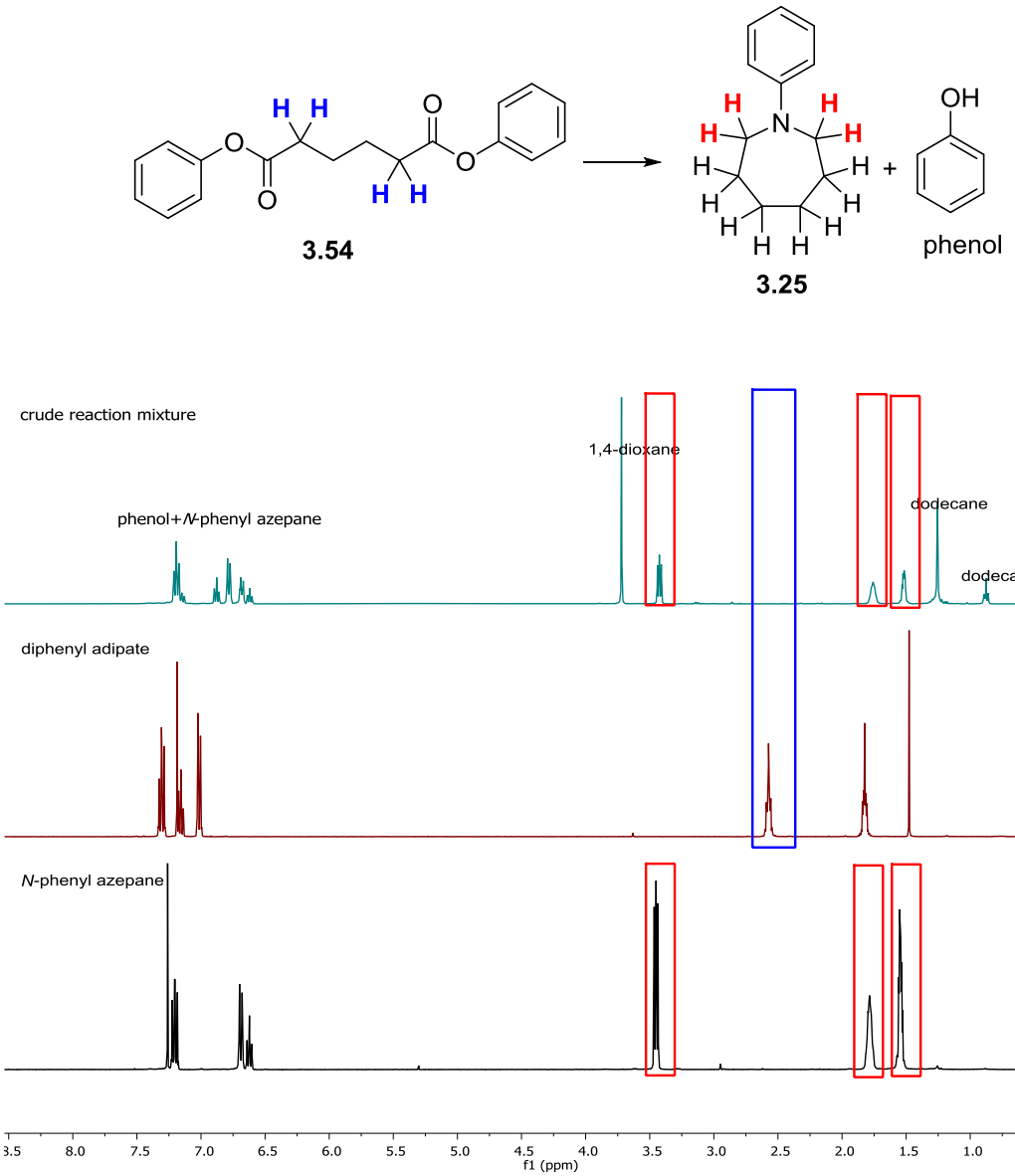
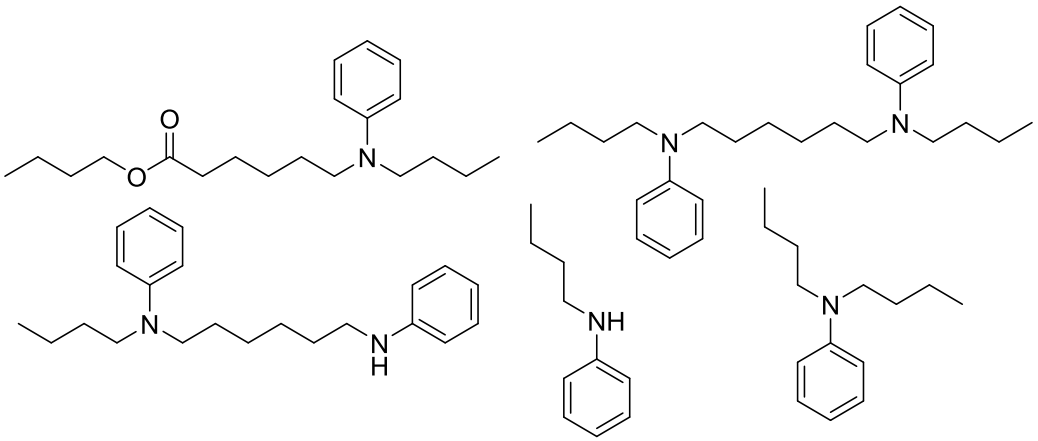


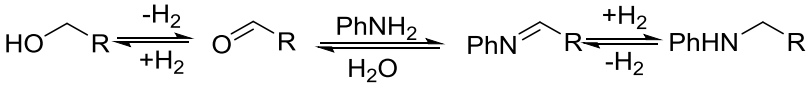
Figure 3.7. ^{1}H NMR of reaction mixture using diphenyl adipate, **3.54**. Dodecane was used as the internal standard for quantitative GC analysis.

When di-n-butyl adipate, **3.50**, was used as substrate, only 63% yield of *N*-phenyl azepane, **3.39**, was obtained. The crude reaction mixture was then analysed by mass spectrometry. The tentative assignments of the observed products are illustrated in Scheme 3.10.



Scheme 3.10. Side products from the reaction of di-*n*-butyl adipate, **3.50**.

When hydrogenating esters, the corresponding alcohols are obtained as a by-products, for example, methanol can be obtained from the hydrogenation of methyl ester, as mentioned earlier. The amination between aniline and the corresponding alcohol was not observed when using *tert*-butyl, **3.51**, or phenyl, **3.54**, esters. This observation could be explained if the hydrogen borrowing mechanism proposed by Beller's group[37] for the amination between alcohols and amines (Scheme 3.11) operates rather than direct attack of the amine on the protonated alcohol.

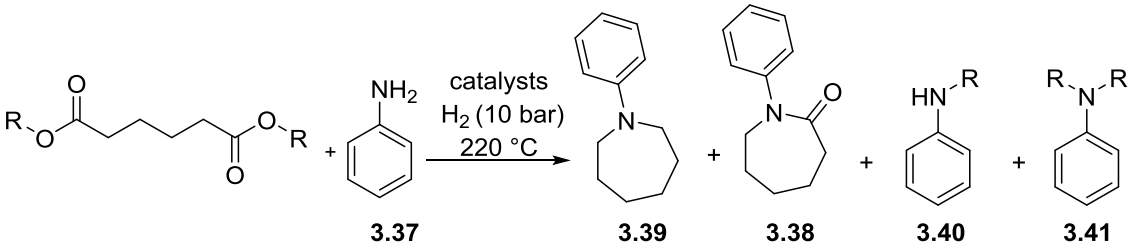


Scheme 3.11. Proposed hydrogen borrowing mechanism for the alkylation between alcohol and amine.[37]

Tertiary alcohols and phenols cannot form the corresponding aldehyde; therefore, no amination reaction occurred. The alkylation of aniline was found only to be severely detrimental to the yield of **3.39** when using the dimethyl ester, most probably because methanol is more effective in the hydrogen borrowing reactions than the other alcohols.

To limit the detrimental effect of the alkylation side reaction, an excess of aniline was used (1.5 equivalent). In order to find out where aniline was used during the reaction, the percentage yields in Figure 3.8 are calculated based on the number of moles of aniline. As previously mentioned, there was no amination product when di-*tert*-butyl, **3.51**, and diphenyl, **3.54**, adipates were reacted with aniline.

When di-*tert*-butyl adipate, **3.51**, was used, lactam **3.38** was also obtained. For long and branched esters, such as *bis*-ethylhexyl, **3.52**, diisopropyl, **3.49**, and diisobutyl adipates, **3.46**, the di-alkylated products of aniline, **3.41**, were not obtained. Dimethyl, **3.28**, diethyl, **3.47**, dibenzyl, **3.55**, and di-*n*-butyl adipates, **3.50**, gave a mixture of mono- and di- substituted anilines, **3.40** and **3.41**.



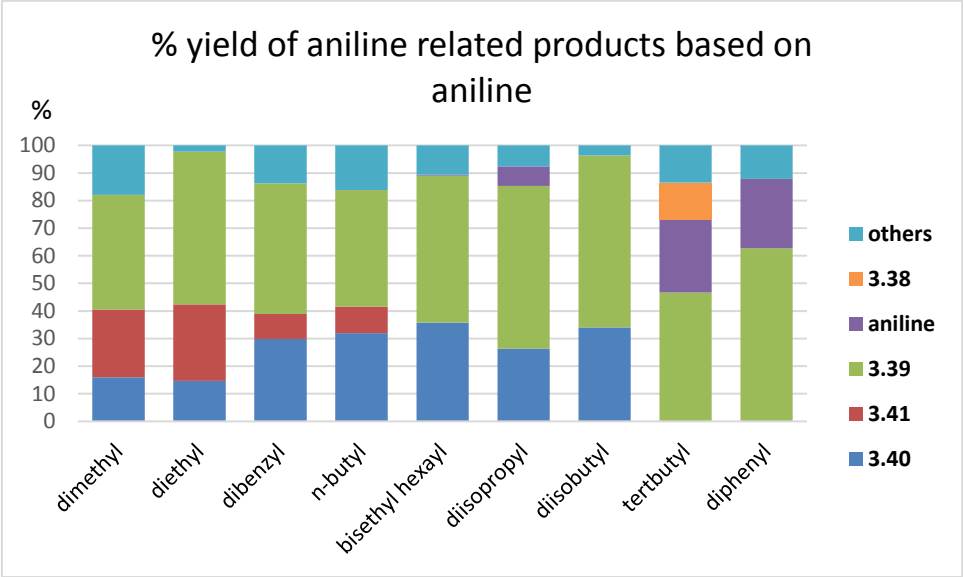
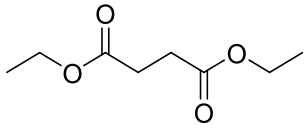
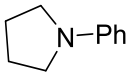
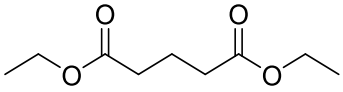
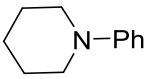
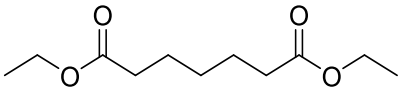
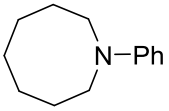
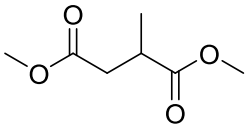
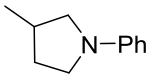
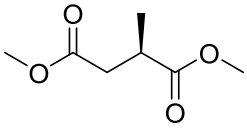
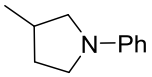
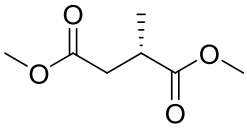
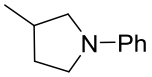


Figure 3.8. % yield of aniline related products by GC-FID.

In principle, the alkylation reaction can be completely eliminated by using 1,6-hexanedioic acid, **3.25**, as the substrate. However, under the same reaction conditions as for the diesters, the dicarboxylic acid gave a poorer yield to **3.39** (13%), and *N*-phenyl-ε-caprolactam, **3.38**, was also obtained as the major side product (30%, Table 3.5, Entry 13). Reactions starting from the dicarboxylic acid could not be easily monitored over time because solid adipamide, **3.29**, formed during the reaction and the white solid blocked the sampling tube.

Diesters with other chain lengths (4-7 carbon chain, **3.56**, **3.57**, **3.58**) are also studied to form different ring size *N*-heterocycles. Five, **3.59**, six, **3.60**, and eight membered, **3.61**, *N*-heterocycles could also be prepared in good to excellent yields (Table 3.6, Entries 1-3).

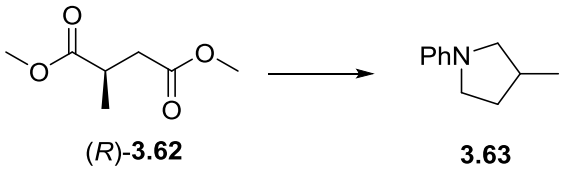
Table 3.6. Cyclisation with various substrates.[a]

Entry	Substrate	Conv. (%)	Product	Yield[b] (%)
1	 **3.56**	89	 **3.59**	66
2	 **3.57**	100	 **3.60**	92
3	 **3.58**	96	 **3.61**	66
4	 (*rac*)-**3.62**	100	 **3.63**	78 (75)[c]
5	 (*R*)- **3.62**	100	 **3.63**	78
6	 (*S*)- **3.62**	100	 **3.63**	79

[(a)]Conditions: $[Ru(acac)_3]$ (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), aniline (1.5 equiv.), H_2 (10 bar), 220 °C, 42 h. [(b)]NMR yield. [(c)]Isolated yield.

Racemic and chiral dimethyl 2-methylbutanedioate, **3.62,** were studied. The corresponding cyclic *N*-phenyl 3-methylpyrrolidine, **3.63**, was obtained in good yield (~78%, Table 3.6, Entries 4-6) but with a complete loss of optical purity. As expected the reaction product derived from racemic dimethyl 2-methylbutanedioate, **3.62,** has an optical rotation of 0. When the same reaction

was performed using (*R*)-(+)-2-methylbutanedioate ((*R*)-**3.62**) and (*S*)-(-)-2-methylbutanedioate ((*S*)-**3.62**), optical rotation values close to zero (+0.01 and -0.002) were obtained. Chiral GC analysis supported these results (Figure 3.9 and Figure 3.10). The two peaks at around 22 minutes correlate to the two stereoisomers of the cyclic amine.



(*R*)-**3.62** **3.63**

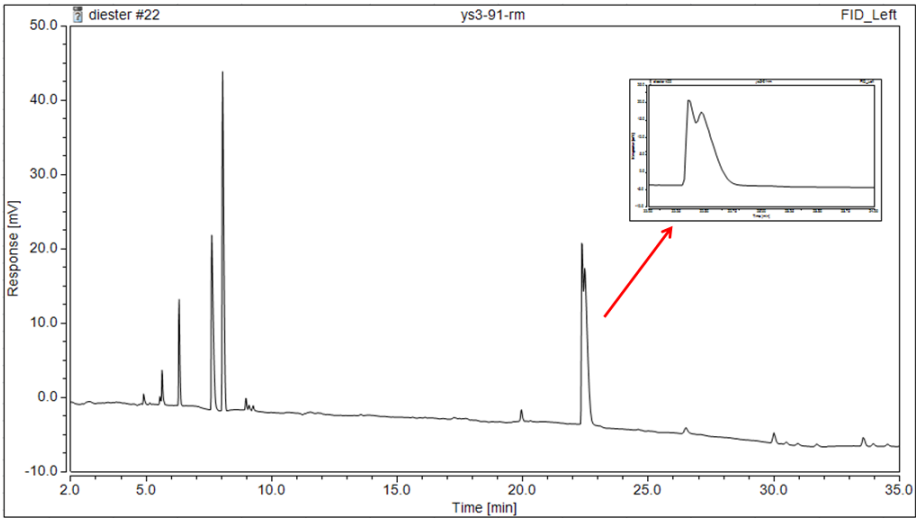
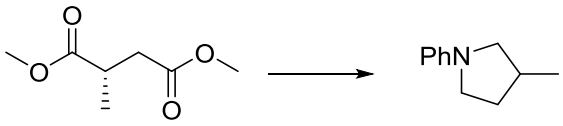


Figure 3.9. Chiral GC spectra starting with (*R*)-(+)-2-methylbutanedioate, (*R*)-**3.62**.



(*S*)-**3.62** **3.63**

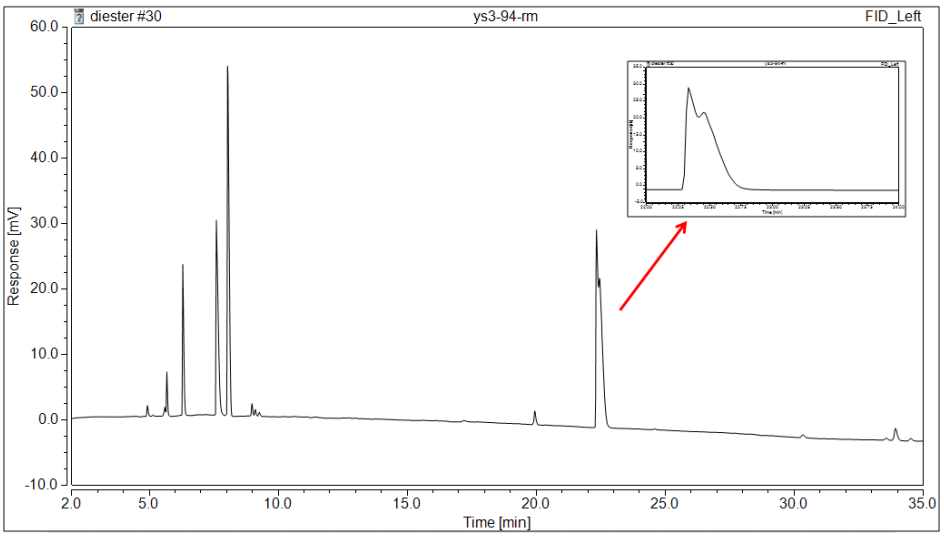
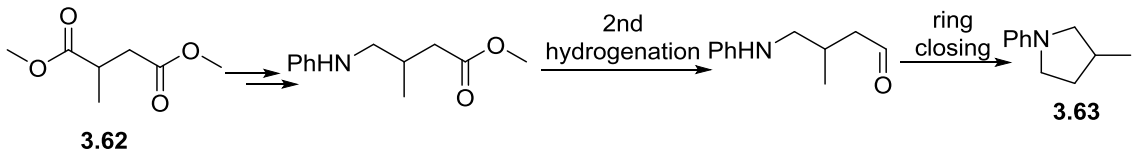


Figure 3.10. Chiral GC spectra starting with (*S*)-(-)-2-methylbutanedioate, (*S*)-**3.62**.

In order to determine what caused the optical purity loss, shorter reaction times were used, with the aim of isolating reaction intermediates. After 3 hours of this reaction ([Ru(acac)$_3$] (2 mol%), triphos (4 mol%), MSA (2 mol%), 1,4-dioxane (15 mL), substrate (2.5 mmol), aniline (1.5 equiv.), H_2 (10 bar), 220 °C), *N*-phenyl 3-methylpyrrolidine, **3.63**, was still the major product, and only trace amounts of the two ester amines, **3.64** and **3.65**, were observed (the detail will be discussed later), which suggest that the second hydrogenation and ring closing steps are much faster for the 5 than for the 7 membered ring (Scheme 3.12).



3.62 **3.63**

Scheme 3.12. Synthesis of *N*-phenyl 3-methylpyrrolidine, **3.63**, from dimethyl-2-methyl butanedioate, **3.62**.

The Gas chromatography–mass spectrometry (GCMS) spectra for the reaction mixture after 3 hours are shown in Figure 3.11. Peaks A and B at 5.06 and 5.70 minutes both

have m/z = 207, which correlates to the ester amine intermediates, **3.64** and **3.65**. Peak A has a fragment peak of m/z 135.10 which relates to **3.65** in Figure 3.11.

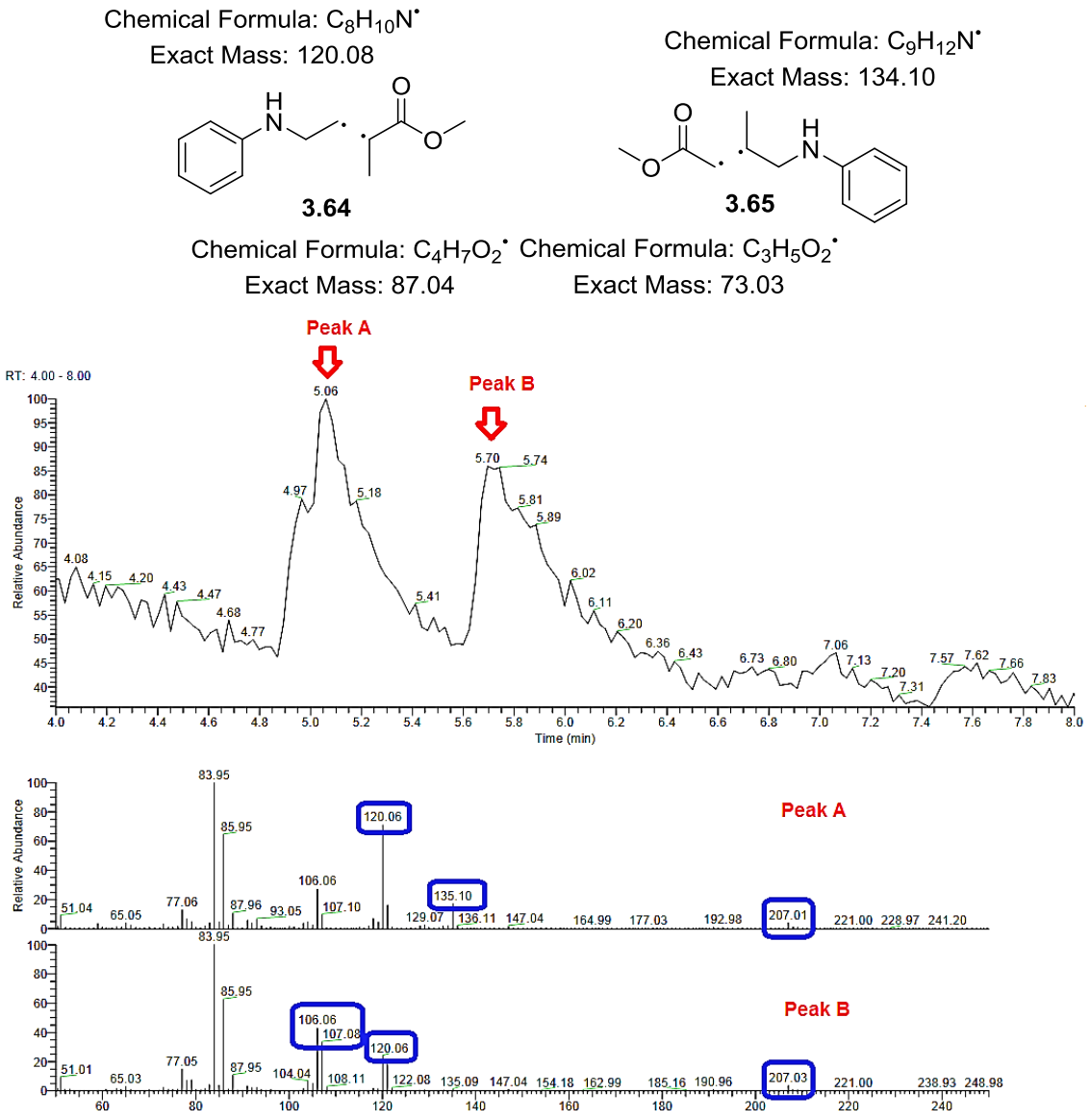


Figure 3.11. GCMS of the reaction mixture after 3 hours starting with dimethyl 2-methylbutanedioate esters, **3.62**.

3-Methyl-1-phenylpyrrolidine, **3.63**, obtained from this reaction was purified by prep-TLC and analysed by NMR. The product was already reported in the literature but it was not fully characterised.

Full characterisation of **3.63** was carried out by both 1D and 2D NMR. The aliphatic region is shown in Figure 3.12. The doublet at 1.15 ppm is the pendant methyl group,

which can be either equatorial or axial. The other protons will be assigned as on the same side or opposite side compare to the methyl group.

From HSQC (Figure 3.13), the protons in red are from the same carbon, the protons in green are from the same carbon, and the protons in blue are from the same carbon. The proton in purple is connected to the same carbon as the methyl group, therefore it is proton $H_{(3)}$. From the COSY NMR (Figure 3.14), the only protons which do not see $H_{(3)}$ (in purple) are the ones giving the green resonances. Therefore, the peaks in green are from $H_{(7, 8)}$. The downfield peak is from $H_{(7)}$, and the up field one is from $H_{(8)}$, which are differentiated by NOSEY NMR (Figure 3.15). The proton giving rise to the higher frequency peak (δ = 3.34 ppm) is close in space to $H_{(3)}$ (δ = 2.43 ppm). The protons giving the red signals do not see $H_{(8)}$. Therefore the red signals are from $H_{(2)}$ and $H_{(1)}$. In order to differentiate between $H_{(2)}$ and $H_{(1)}$, NOESY NMR (Figure 3.16) was used. $H_{(4)}$ was used as a reference. Clearly, the proton giving the peak around δ = 2.9 ppm is close in space to $H_{(4)}$, therefore, this proton is *syn* to the methyl group, and is $H_{(1)}$, the one around 3.5 ppm is therefore $H_{(2)}$. The signals in blue must be from protons $H_{(5)}$ and $_{(6)}$, with the same NOSEY NMR (Figure 3.16), the peak around δ = 1.6 ppm is from a proton *syn* to the methyl group, i.e. $H_{(5)}$, the last resonance at around 2.15 ppm is from $H_{(6)}$.

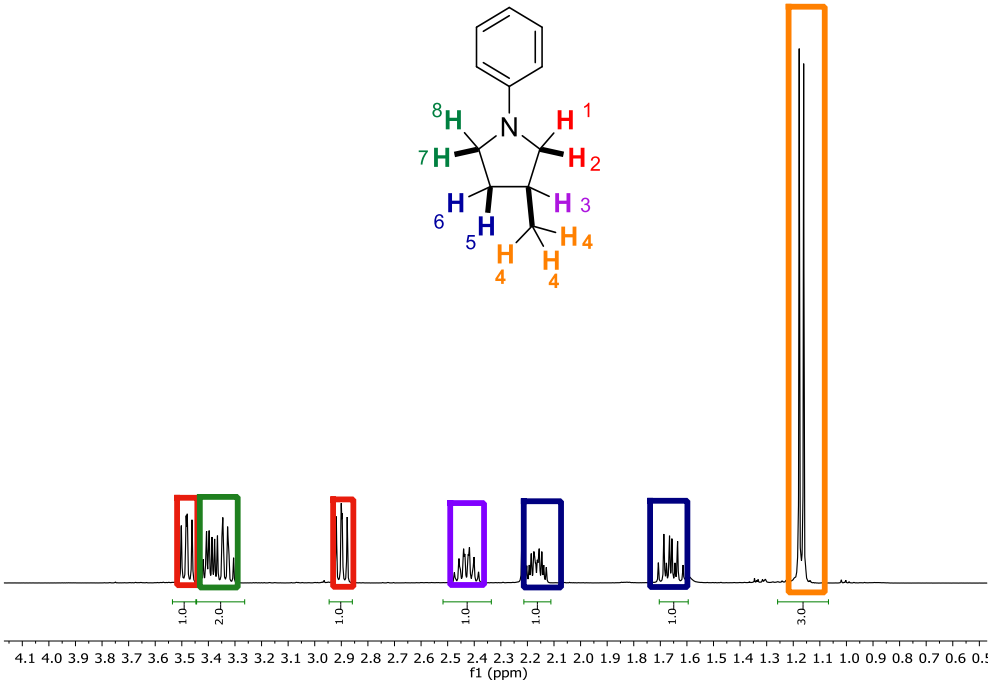


Figure 3.12. ^{1}H NMR (400 MHz, $CDCl_3$) of 3-methyl-1-phenylpyrrolidine.

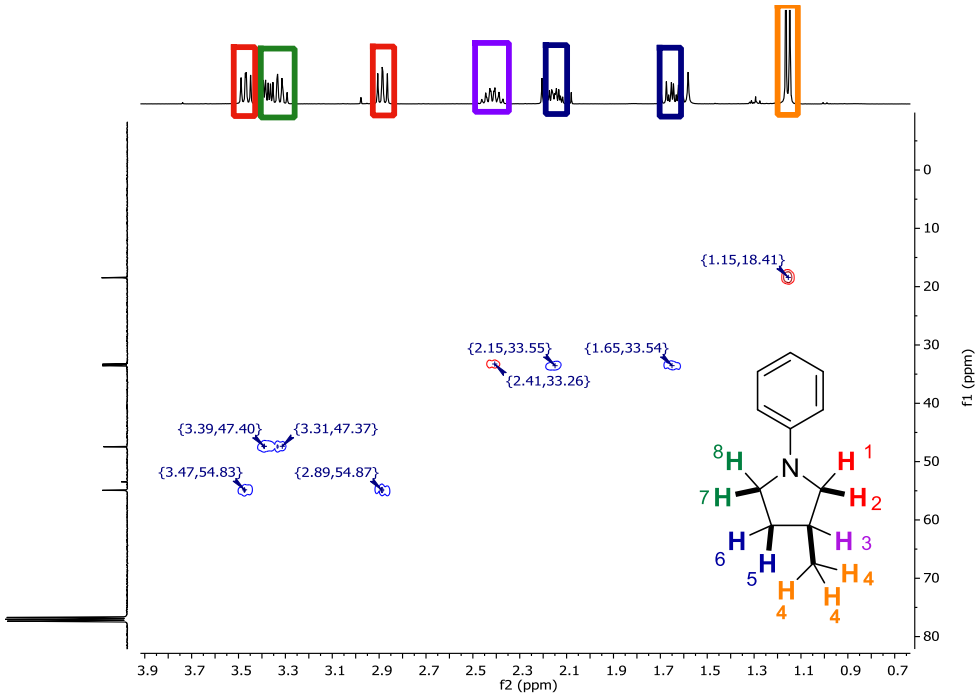


Figure 3.13. HSQC (400Hz for ^{1}H NMR, 101 Hz for ^{13}C NMR, $CDCl_3$) of 3-methyl-1-phenylpyrrolidine.

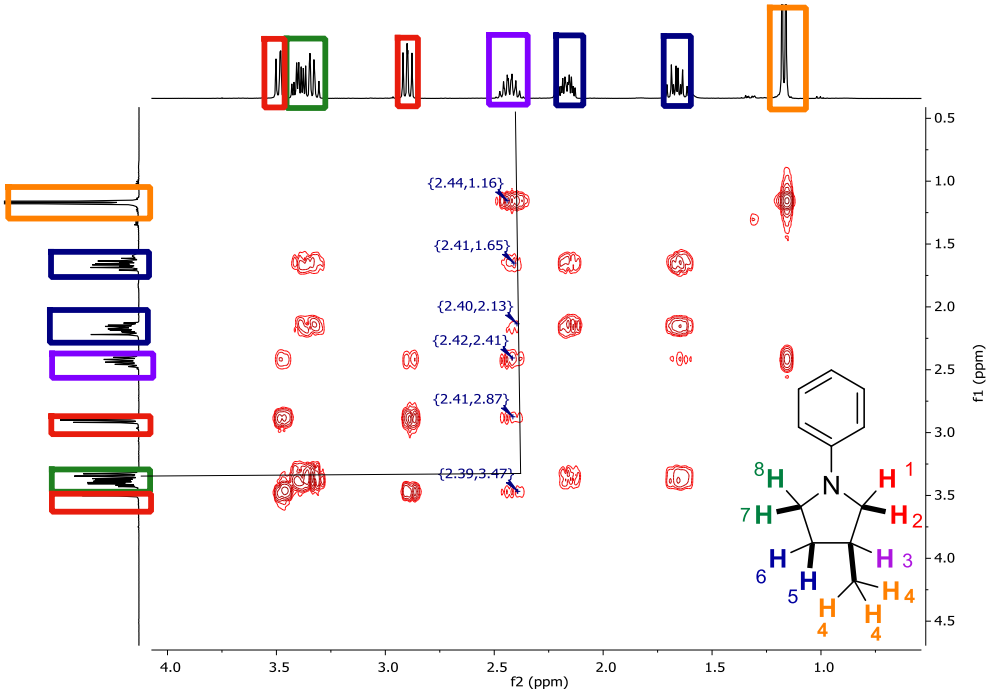


Figure 3.14. COESY (400Hz, $CDCl_3$) of 3-methyl-1-phenylpyrrolidine.

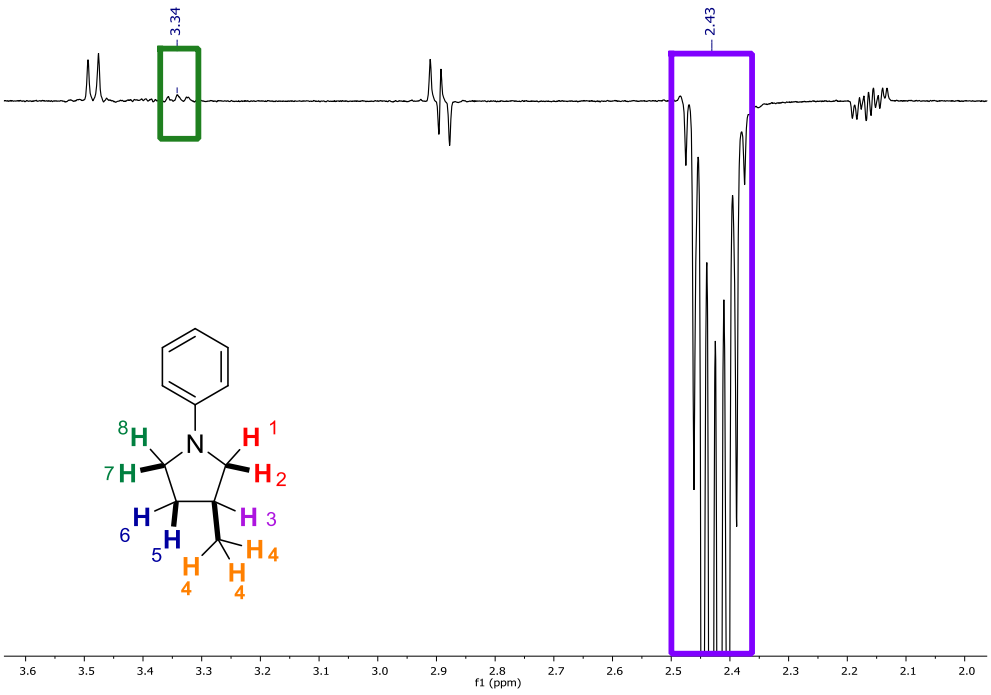


Figure 3.15. 1D NOESY (500Hz, $CDCl_3$) NMR relative to peak δ = 2.43.

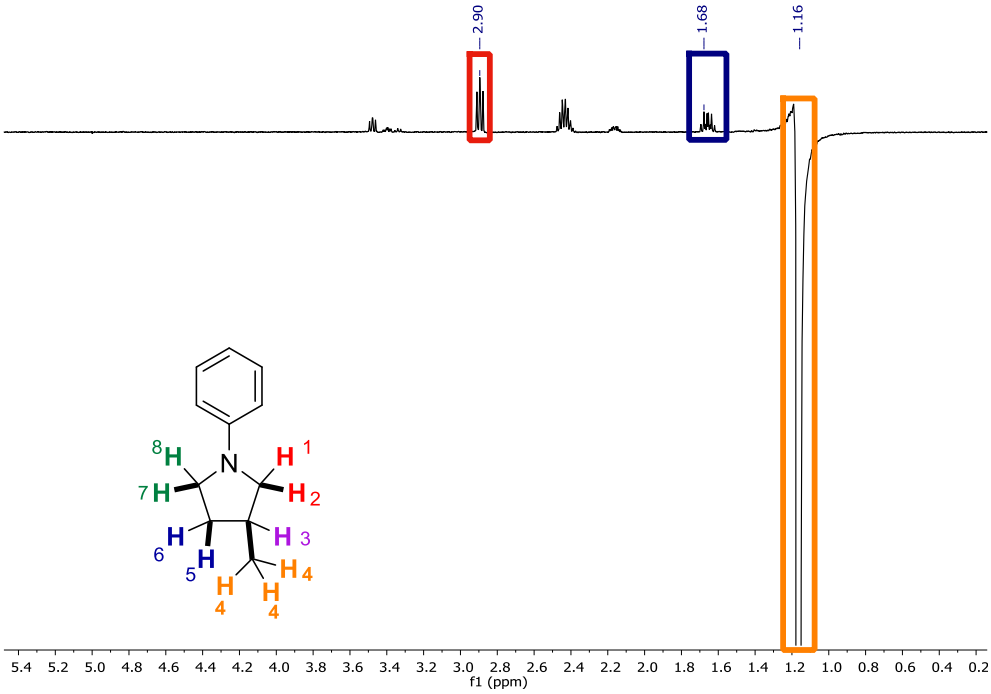
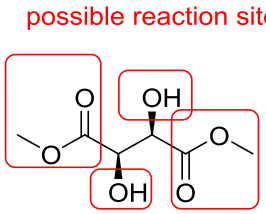


Figure 3.16. 1D NOESY (500Hz, $CDCl_3$) NMR relative to peak δ = 1.16.

When (+)-Dimethyl-L-tartrate, **3.66**, was tested as substrate, the reaction did not work, possibly because there are so many potential active sites for this reaction (Figure 3.17).

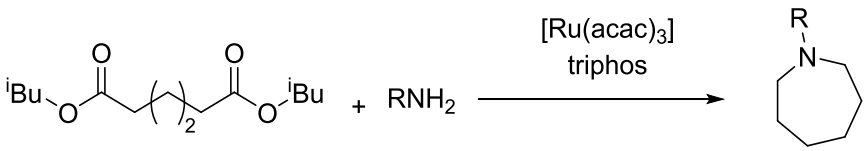


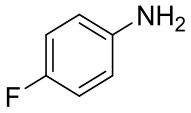
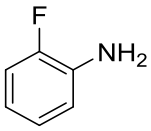
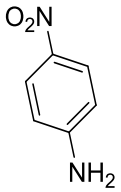
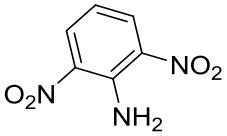
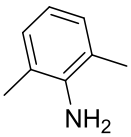
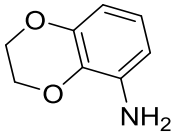
3.66

Figure 3.17. Structure of dimethyl (2*R*,3*R*)-2,3-dihydroxysuccinate, **3.66**.

Aniline derivatives were also tested. The reaction gave good yields when 4-, **3.67**, or 2-fluoroaniline, **3.68**, were used, 94% and 78% yield respectively (Table 3.7, Entry 1 and 2). Strong electron withdrawing nitro groups in the 4-, **3.69**, or the 2,6-positions, **3.70** (Table 3.7, Entry 3 and 4) completely inhibited the reaction leading to catalyst decomposition. 2,6-Dimethylaniline, **3.71**, gave 54% yield (Table 3.7, Entry 5) whilst 1,4-dibenzodioxan-6-amine, **3.72**, gave an almost quantitative yield of the azepane (96% yield) (Table 3.7, Entry 6).

Table 3.7. Cyclisation of diisobutyl adipate in the presence of various amines.[a]



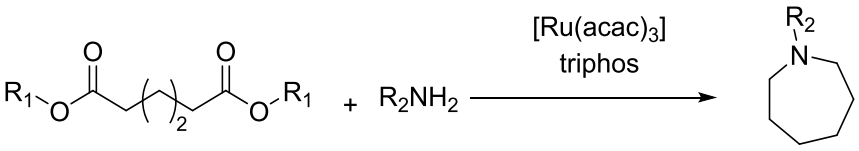
Entry	RNH_2	Conversion (%)	Product	Yield (%)
1	 **3.67**	100	**3.73**	94
2	 **3.68**	94	**3.74**	78
3	 **3.69**	69	**3.75**	7
4	 **3.70**	16	**3.76**	0
5	 **3.71**	100	**3.77**	54
6	 **3.72**	100	**3.78**	96

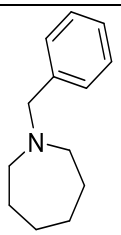
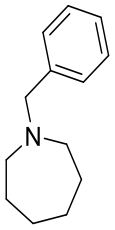
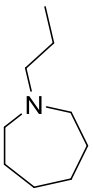
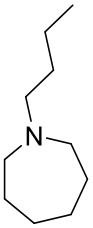
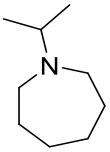
[a][Ru(acac)3] (2 mol%), triphos (4 mol%), MSA (2 mol%), amine (1.5 equiv.), 1,4-dioxane (15 mL), H_2 (10 bar), 42 h, 220 °C. Conversions and yields were calculated by ^{1}H NMR using 1,4-dinitrobenzene as internal standard.

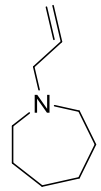
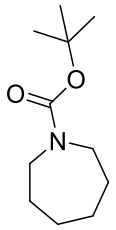
When alkyl, allyl or other aryl amines were used, lower yields were obtained (Table 3.8). The best result was obtained with benzylamine, **3.79**, which afforded *N*-benzylazepane, **3.80**, with a yield of 53% (Table 3.8, Entry 2). Other aliphatic amines gave only less than 20% yield to the corresponding cyclic amines (Table

3.8, Entry 3-5). When allyl amine, **3.87**, and *tert*-butyl carbamate, **3.89**, was used, the corresponding cyclic products **3.88** or **3.90** were not obtained (Table 3.8, Entry 7).

Table 3.8. Cyclisation of diesters in the presence of various amines.[a]



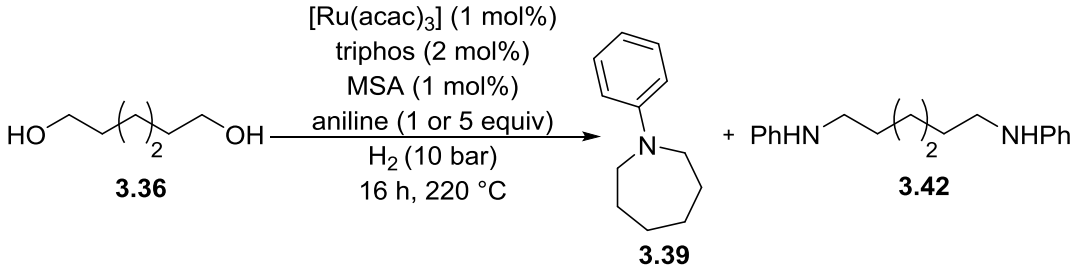
Entry	R_1	R_2NH_2	Conversion (%)	Product	Yield (%)
1[b]	Me	Benzylamine **3.79**	99	 **3.80**	38
2	^{i}Bu	Benzylamine **3.79**	92	 **3.80**	53
3	^{i}Bu	^{n}Pr **3.81**	65	 **3.82**	15
4	^{i}Bu	^{n}Bu **3.83**	70	 **3.84**	21
5	^{i}Bu	^{i}Pr **3.85**	90	 **3.86**	16

6	^{i}Bu	allyl amine **3.87**	40	 **3.88**	0
7	^{i}Bu	*tert*-butyl carbamate **3.89**	50	 **3.90**	0

[(a)][Ru(acac)$_3$], **3.32** (2 mol%), triphos, **3.33** (4 mol%), MSA (2 mol%), amine (1.5 equiv.), 1,4-dioxane (15 mL), H_2 (10 bar), 42 h, 220 °C. Conversions and yields are calculated using 1,4-dinitrobenzene as internal standard. [(b)][Ru(acac)$_3$], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (1 mol%), amine (1.5 equiv.), 1,4-dioxane (15 mL), H_2 (10 bar), 70 h, 220 °C. Conversions and yields are calculated by ^{1}H NMR using 1,4-dinitrobenzene as internal standard.

Beller showed by sampling a reaction over time that amide hydrogenations using Ru/triphos and Lewis acids, such as Yb(OTf)$_3$.H$_2$O, occur *via* initial formation of the free alcohol followed by amination through a hydrogen borrowing mechanism.[37] In order to test the viability of this mechanism under our reaction conditions, 1,6-hexan-diol, **3.36**, was reacted with aniline under the same conditions as the ones used with dicarboxylic acids and esters. When one equivalent of aniline was used, *N*-phenyl azepane, **3.39**, was obtained in 92% yield, without formation of the lactam, **3.38** (Table 3.9, Entry 1). With 5 equivalents of aniline, the diol, **3.36**, was mainly converted to the linear diamine, **3.42** (88%), with less than 10% yield of the azepane, **3.39** (Table 3.9, Entry 2). This result is similar to what was obtained when dimethyl adipate was hydrogenated in the presence of 5 equivalents of aniline (Table 3.4, Entry 5). This suggests that 1,6-diaminohexane does not cyclise to **3.39** under the reaction conditions, at least when excess aniline is present.

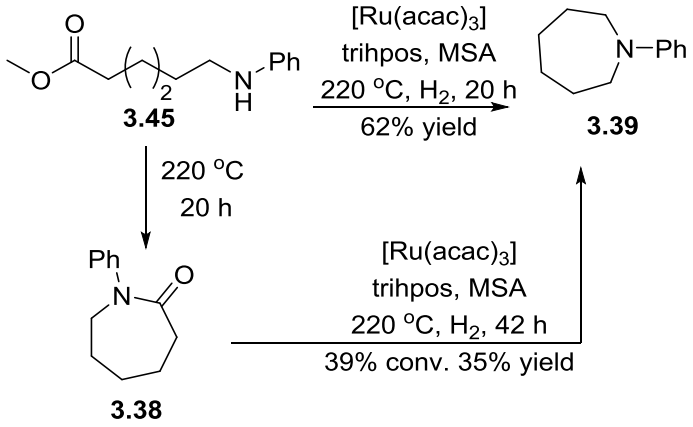
Table 3.9. Hydrogenation 1,6-hexan-diol, **3.36**, with aniline.[a]



Entry	Equiv. aniline	Conv. (%)	Yield 3.39 (%)	Yield 3.42 (%)
1	1	100	92	0
2	5	100	9.5	88

[(a)][Ru(acac)$_3$], **3.32** (1 mol%), triphos, **3.33** (2 mol%), MSA (1 mol%), aniline (1 or 5 equiv.), H_2 (10 bar), 220 °C, 16 h, selectivity calculated by calibrated GC.

When ester amine, **3.45**, was used as the starting material, in the absence of aniline, 62% yield of **3.39** was obtained after 20 hours under the normal catalytic conditions (Scheme 3.13). When heating the ester amine, **3.45**, in the absence of catalysts at 220 °C, *N*-phenyl lactam, **3.38**, was observed in 64% yield (Scheme 3.13). **3.38** could also be hydrogenated to **3.39** under similar conditions, but the conversion (39%) and yield (35%) of the hydrogenation were lower, suggesting that **3.38** is not an intermediate since it does not build up during the hydrogenation of hexanedioate esters in the presence of aniline.



Scheme 3.13. Synthesis of **3.39** from ester amine, **3.45**, and *N*-phenyl lactam, **3.38**.

3.2.4 Proposed reaction pathway

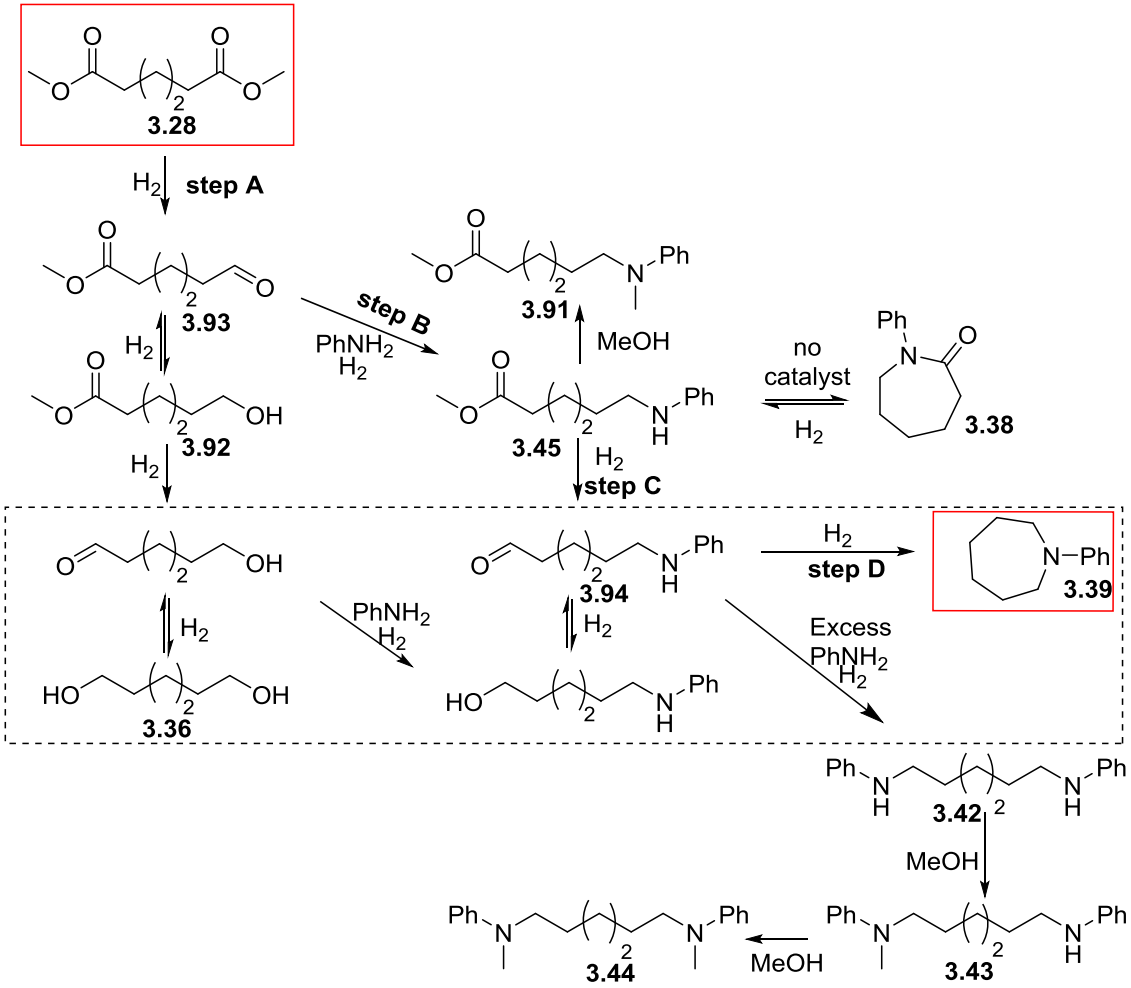
Summarising the results described above, *N*-phenyl heterocycles such as **3.39** can be formed in high yields by the Ru/triphos catalysed hydrogenation of diesters in the presence of aniline. The only observable intermediate is the amino ester, **3.45**. In the absence of catalyst, **3.45** converts to *N*-phenyl ε-caprolactam, **3.38**, which can also be hydrogenated to **3.39**, but more slowly than dimethyl adipate, **3.28**. Diol, **3.36**, is converted smoothly to **3.39** but gives linear diamine, **3.42**, in the presence of excess aniline. A number of the products (**3.43**, **3.44** and **3.91**) are formed by *N*-methylation if the substrate is a dimethyl diester.

Beller and co-workers have shown, by sampling the reaction over time, that amide hydrogenations using Ru/triphos and a Lewis acid, in place of a Brønsted acid, proceeds *via* the formation of an alcohol which then undergoes amination by a hydrogen borrowing mechanism.[37] The formation of free alcohol was not observed during our reactions. DFT calculations reported by Leitner on the hydrogenation of methyl benzoate to benzyl alcohol suggest that free benzaldehyde is an intermediate.[38] The hydrogen borrowing mechanism proposed for the transformation of an intermediate alcohol into an amide involves the oxidation of the alcohol to aldehyde (Scheme 3.11). It is difficult to distinguish whether ester alcohol, **3.92**, is intermediate or whether aldehyde **3.93** is trapped by the amine before hydrogenation in the reaction system. Which occurs will depend on the relative rates of hydrogenation and reaction with aniline of **3.93**. We do know that diol, **3.36**, transforms to **3.39** under the reaction conditions so it cannot be ruled out as an intermediate on that basis.

The simplest mechanism that is consistent with our observations is shown in Scheme 3.14, Steps A-D. It involves hydrogenation of the diester, dimethyl adipate **3.28**, to the ester aldehyde, **3.93** (Step A). **3.93** is trapped by aniline to give an imine (not shown), which in turn is hydrogenated to the observed ester amine, **3.45** (Step B). **3.45** is then hydrogenated to the amino aldehyde, **3.94**, (Step C) which reacts intramolecularly and is hydrogenated to **3.39** (Step D).

Possible side reactions are also shown in Scheme 3.14. Diol, **3.36**, can give final product **3.39** under the reaction conditions (dotted box). The formation of *N*-phenyl ε-

caprolactam, **3.38**, is possible from **3.45** only when the catalyst is not present, and when the catalyst is added, its hydrogenation to **3.39**, is possible but rather inefficient. When an excess of aniline is used, the formation of diamine **3.42** is detected. Lastly, when MeOH is present in the reaction mixture (from the hydrogenation of methyl esters) various byproducts (**3.43**, **3.44**), derived from the methylation of diamine **3.42** are also detected.

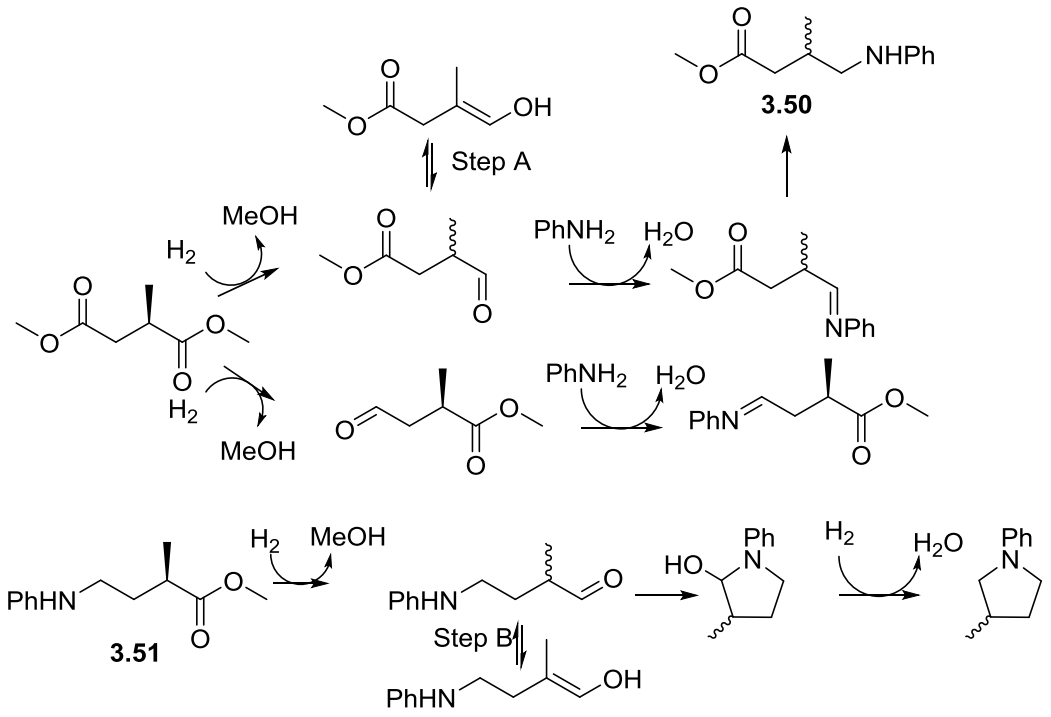


Scheme 3.14. Proposed reaction pathway for the hydrogenation of dimethyl adipate **3.28** in the presence of aniline to give **3.39**. The main mechanism is proposed to proceed by steps A-D. The dotted box shows the formation of **3.39** from diol **3.36**. The origin of side products is also shown.

The intermediacy of aldehydes in the formation of **3.45** from dimethyl adipate, **3.28,** and of **3.39** from **3.45** is consistent with the results of reactions using (*S*) or (*R*)-dimethyl 2-methylsuccinate (Table 3.5, Entries 5 and 6), which both give racemic *N*-phenyl 3-methypyrolidine, **3.63**. This result implies that the chiral carbon atom becomes planar during the reaction and this is most likely to be as a result of enolisation

of the intermediate aldehydes (Scheme 3.15), which is very likely at 220 °C in the presence of amine and added acid.

Dimethyl (*S*)-2-methylsuccinate, **3.62**, can form two amino esters (**3.64** and **3.65** in Scheme 3.15). In one, the chiral carbon is α to the carbonyl so it will racemise in step A (Scheme 3.15), whilst in the other the chiral carbon is β to the carbonyl so it should be configurationally stable. The observation that the final product is racemic strongly suggests that the final ring closing step also involves an enolisable aldehyde since this will racemise the chiral centre that remained stable during the first step (Scheme 3.15). Unfortunately, the ester amides in this case are only formed in trace amounts even after short reaction times so it is not possible to measure their optical purity nor absolute configuration.



Scheme 3.15. Proposed steps in which racemisation of the chiral centre originally in 2-methylsuccinic acid occurs during hydrogen borrowing steps in the formation of 2-methyltetrahydropyrrole.

3.3 Conclusions

A new simple and selective route to *N*-phenyl heterocycles from the hydrogenation of diesters in the presence of aniline and a Ru/triphos catalyst has been developed. When methyl esters were used, a competing methylation of the aniline compromised the conversion, but esters with longer or/and branched chains gave excellent conversions and yields. It is believed that this reaction undergoes hydrogenation of the diester to the corresponding ester aldehyde, followed by reductive amination, hydrogenation of the second ester again to an aldehyde and cyclisation to the corresponding heterocycle. The enolisable aldehyde intermediates, which are present in both steps, could explain the loss of chirality when enantiopure dimethyl 2-methyl-1,4-butanedioate, **3.62**, was used. ε-Caprolactam, **3.30**, was obtained in 60% yield from dimethyl adipate, **3.28**, in the presence of aqueous ammonia which is better compared to the previous literature which reports only 17% yield of ε-caprolactam.[22]

3.4 Experimental

3.4.1 General procedure

All the commercially available reagents were used without further purification unless specified. Diethyl adipate, diethyl succinate, diethyl glutarate, bis(2-ethylhexyl) adipate, *tert*-butyl carbamate, 1,4-dinitrobenzene, 4-nitroaniline, 2,6-dinitroaniline, 2-fluoroaniline, 1,4-benzodioxan-6-amine, isobutylaniline, *N*,*N*-dimethylaniline, adipic acid, 1-butylamine, benzylamine, tris(dibenzylideneacetone)dipalladium(0) and 1,4-dioxane were purchased from Alfa Aesar; diisobutyl adipate, dibutyl adipate, racemic dimethyl 2-methylsuccinate, dimethyl (*R*)-2-methylsuccinate, dodecane, *tris*(2,4-diethylpentanedioato)ruthenium(III) ($[Ru(acac)_3]$) 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos), 2,6-dimethylaniline and *N*-methylaniline were purchased from Sigma Aldrich; diisopropyl adipate, diisodecyl adipate, dimethyl (*S*)-2-methylsuccinate, diethyl heptanedioate, 4-fluoroaniline and methyl 6-bromohexanoate were purchased from Fluorochem. Aniline was distilled over zinc powder and KOH under vacuum. Air sensitive or moisture sensitive reactions were carried out under argon in a fume hood using standard Schlenk techniques with oven-dried glassware. Flash column chromatography was performed manually using silica gel

(pore size 60 Å, 70-230 mesh particle size, 40-63 μm particle size). Analytical TLC was performed on pre-coated polyester sheets of silica (60 F254 nm) and visualised by short-wave UV light at 254 nm. Permanganate TLC stains was used for compounds with no UV visible chromophore. Ninhydrin stain was also used for primary and secondary amines, which gave a dark purple spot for primary amines, and a yellow/orange spot for secondary amines. Mass spectra were recorded on a Micromass LCT with a TOF mass spectrometer coupled to a Waters 2795 HPLC and a Waters 2996 detector. NMR spectra were recorded on Bruker Avance II 400 and Bruker Avance II 500 spectrometers, ^{13}C spectra were measured with ^{1}H decoupling. Residual protio peaks from deuterated solvents were used as reference with TMS at 0 ppm. GC was run with a Thermo Scientific Trace 1300 Gas Chromatograph (Rtx®-35ms, 30 m × 0.25 mm (ID) × 0.5 μm (df), Crossbond® 35% diphenyl/ 65% dimethyl polysiloxane); Data was analysed using a Chromeleon data system. Method: 0-50 °C, ramp rate 20 °C/min, hold for 4 mins; 50-130 °C, ramp rate 20 °C/min, hold for 2 mins; 130-220 °C, ramp rate 20 °C/min, hold for 15.5 mins.

GC for chiral compounds was performed on a Thermo Trace GC Ultra (Beta DEX™ 225, 30 m × 0.25 mm (ID) × 0.25 μm (df), Fused silica capillary column). Method: 90-150 °C, ramp rate 2 °C/min, hold for 5 mins.

GCMS was carried out using a Thermo Electron Corporation DSQ II for the GC, and Trace GC ULTRA Thermo Electron Corporation mass spectrometer for the MS with a Supelco SPB-35 (Poly(35% diphenyl/65% dimethyl siloxane)) column. Method: 50-300 °C, ramp rate 15 °C/min, hold for 10 mins.

3.4.2 Experimental procedures

3.4.2.1 Synthesis of various diesters

General procedure 1: To a solution of carboxylic acid (20 g, 1.0 equiv.) in alcohol (50 mL) was slowly added concentrated sulfuric acid (0.3 equiv.). The resulting mixture was stirred at reflux for 2 h until TLC analysis indicated complete consumption of the starting material. The excess alcohol was removed under vacuum to give the crude product, which was poured into crushed ice and then extracted with dichloromethane

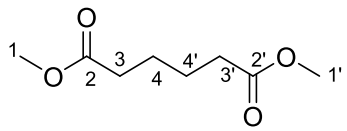
(DCM, 5×50 mL). The organic layers were washed with 5% aq. $NaHCO_3$ solution (50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure.

3.4.2.2 Cyclisation of difunctional esters with an amine source

General procedure 2: $[Ru(acac)_3]$ (0.010-0.020 g, 0.025-0.05 mmol, 1-2 mol%), 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos, 0.031-0.062 g, 0.05-0.1 mmol, 2-4 mol%) and the substrate (2.5 mmol) were weighed in air and introduced into a 250 mL Hastolloy autoclave fitted with a stirrer bar. The autoclave was sealed and purged by three vacuum/Ar cycles. Methanesulfonic acid (1.62-3.24 μL, 0.025-0.05 mmol, 1-2 mol%) in degassed 1,4-dioxane (15 mL) was introduced into the autoclave through a septum using a syringe. Amine (eg. aqueous ammonia or aniline) (1-5 equiv.) was also introduced into the autoclave. The autoclave was sealed again, connected to the high pressure system, and purged six times with 10 bar of H_2. The autoclave was charged with 10 bar of H_2, and heated to 220 °C for the required amount of time. The autoclave was cooled, vented and opened. The crude mixtures were analysed using GC-MS, GC-FID, NMR spectroscopy, and mass spectrometry, examples of spectra are shown below. Quantitative calculations were based on the analysis of ^1H NMR spectra with 1,4-dinitrobenzene as an external standard, calibrated GC using dodecane as internal standard or calculated GC response factor using dodecane as internal standard.

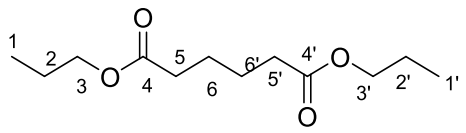
3.4.3 Experimental results

Dimethyl adipate, 3.28



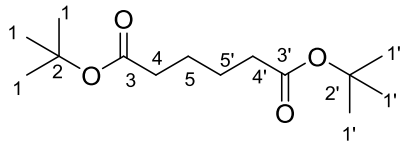
General procedure 1 was applied using adipic acid (20 g) and methanol. Dimethyl adipate was obtained as a colourless oil (20.5 g, 86% yield). δ_H (400 MHz, $CDCl_3$) 1.61-1.69 (4H, m, $H_{4,4'}$), 2.28-2.37 (4H, m, $H_{3,3'}$), 3.66 (6H, s, $H_{1,1'}$); δ_C (101 MHz, $CDCl_3$) 24.5 ($C_{4,4'}$), 33.8 ($C_{3,3'}$), 51.7 ($C_{1,1'}$), 173.9 ($C_{2,2'}$). *The spectroscopic properties of this compound were consistent with literature data.*[39]

Di-*n*-propyl adipate, 3.48



General procedure 1 was applied using adipic acid (20 g) and 1-propanol. Di-*n*-propyl adipate was obtained as a colourless oil (25 g, 80% yield). δ_H (400 MHz, $CDCl_3$) 0.94 (6H, t, J = 7.2 Hz, $H_{1,1'}$), 1.54-1.73 (8H, m, $H_{2,2',6,6'}$), 2.28-2.38 (4H, m, $H_{5,5'}$), 4.03 (4H, t, J = 6.8 Hz, $H_{3,3'}$); δ_C (126 MHz, $CDCl_3$) 10.5 ($C_{1,1'}$), 22.1 ($C_{2,2'}$), 24.6 ($C_{6,6'}$), 34.1 ($C_{5,5'}$), 66.1 ($C_{3,3'}$), 173.6 ($C_{4,4'}$). *The spectroscopic properties of this compound were consistent with literature data.*[39]

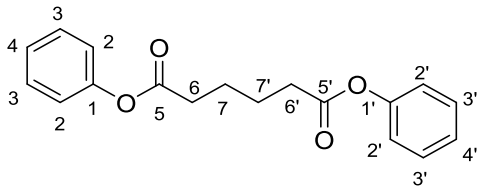
Di-*tert*-butyl adipate, 3.51



A mixture of adipic acid (4.76 g, 33 mmol, 1 equiv.), thionyl chloride (10 mL, 138 mmol, 4 equiv.) in 2:1 (v/v) benzene-cyclohexane (15 mL) was heated under reflux for 2.5 h. The reaction mixture was concentrated under vacuum to removed thionyl chloride, benzene and cyclohexane. The resulting yellow oil was dissolved in anhydrous ether (5 mL) and added dropwise to a solution of dimethylaniline (13 mL, 102 mmol, 3 equiv.), *tert*-butanol (10 mL, 105 mmol, 3 equiv.) in anhydrous ether (5 mL). The reaction mixture was stirred at room temperature for 20 hours before being diluted with 10% (w/v) aqueous sodium chloride (100 mL) and extracted 3 times with Et_2O (50 mL). The organic layer was washed with 3:1 (v/v) 2 M aqueous HCl/ sat. brine (100 mL), then with 3:1 (v/v) 1 M aqueous NaOH/ brine (2 x100 mL), then brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. The orange crude product was purified by flash column chromatography (10% ethyl acetate/ petroleum ether) to afford the product as a colourless solid (6 g, 71% yield). δ_H (400 MHz, $CDCl_3$) 1.42 (18H, s, $H_{1,1'}$), 1.48-1.66 (4H, m, $H_{5,5'}$), 2.14-2.28 (4H, m, $H_{4,4'}$); δ_C (101 MHz, $CDCl_3$) 24.7 ($C_{5,5'}$), 28.2 ($C_{1,1'}$),

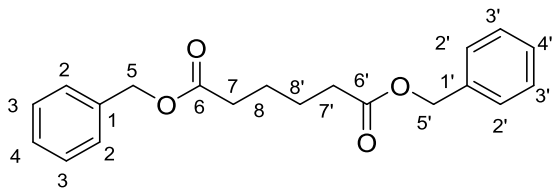
35.4 ($C_{4,4'}$), 80.2 ($C_{2,2'}$), 173.0 ($C_{3,3'}$). *The spectroscopic properties of this compound were consistent with literature data.*[40] mp: 28-29 °C.

Diphenyl adipate, 3.54



Reaction conditions adopted from the literature.[41] Adipic acid (15 g, 103 mmol, 1 equiv.), diphenyl carbonate (44 g, 205.4 mmol, 2 equiv.) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.56 g, 10.3 mmol, 10 mol%) were added into a flask and heated at 160 °C for 24 h. The reaction mixture was dried under vacuum to remove phenol. The crude product was recrystalised from ethyl acetate/ hexane (1:3) to afford diphenyl adipate as a white solid (25 g, 61%). δ_H (400 MHz, $CDCl_3$) 1.82-1.97 (4H, m, $H_{7,7'}$), 2.57-2.71 (4H, m, $H_{6,6'}$), 7.04-7.13 (4H, m, $H_{2,2'}$), 7.20-7.25 (2H, m, $H_{4,4'}$), 7.33-7.43 (4H, m, $H_{3,3'}$); δ_C (101 MHz, $CDCl_3$) 24.5 ($C_{7,7'}$), 34.1 ($C_{6,6'}$), 121.7 ($C_{2,2'}$), 126.0 ($C_{4,4'}$), 129.6 ($C_{3,3'}$), 150.8 ($C_{1,1'}$), 171.9 ($C_{5,5'}$). *The spectroscopic properties of this compound were consistent with literature data.* [41] mp: 96-98 °C.

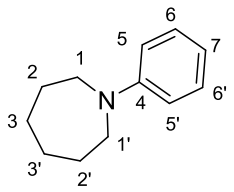
Dibenzyl adipate, 3.55



Reaction conditions adopted from the literature[42]. Adipic acid (20 g, 137 mmol, 1 equiv.), benzyl alcohol (32.5 g, 300 mmol, 2.2 equiv.) and *p*-toluenesulfuric acid monohydrate (0.3 g, 1.6 mmol, 1.2 mol%) were added into a 250 mL round bottom flask together with toluene (20 mL). The round bottom flask was fitted to a Dean Stark condenser and heated under reflux for 16 h. The reaction was cooled and neutralized with sodium carbonate (0.4 g), then washed with water (100 g). The toluene was removed under vacuum. The crude product was washed with petroleum ether, and

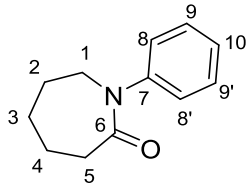
dibenzyl adipate was obtained as a white solid (32 g, 72% yield). δ_H (400 MHz, $CDCl_3$) 1.63-1.76 (4H, m, $H_{8,8'}$), 2.31-2.44 (4H, m, $H_{7,7'}$), 5.11 (4H, s, $H_{5,5'}$), 7.29-7.40 (10H, m, $H_{2\text{-}4;2'\text{-}4'}$); δ_C (101 MHz, $CDCl_3$) 24.5 ($C_{8,8'}$), 34.0 ($C_{7,7'}$), 66.3 ($C_{5,5'}$), 128.3, 128.7 ($C_{2\text{-}4;2'\text{-}4'}$), 136.1 ($C_{1,1'}$), 173.2 ($C_{6,6'}$). mp: 35-37 °C.

_N_-phenylazepane, 3.39



General procedure 2 was applied using dimethyl adipate. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (10% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.50-1.59 (4H, m, $H_{3,3'}$), 1.70-1.87 (4H, m, $H_{2,2'}$), 3.45 (4H, t, J = 6.0 Hz, $H_{1,1,}$), 6.62 (1H, t, J = 7.2 Hz, H_7), 6.69 (2H, d, J = 8.0 Hz, $H_{5,5'}$), 7.14-7.24 (2H, m, $H_{6,6'}$); δ_C (101 MHz, $CDCl_3$) 27.3 ($C_{3,3'}$), 27.9 ($C_{2,2'}$), 49.2 ($C_{1,1'}$), 111.3 ($C_{5,5'}$), 115.3 (C_7), 129.4 ($C_{6,6'}$), 149.0 (C_4). Micro Anal. Found: C, 82.09; H, 9.70; N, 8.15. Calc'd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. HRMS: (NSI^+) Found: $[M+H]^+$ 176.1430, $C_{12}H_{18}N$ requires 176.1434. *The spectroscopic properties of this compound were consistent with literature data.*[43]

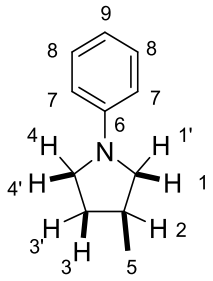
_N_-phenyl caprolactam, 3.38



Reaction conditions adopted from the literature.[44] ε-Caprolactam (4.53 g, 40 mmol), $[Pd_2(dba)_3]$ (405 mg, 0.4 mmol, 1 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (767 mg, 1.3 mmol, 3 mol%), cesium carbonate (17 g, 51 mmol) were dissolved in 1,4-dioxane (40 mL) in a flask, bromobenzene (3.8 mL, 36 mmol) was added slowly into the flask. The reaction mixture was heated under reflux for 16 h. The reaction mixture was then cooled and filtered to removed palladium catalyst, and

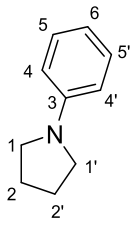
concentrated under reduced pressure. The crude product was purified by flash column chromatography (40% ethyl acetate/ petroleum ether) to afford the product as a yellow solid (6.5 g, 86% yield). δ_H (400 MHz, $CDCl_3$) 1.83 (6H, app s, $H_{2,3,4}$), 2.67-2.76 (2H, m, H_5), 3.69-3.80 (2H, m, H_1), 7.15-7.25 (3H, m, $H_{8,10}$), 7.32-7.42 (2H, m, H_9); δ_H (500 MHz, d_8-toluene, 295 K) 1.24-1.34 (4H, m, $H_{2,4}$), 1.41-1.47 (2H, m, H_3) 2.34-2.40 (2H, m, H_5), 3.16 (2H, t, J = 5 Hz, H_1), 6.94-6.98 (3H, m, H_{10}), 7.12-7.17 (4H, m, $H_{8,8',9,9'}$); δ_C (101 MHz, $CDCl_3$) 23.7 (C_4), 29.1 (C_2), 30.0 (C_3), 37.8 (C_5), 53.2 (C_1), 126.4 ($C_{8,8'}$), 126.6 (C_{10}), 129.2 ($C_{9,9'}$), 144.7 (C_7), 175.7 (C_6). *The spectroscopic properties of this compound were consistent with literature data.*[44]

3-Methyl-1-phenylpyrrolidine, 3.63



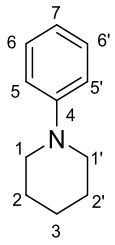
General procedure 2 was applied using dimethyl methyl succinate. The product was isolated by preparative TLC ((pre-coated polyester sheets of silica (60 F254 nm))) (10% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, J = 6.8 Hz, H_5), 1.57-1.68 (1H, m, H_3), 2.09-2.19 (1H, m, $H_{3'}$), 2.33-2.48 (1H, m, H_2), 2.84-2.92 (1H, m, $H_{1'}$), 3.24-3.42 (2H, m, $H_{4,4'}$), 3.43-3.51 (1H, m, H_1), 6.56 (2H, d, J = 7.2 Hz, H_7), 6.67 (1H, t, J = 7.2 Hz, H_9), 7.22-7.28 (2H, m, H_8); δ_C (101 MHz, $CDCl_3$) 18.6 (C_5), 33.4, 33.7 ($C_{2,3}$), 47.6 (C_4), 55.0 (C_1), 111.5 (C_7), 115.3 (C_9), 129.2 (C_8), 148.0 (C_6). *The spectroscopic properties of this compound were consistent with literature data.*[45]

***N*-phenylpyrrolidine, 3.59**



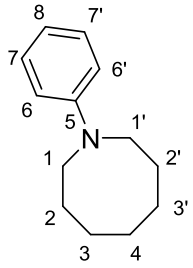
General procedure 2 was applied using diethyl succinate. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (1% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.97-2.11 (4H, m, $H_{2,2'}$), 3.25-3.39 (4H, m, $H_{1,1'}$), 6.57-6.66 (2H, m, $H_{4,4'}$), 6.66-6.75 (1H, m, H_6), 7.22-7.32 (2H, m, $H_{5,5'}$); δ_C (101 MHz, $CDCl_3$) 25.6 (C_2), 47.7 ($C_{1,1'}$), 111.7 ($C_{4,4'}$), 115.5 (C_6), 129.3 ($C_{5,5'}$), 149.1 (C_3). HRMS: (NSI^+) Found: $[M+H]^+$ 148.1117, $C_{10}H_{14}N$ requires 148.1121.*The spectroscopic properties of this compound were consistent with literature data.*[46]

_N_-phenylpiperidine, 3.60



General procedure 2 was applied using diethyl glutarate. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (1% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.55-1.68 (2H, m, H_3), 1.70-1.84 (4H, m, $H_{2,2'}$), 3.21 (4H, t, J = 5.5 Hz, $H_{1,1'}$), 6.88 (1H, tt, J = 7.2, 1.0 Hz, H_7), 6.95-7.04 (2H, m, $H_{5,5'}$), 7.26-7.35 (2H, m, $H_{6,6'}$); δ_C (101 MHz, $CDCl_3$) 24.5 (C_3), 26.0 ($C_{2,2'}$), 50.8 ($C_{1,1'}$), 116.7 ($C_{5,5'}$), 119.3 (C_7), 129.1 ($C_{6,6'}$), 152.4 (C_4). *The spectroscopic properties of this compound were consistent with literature data.*[47]

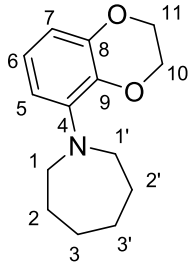
_N_-phenylazocane, 3.61



General procedure 2 applied using diethyl heptanedioate. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (10%

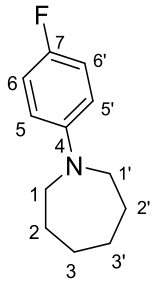
ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.51-1.62 (6H, m, $H_{3,3',4}$), 1.71-1.81 (4H, m, $H_{2,2'}$), 3.45 (4H, t, J = 5.6 Hz, $H_{1,1'}$), 6.64 (1H, t, J = 7.2 Hz, H_8), 6.68 (2H, d, J = 8.0 Hz, $H_{6,6'}$), 7.17-7.26 (2H, m, $H_{7,7'}$); δ_C (101 MHz, $CDCl_3$) 27.0, 27.2, 27.4 ($C_{2,2'-4,4'}$), 50.7 ($C_{1,1'}$), 111.2 ($C_{6,6'}$), 115.1 (C_8), 129.3 ($C_{7,7'}$), 148.4 (C_5). HRMS: (ESI^+) Found: $[M]^+$ 189.1518, $C_{13}H_{19}N$ requires 189.1517. *The spectroscopic properties of this compound were consistent with literature data.*[48]

_N_-(2,3-dihydrobenzo[1,4]dioxin-5-yl)azepane



General procedure 2 was applied using diisobutyl adipate and 1,4-dibenzodioxan-6-amine. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (10% ethyl acetate/ petroleum ether). δ_H (500 MHz, $CDCl_3$) 1.49-1.59 (4H, m, $H_{3,3'}$), 1.70-1.83 (4H, m, $H_{2,2'}$), 3.45 (4H, t, J = 6.0 Hz, $H_{1,1'}$), 4.17-4.21 (2H, m), 4.22-4.27 (2H, m) ($H_{10,11}$), 6.19-6.25 (2H, m), 6.72-6.76 (1H, m) ($H_{5,6,7}$); δ_C (126 MHz, $CDCl_3$) 27.3 (C_3), 28.0 (C_2), 49.6 (C_1), 64.5, 65.0 ($C_{10,11}$), 100.0, 104.8, 117.6 ($C_{5,6,7}$), 134.0, 144.1, 144.6 ($C_{4,8,9}$). HRMS: (ESI^+) Found: $[M]^+$ 233.1412, $C_{14}H_{19}NO_2$ requires 233.1416.

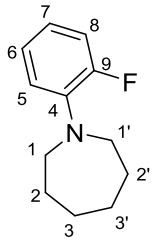
_N_-(4-fluorophenyl)azepane



General procedure 2 was applied using diisobutyl adipate and 4-fluoroaniline. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60

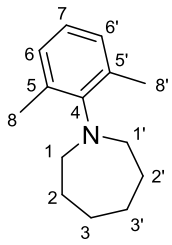
F254 nm)) (10% ethyl acetate/ petroleum ether). δ_H (500 MHz, $CDCl_3$) 1.56 (4H, m, $H_{3,3'}$), 1.79 (4H, m, $H_{2,2'}$), 3.44 (4H, t, J = 6.0 Hz, $H_{1,1'}$), 6.61 (2H, m, $H_{5,5'}$), 6.93 (2H, t, J = 9.0 Hz, $H_{6,6'}$); δ_C (126 MHz, $CDCl_3$) 27.2 ($C_{3,3'}$), 27.9 ($C_{2,2'}$), 49.6 ($C_{1,1'}$), 111.8 (d, J = 7.1 Hz, $C_{5,5'}$), 115.6 (d, J = 21.8 Hz, $C_{6,6'}$), 145.7 (C_4), 154.6 (d, J = 233.4 Hz, C_7). δ_F (376 MHz, $CDCl_3$) -131.3. HRMS: (ESI^+) Found: $[M]^+$ 193.1262, $C_{12}H_{16}NF$ requires 193.1267.

_N_-(2-fluorophenyl)azepane



General procedure 2 was applied using diisobutyl adipate and 2-fluoroaniline. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of silica (60 F254 nm)) (1% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.58-1.68 (4H, m, $H_{3,3'}$), 1.78-1.87 (4H, m, $H_{2,2'}$), 3.36 (4H, td, J = 1.5 Hz, 5.8 Hz, $H_{1,1'}$), 6.70 (1H, ttd, J = 1.6, 4.3, 7.5 Hz, H_7), 6.85 (1H, ddd, J = 1.6, 8.4, 9.6 Hz, H_5), 6.92-7.03 (2H, m, $H_{6,8}$); δ_C (101 MHz, $CDCl_3$) 27.5 ($C_{3,3'}$), 29.3 ($C_{2,2'}$), 52.2 (d, J = 4.3 Hz, $C_{1,1'}$), 116.5 (d, J = 22.0 Hz, C_8), 117.2 (d, J = 4.3 Hz, C_5), 118.4 (d, J = 7.6 Hz, C_7), 124.4 (d, J = 3.3 Hz, C_6), 140.3 (d, J = 8.0 Hz, C_4), 153.7 (d, J = 242.4 Hz, C_9). δ_F (377 MHz, $CDCl_3$) -123.4. HRMS: (NSI^+) Found: $[M+H]^+$ 194.1338, $C_{12}H_{17}NF$ requires 194.1340.

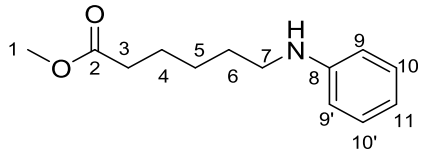
_N_-(2,6-dimethylphenyl)azepane



General procedure 2 was applied using diisobutyl adipate and 2,6-dimethylaniline. A sample for analysis was purified by preparative TLC (pre-coated polyester sheets of

silica (60 F254 nm)) (1% ethyl acetate/ petroleum ether). δ_H (400 MHz, $CDCl_3$) 1.75 (8H, app s, $H_{2,2',3,3'}$), 2.35 (6H, s, $H_{8,8'}$), 3.12 (4H, t, J = 6.0 Hz, $H_{1,1'}$), 6.98 (1H, app dd, J = 6.3 Hz, 8.4 Hz, H_7), 7.05 (2H, d, J = 7.2 Hz, $H_{6,6'}$); δ_C (101 MHz, $CDCl_3$) 19.3 ($C_{8,8'}$), 28.3, 31.6 ($C_{2,2',3,3'}$), 53.3 ($C_{1,1'}$), 124.9 (C_7), 128.8 ($C_{6,6'}$), 137.5 ($C_{5,5'}$), 151.5 (C_4). HRMS: (NSI^+) Found: $[M+H]^+$ 204.1747, $C_{14}H_{22}N$ requires 204.1746.

Methyl 6-(phenylamino)hexanoate



Reaction conditions modified from the literature.[49] Aniline (5.5 mL, 60 mmol, 1 equiv.), methyl 6-bromohexanoate (12.54 g, 60 mmol, 1 equiv.) and sodium acetate trihydrate (24.48 g, 180 mmol) in ethanol (30 mL) were heated under reflux for 16 h. The reaction mixture was cooled and ethanol removed under reduced pressure. The crude material was redissolved in DCM, washed with water and purified by flash column chromatography (20% ethyl acetate/ petroleum ether) to a mixture of monomer and dimer. The desired monomer was further purified by vacuum distillation (0.13 mmbar, 100 °C). The product was obtained as white crystals (5 g, 38%). δ_H (400 MHz, $CDCl_3$) 1.41-1.48 (2H, m, H_5), 1.61-1.72 (4H, m, $H_{4,6}$), 2.34 (2H, t, J = 7.6 Hz, H_3), 3.12 (2H, t, J= 7.2 Hz, H_7), 3.61 (1H, br s, NH), 3.68 (3H, s, H_1), 6.60 (2H, d, J = 8.4 Hz, $H_{9,9'}$), 6.69 (1H, t, J = 7.6 Hz, H_{11}), 7.17 (2H, t, J = 8.0 Hz, $H_{10,10'}$); δ_C (101 MHz, $CDCl_3$) 24.8 (C_4), 26.8 (C_5), 29.3 (C_6), 34.1(C_3), 43.8 (C_7), 51.7 (C_1), 112.8 ($C_{9,9'}$), 117.3 (C_{11}), 129.4 ($C_{10,10'}$), 148.5 (C_8), 174.2 (C_2). HRMS: (NSI^+) Found: $[M+H]^+$ 222.1487, $C_{13}H_{20}NO_2$ requires 222.1489. Micro Anal. Found: C, 70.66; H, 8.62; N, 6.41. Calc'd for $C_{12}H_{17}N$: C, 70.56; H, 8.65; N, 6.33. mp: 39-41 °C.

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Chapter 4 Synthesis of pharmaceutical drugs from waste cashew nut shell liquid

4.1 Cashew nut shell liquid

The cashew tree is a equatorial evergreen tree, largely grown in Brazil, Tanzania, Nigeria India, Mozambique, Sri Lanka, Vietnam *etc*.[1] There are two components of the fruits from the cashew trees: cashew apples and cashew nuts. The cashew apple can be eaten directly as a fruit, or it can be fermented into vinegars or alcoholic drinks. The cashew nuts are covered in honey comb structured shells, and are consumed worldwide. The cashew nut shell contains cashew nut shell liquid (CNSL) which is a byproduct from cashew nut production. The illustration of the cashew plants is shown in Figure 4.1.

Figure 4.1. Illustration of the origin of cashew nut shell liquid.[2]

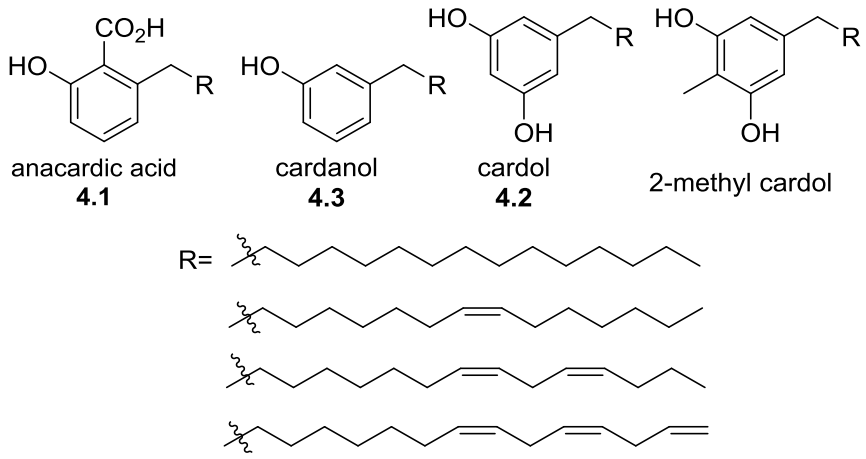
Cashew nut shells are toxic, which is the reason that the shells are removed before selling to customers. Cashew nut shell liquid (CNSL) is a natural resin and a byproduct of cashew nut manufacture. Around 30-35% CNSL is present in the shell,[3] and about 4439960 tonnes of CNSL is produced annually worldwide.[2] Presently, in the cashew nut

industry, cashew nut shells are disposed of as furnace materials, and are burnt in a semi-open pit for thermal energy generation for roasting the nuts. They are also burnt for cooking applications, which is a quick and cheap way for disposal. However, these applications have very low combustion efficiency.[4]

Cashew nut shell liquid (CNSL), obtained from cashew nut shells has versatile applications. CNSL can be used to produce fuel to run CI (diesel) engines.[5] CNSL or its derivatives (eg. cashew nut shell liquid prepolymer) can be used as chemical intermediates, additives,[6,7] stabilizers,[8] lubricants,[9] diesel engine fuel alternatives,[10] anti-oxidants,[11] anticorrosive paints, sodium cardanol sulfate detergent,[12] coating, brake linings[13] and resins.[14]

Cashew nut shell liquid can be obtained from cashew nut shells in three different ways: Cold press, solvent extraction and roasting. The chemical composition of CNSL differs depending upon the way it is processed. Cold-pressed or solvent extracted CNSL consist mainly of anacardic acid, **4.1**, together with small amounts of cardol, **4.2**, and cardanol, **4.3** and 2-methyl cardol. However, roasting of CNSL can result in decarboxylation of the anacardic acid, which gives a high percentage of cardanol, **4.3** (the percentages of each component by different methods are shown in Table 4.1).[15] A detailed method to obtain CNSL was described by Rao and coworkers in 2001.[16] The structures of the different components of CNSL all contain a 15-carbon side chain located *meta* to the phenolic group, and involve different degrees of unsaturation.[15]

Table 4.1. Components of cashew nut shell liquid by different processing methods.[15]



Component	Anacardic acid (%)	Cardanol (%)	Cardol (%)	2-Methylcardol (%)
Solvent extraction or cold press	65	10	15	Trace
roasting	10	85	--	2

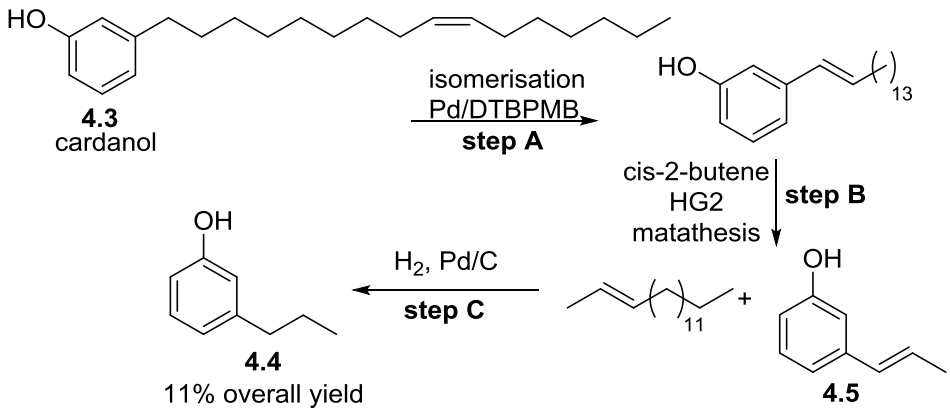
[(a)]R is a C15 chain with 1-3 double bonds, some polymer is formed upon roasting.

Anacardic acid, **4.1**, has been found to be a potent antibacterial, relative to salicylic acid, although the activity of anacardic acid is limited mainly to gram-positive bacteria.[17] Cardanol, **4.3**, can be formed by thermal decomposition of anacardic acid, **4.1**, and can also be separated directly from CNSL by double vacuum distillation, it is toxic with a lethal concentration 50 (LC_{50}) of 0.42 mg/L after 48 hours exposures.[18] Cardanol, **4.3**, contains a structure similar to linear alkyl benzenes (LABs), which can be used as good surfactants for both industrial and household settings after sulfonation. Therefore, cardanol is a sustainable alternative to the petroleum-based LAB surfactants, and so could potentially reduce the use of fossil fuels. Cardanol, **4.3**, in its pure form is also known as a good replacement of cholesterol, which is a popular liposome stabilizer.[19]

Although there are a large number of applications of cashew nut shell liquid (CNSL) and its components: anacardic acid and cardanol, there are very few examples of the transformation of cashew nut shell liquid and its components into small value-added molecules. The examples predominantly focused on the metathesis of the double bonds in anacardic acid and cardanols. Metathesis of anacardic acid and cardanol was reported by using either homogeneous or heterogeneous catalysis (the latter with Ru catalysts supported on mesoporous molecular sieve SBA-15).[20] Metathesis reactions of anacardic acid and cardanol for the synthesis of fine chemicals and new hybrid functional materials have been reviewed.[21] Cardanol porphyrins, cardanol phthalocyanines and cardanol fullerenes can all be produced by metathesis of cardanol derivatives.[21] These interesting studies enabled the synthesis of challenging molecules. However, it would be more interesting to synthesis products with practical use.

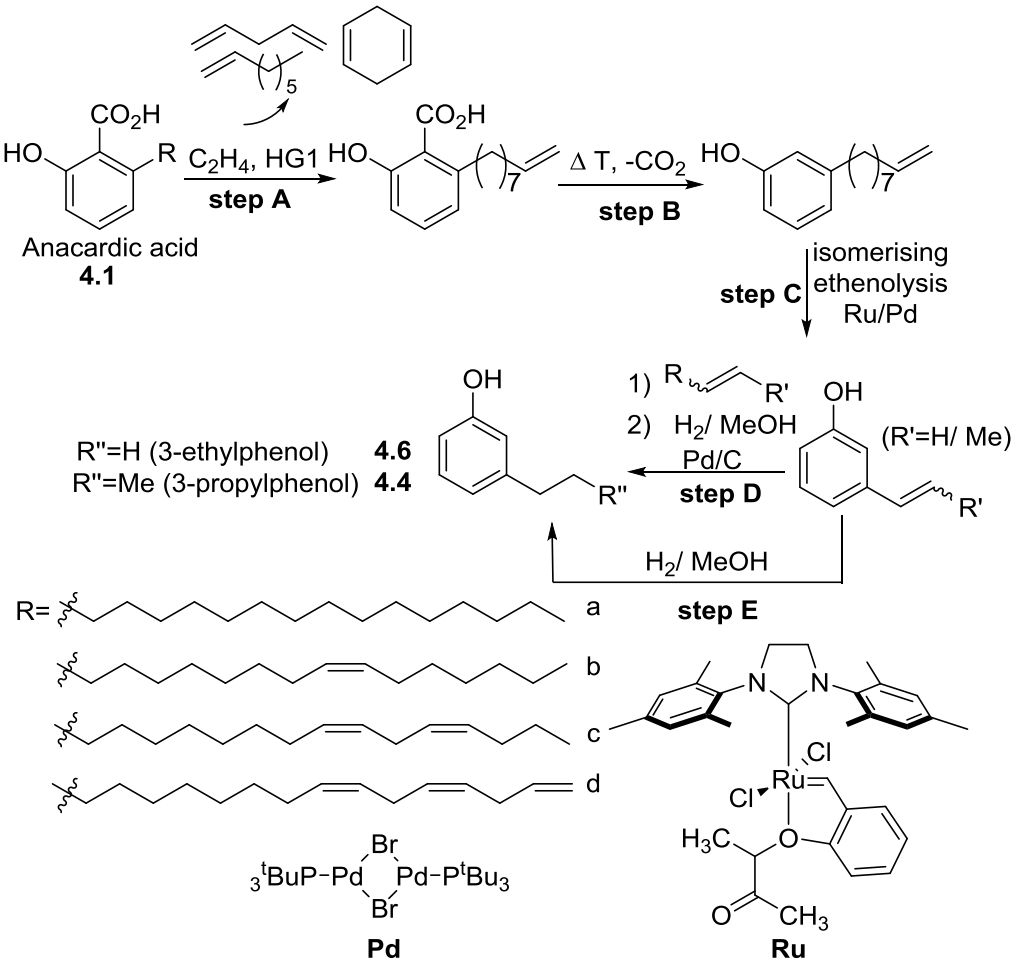
One practical example involves the synthesis of 3-propylphenol, **4.4**, which is a tsetse fly attractant and was synthesised from cardanol in a three-step synthesis (Scheme 4.1): isomerising of the double bond to the benzylic position in cardanol (Scheme 4.1, Step A), followed by cross-metathesis to the *trans*-3-(prop-2-enyl) phenol, **4.5** (Scheme 4.1,

Step B), and finally a hydrogenation (Scheme 4.1, Step C) afforded compound **4.4**. However, the yield was only 11% which was not satisfactory (Scheme 4.1).[15]



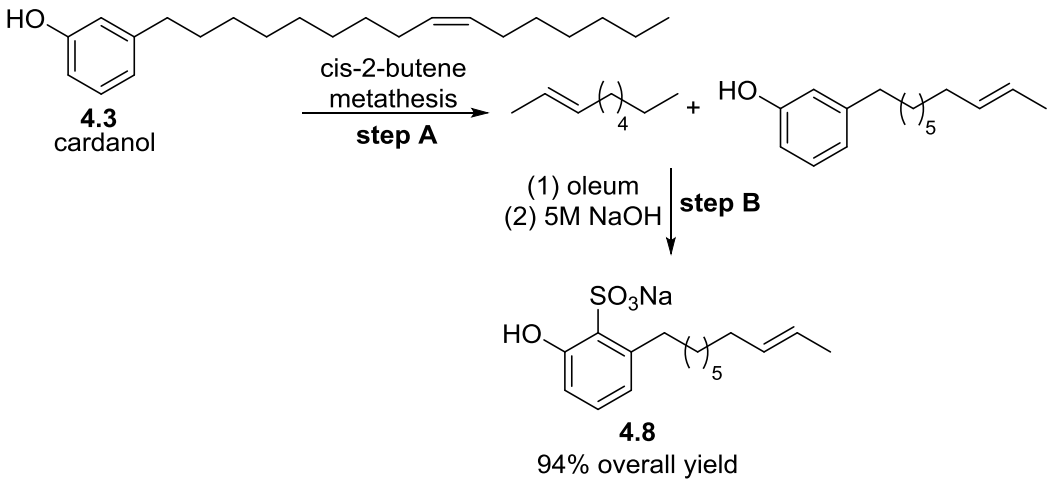
Scheme 4.1. Synthesis of tsetse fly attractants.[15]

Later on, the synthesis of tsetse fly attractants, 3-propylphenol, **4.4**, and 3-ethylphenol, **4.6**, were both performed in good yields with an alternative reaction pathway (Scheme 4.2).[22] Ethenolysis of the anacardic acids (Scheme 4.2, Step A) followed by decarboxylation (Scheme 4.2, Step B) shortened the mono-, di- and tri-unsaturated side chains, and gave 3-(non-8-enyl)phenol, **4.7**, as the intermediate. Isomerising ethenolysis (Scheme 4.2, Step C), followed by ethenolysis/butenolysis then hydrogenation (Scheme 4.2, Step D) furnishes the desired 3-ethylphenol, **4.6**, and 3-propylphenol, **4.4**, either in pure form (84% and 78%) or as a mixture (Scheme 4.2, Step E). The details of the reaction steps are illustrated in Scheme 4.2.[22] This is an interesting application because it takes a low value bio-oil grown in equatorial regions and converts it into 1-octene, a highly desirable comonomer used in polyethylene formation, and kairomone, which is required to attract tsetse flies, which cause African sleeping sickness, also in equatorial regions.



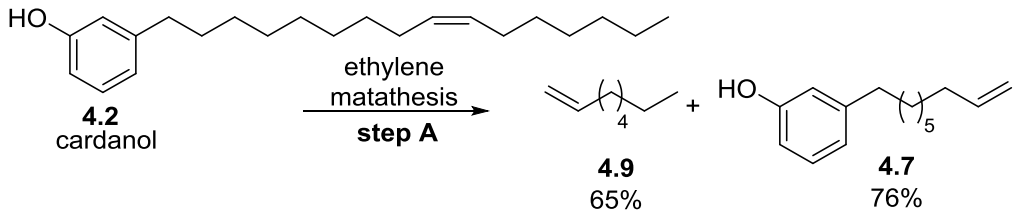
Scheme 4.2. Synthesis of tsetse fly attractants.[22]

Another value-added product, sodium (*E*)-2-(dec-8-en-1-yl)-6-hydroxybenzenesulfonate, **4.8**, a new detergent, can also be obtained from CNSL. Sodium (*E*)-2-(dec-8-en-1-yl)-6-hydroxybenzenesulfonate can be formed in a three step reaction process as shown in Scheme 4.3. The initial step, metathesis of cardanol with *cis*-2-butene (Scheme 4.3, Step A), is followed by sulfonation with oleum and neutralisation with sodium hydroxide solution (Scheme 4.3, Step B). An overall yield of 94% was obtained.



Scheme 4.3. Synthesis of sodium (E)-2-(dec-8-en-1-yl)-6-hydroxybenzenesulfonate.[15]

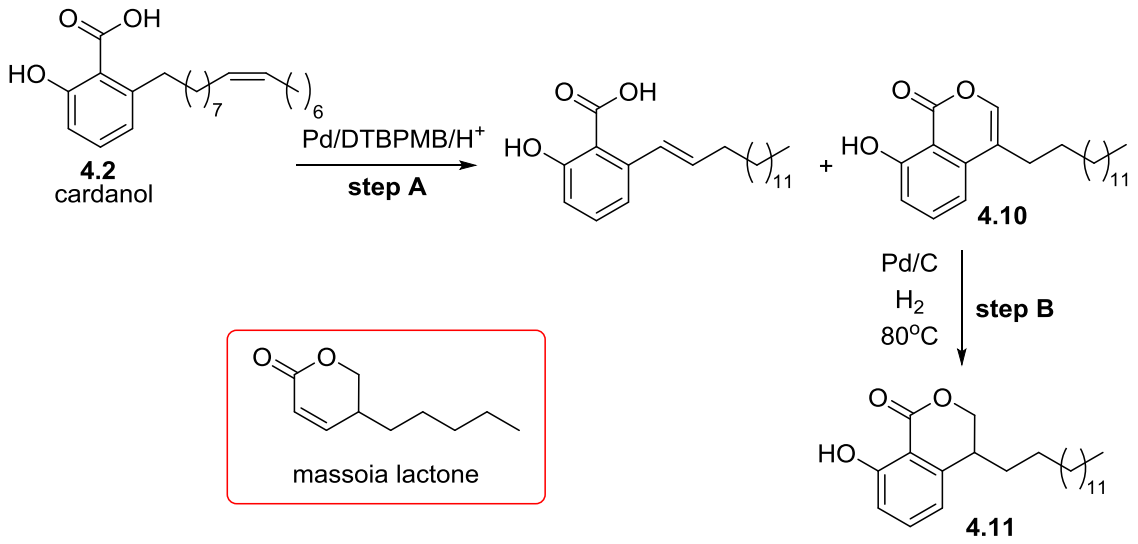
The synthesis of 1-octene, **4.9**, and 3-(non-8-enyl)phenol, **4.7**, required only one step from cardanol, **4.3**. Cross-metathesis of cardanol, **4.3**, with ethylene followed by distillation gave 1-octene, **4.9**, in 65% yield, together with 76% yield of **4.7**, which is obtained as a residue from the distillation of **4.9** (Scheme 4.4).[15]



Scheme 4.4. Synthesis of 1-octene and 3-(non-8-enyl)phenol.[15]

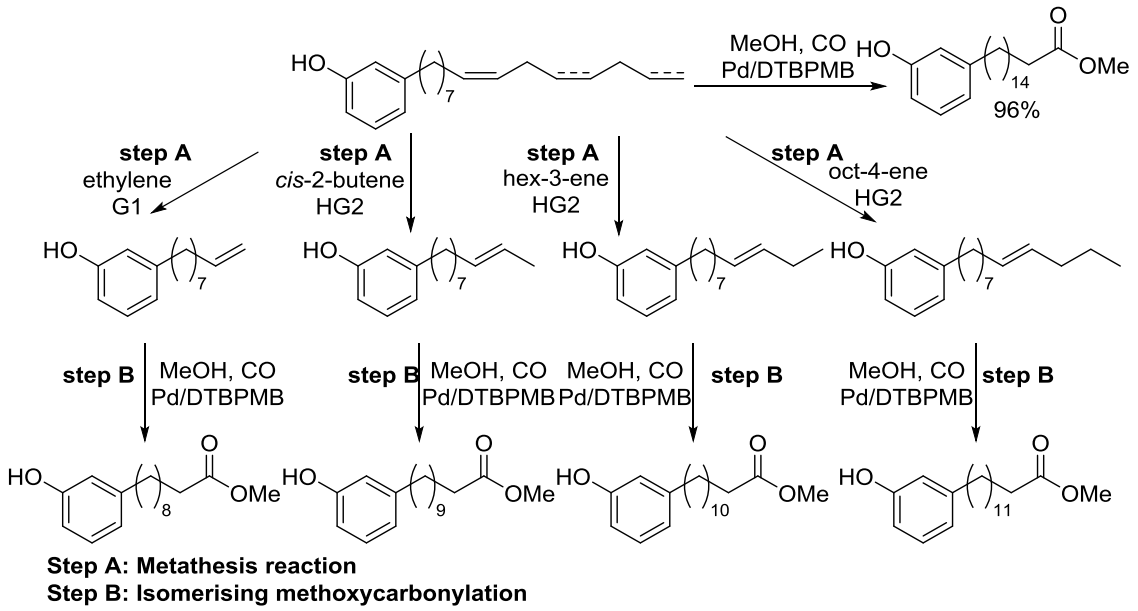
The produced 3-(non-8-enyl)phenol, **4.7**, can be used as a replacement of 4-nonylphenol, which was a detergent but has been banned because of its endocrine disrupting properties. It was found that 3-(non-8-enyl)phenol, **4.7**, causes a significant loss of oestrogenicity. However, more robust investigations are still required to have better understanding of the biological/toxicological hazards.[23]

Unsaturated benzolactone, **4.10**, can also be synthesised from isomerisation of anacardic acid using Pd/DTBPMB with H^+ in 15% yield (Scheme 4.5, Step A).[24] Reduction of the unsaturated benzolactone with Pd/C and hydrogen gas affords the saturated 8-hydroxy-3,4-dihydroisochromen-1-one, **4.11**, in 97% yield (Scheme 4.5, Step B,). The saturated 8-hydroxy-3,4-dihydroisochromen-1-one has a similar structure as massoia lactone, which has been used as a constituent of native medicines.[25]



Scheme 4.5. 8-Hydroxy-3,4-dihydroisochromen-1-one.[24]

Isomerising methoxycarbonylation of cardanol can give methyl 16-(3-hydroxyphenyl)hexadecanoate in 96% yield (calculated based on mono-ene cardanol). Metathesis (Scheme 4.6, Step A) followed by isomerising methoxycarbonylation (Scheme 4.6, Step B) of CNSL can give a series of polymer precursors: hydroxy phenyl esters with one end-group being phenol and the other end-group an ester (Scheme 4.6).[26] The polymers formed from those ester phenols could potentially have fire retardant properties because of the in-chain aromatic rings.



Scheme 4.6. Literature synthesis of ester phenols with different chain length.[26]

To the best of our knowledge, there has been no reported literature about converting CNSL, anacardic acid or cardanol into pharmaceutical drugs. Pharmaceutical drugs are mainly synthesised from fossil fuels by stoichiometric reactions, and in some cases toxic reagents such as cyanide and phosphorus tribromide are involved, which renders the synthesis environmentally unfriendly. Our target is to synthesise pharmaceutical drugs from renewable feedstocks which do not compete with food. Waste biomass, in this case cashew nut shell liquid, is therefore a very good starting material. The aromatic and olefin functional groups made them suitable for this purpose. After searching through the drug bank database, five drugs (fenoprofen, norfenefrine, phenylephrine, etilefrine and metaraminol) were found to be of potential interest, the importance and the current synthesis of these drugs will be discussed in detail later. Their general structures, containing a *meta*-hydroxyl group, are similar to the ones in cardanol or anacardic acid from CNSL (highlighted in red, Figure 4.2). Only a few steps of modification are needed to convert waste materials into the expensive and important medicines, which will be discussed in detail later.

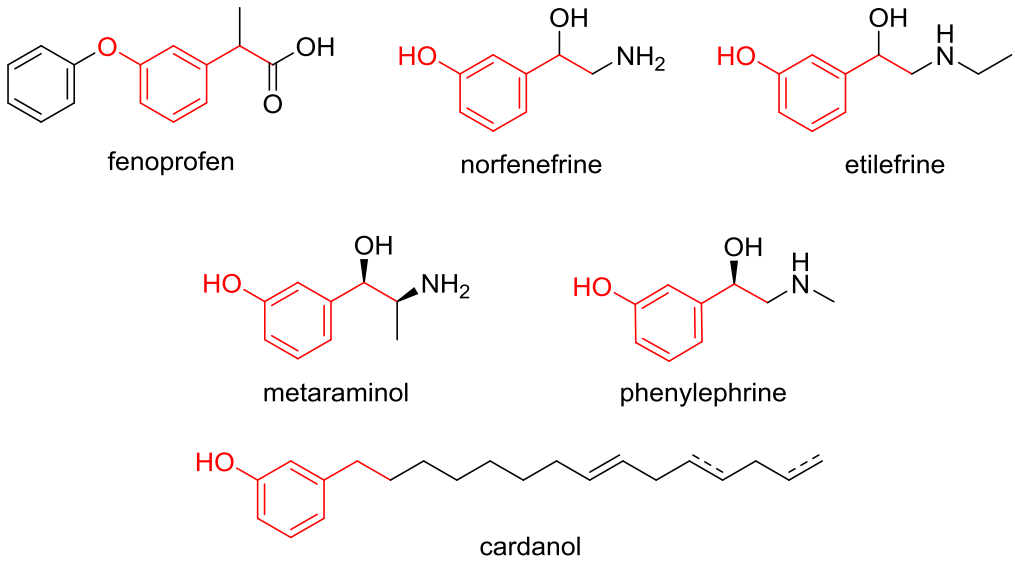


Figure 4.2. Structures of target pharmaceutical drugs.

4.2 Results and discussion

4.2.1 Extraction of cashew nut shell liquid from cashew nut shell

Cashew Nut Shell Liquid

Cashew nut shells were kindly provided by James Mgaya from Tanzania, and the cashew nut shell liquid was extracted from the shells using a procedure adopted from literature.[24,27] Clean and dry shells were soaked in petroleum ether for four days (Figure 4.3, Step A). The shells were then separated from the solution by decantation followed by filtration to remove other solid particles. The resulting solution was concentrated under reduced pressure using a rotary evaporator to obtain cashew nut shell liquid. CNSL was obtained as a brown oil (Figure 4.3, Step B) (10% based on gross amount of shell). In order to increase the yield, the same procedure was repeated to extract any remaining CNSL from the shells, and the cashew nut shell was further soaked in petrol ether for another 4 days, filtered, concentrated under reduced pressure to a brown oil (total yield 14% based on gross amount of shell).

Anacardic acid

CNSL contains a mixture of products including anacardic acid, cardanol, cardol and 2-methyl cardol (Table 4.1). The isolation of anacardic acid from CNSL was performed following a literature procedure reported by Santos.[27] The CNSL was dissolved in 5% aqueous methanol, and calcium hydroxide was added into the solution in portions. The solution turned to a pinkish colour, and was heated to 50 °C until the full consumption of anacardic acid was reached (3 hours) (Figure 4.3, Step C). The calcium anacardate precipitated, was filtered and washed thoroughly with 5% methanol (Figure 4.3, Step D). The crushed cake was then transferred into a flask containing 6 M HCl and ethyl acetate, and stirred for 1 hour. The two layers were separated (Figure 4.3, Step E), the organic layer was washed with distilled water, and dried over magnesium sulphate. Filtration and concentration under reduced pressure afforded the anacardic acid as a brown oil (55% yield) (Figure 4.3, Step F). Decarboxylation of anacardic acid at 200 °C (Figure 4.3, Step G) afforded the cardanol as brownish oil in a high yield (98%).

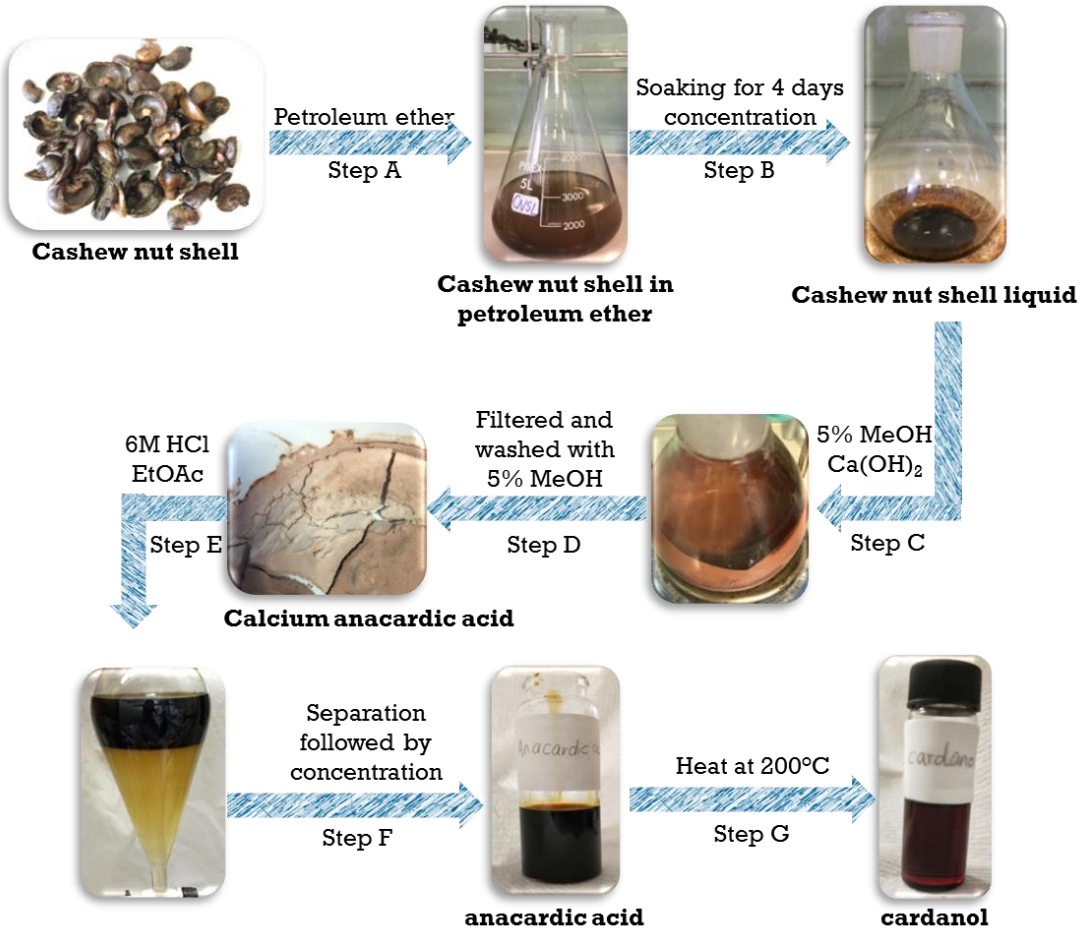
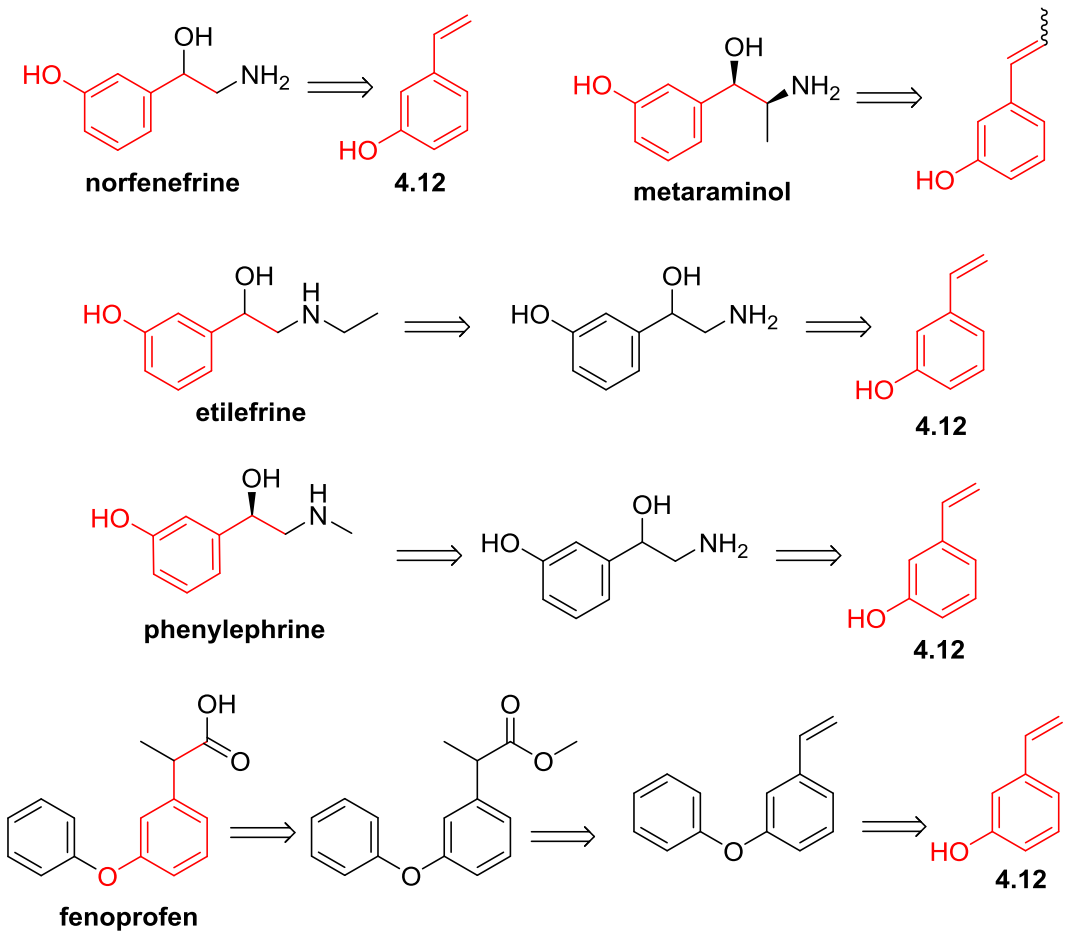


Figure 4.3. Extraction of cashew nut shell liquid and isolation of anacardic acid.

4.2.2 Synthesis of value-added materials

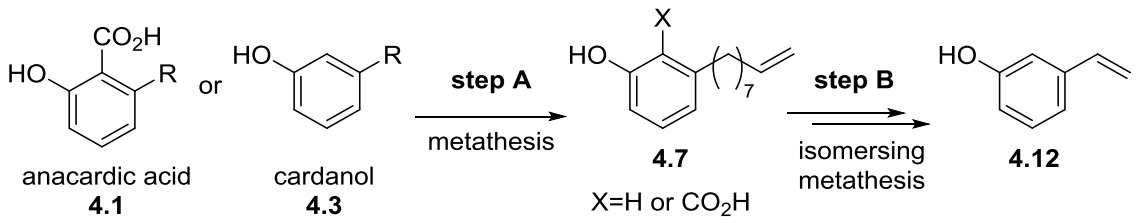
The initial retrosyntheses of the target drugs are summarised in Scheme 4.7, from which it can be concluded that 3-vinylphenol, **4.12**, is the key intermediate for the synthesis of the relevant drugs. Therefore, the initial study was focused on converting CNSL and derivates (e.g. anacardic acid and cardanol) into 3-vinylphenol, **4.12**.



Scheme 4.7. Retrosynthesis of target drugs.

4.2.2.1 Synthesis of 3-Vinylphenol

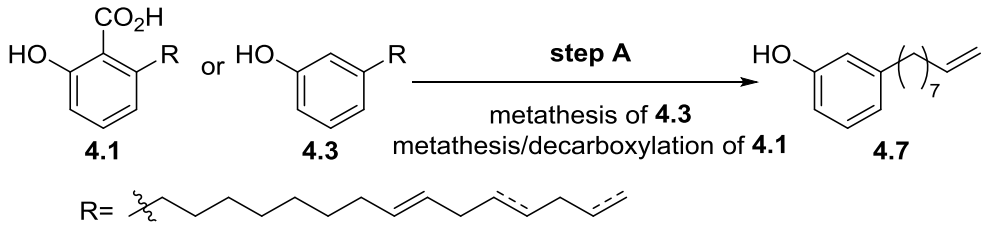
3-Vinylphenol, **4.12**, could be obtained by isomersing ethenolysis of anacardic acid or cardanol. However it has been reported that isomersation of cardanol could only afford the benzylic cardanol in 40% yield,[15] which would result in a poor overall yield for the synthesis of 3-vinylphenol. This is probably because that cardanol has a very long side chain. Although the styrene will be the most thermodynamically favoured isomer, the conjugation energy is insufficient to completely overcome the entropic advantage of having the double bond in other positions in the chain. Therefore, the cardanol or anacardic acid was shortened by ethenolysis to produce 3-(non-8-enyl)phenol, **4.7**, which has only one terminal double bond in a shorter side chain (Scheme 4.8, Step A). Isomerising metathesis of **4.7** could afford the desired 3-vinylphenol, **4.12** (Scheme 4.8, Step B).



Scheme 4.8. Synthesis of 3-vinylphenol.

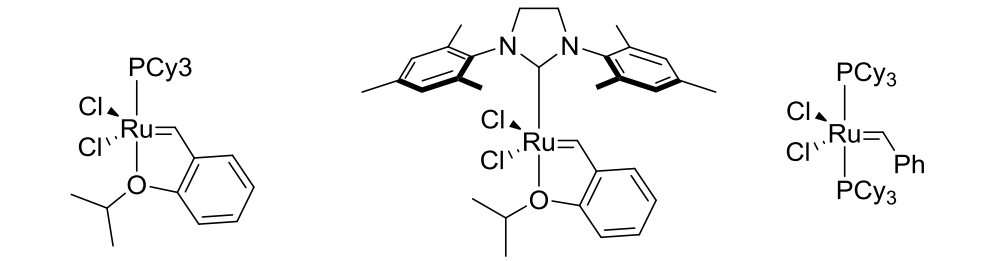
When anacardic acid was used as substrate, very poor conversions were observed using either HG1,**4.13**, or HG2, **4.14**, catalysts (Table 4.2, Entry 1 and 2). But much better results were obtained when cardanol was used as substrate. Excellent yield was observed for the synthesis of 3-(non-8-enyl)phenol (96%, Table 4.2, Entry 3) when cardanol was cross-metathesised with ethylene with HG1 catalyst. The yield was slightly lower with G1 catalyst, **4.15** (85%, Table 4.2, Entry 4), and only 11% yield of 3-(non-8-enyl)phenol, **4.7**, was obtained when metathesised with HG2 catalyst (Table 4.2, Entry 5). Similar results have been obtained previously in the group.[23]

Table 4.2. Metathesis of anacardic acid and cardanol to 3-(non-8-enyl)phenol.



Entry	Substrate	Catalyst	Yield (%)
1	Anacardic acid	HG2	<1
2	Anacardic acid	HG1	1
3	Cardanol	HG1	96
4	Cardanol	G1	85
5	Cardanol	HG2	11

[(a)]Substrate (3 mmol), catalyst (0.3 mol%), anhydrous DCM (7.5 mL), ethene (10 bar), 24 h, r.t.



Hoveyda-Grubbs Catalyst™ 1st Generation (HG1) **4.13**

Hoveyda-Grubbs Catalyst™ 2nd Generation (HG2) **4.14**

Grubb 1st generation (G1) **4.15**

Figure 4.4. Structures of metathesis catalysts.

In the literature,[22] 3-(non-8-enyl)phenol, **4.7**, was usually purified by Kugelrohr distillation (120 °C, 0.1 mbar). However, after connecting to the Kugelrohr, our pump had a pressure of 1.5 mbar, which resulted in a much higher boiling point (200 °C). The GCMS analysis of the crude product, 3-(non-8-enyl)phenol gave a sharp single peak, while, after the distillation, the sharp single peak was replaced by three little peaks with the same molecular weight (m/z = 218.10) (see Figure 4.5). The hypothesis was that the double bond at the terminal position isomerised at high temperature to form a mixture of isomers (92% yields in total). To avoid the isomerisation, in the later cases, 3-(non-8-enyl)phenol was purified by flash column chromatography instead of distillation, which resulted in 96% yield with no migration of the double bond.

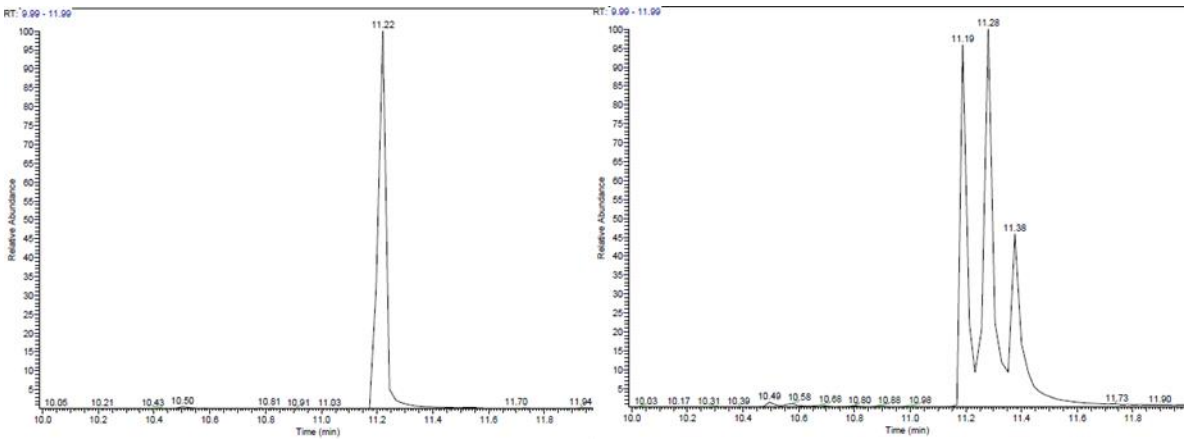


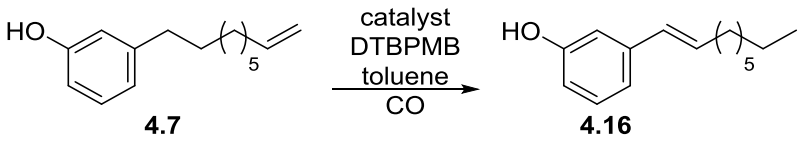
Figure 4.5. GCMS of 3-(non-8-enyl)phenol and its isomers after distillation.

After obtaining 3-(non-8-enyl)phenol, **4.7**, the focus was then moved on to the synthesis of 3-vinylphenol, **4.12**, which required both isomerisation and metathesis steps (Scheme 4.8, Step B).

It has been shown that $[Pd_2(dba)_3]$ /DTBPMB/MSA is a successful candidate for isomerising methoxycarbonylation of methyl oleate.[28] Previous studies in our group also showed that this system is effective in isomerising cardanol, although the yield of benzylic alkene was only 40%. Changing the starting material to 3-(non-8-enyl)phenol in theory could increase the proportion of the benzylic alkene, since the chain length is shorter, and fewer positional isomers are possible. 3-(Non-8-enyl)phenol was isomerised with $[Pd_2(dba)_3]$/DTBPMB/MSA in toluene at 80 °C, after 64 hours, the styrene product, 3-(non-1-en-1-yl)phenol, **4.16**, was obtained in 68% selectivity over all the other isomers (Table 4.3, Entry 1). Heating at 80 °C for 96 hours led to 71% selectivity of **4.16** (Table 4.3, Entry 2).

It has also been reported that $[Rh(acac)(CO)_2]$ together with DTBPMB ligand is effective in isomerising hydroformylation of cardanol,[29] therefore, it is interesting to find out if $[Rh(acac)(CO)_2]$/DTBPMB is effective in the isomerisation reaction in the absence of CO/H_2 gas. However, no styrene was observed after 64 hours, and only 28% of the terminal alkene was converted to other internal alkenes (Table 4.3, Entry 3).

Table 4.3. Optimisation of alkene isomerisation.[a]



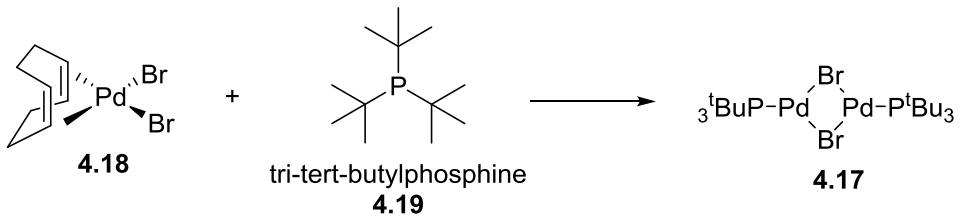
4.7 **4.16**

Entry	Substrate	Cat.	t (h)	Sel. (benzylic alkene/others) (%)
1	3-(non-8-enyl)phenol	$[Pd_2(dba)_3]$	64	68
2	3-(non-8-enyl)phenol	$[Pd_2(dba)_3]$	96	71
3	3-(non-8-enyl)phenol	$[Rh(acac)(CO)_2]$	64	0

[(a)]Substrate (50 mg, 0.2 mmol, 1 equiv.), catalyst (5 mol%) DTBPMB (0.5 equiv.), MSA (0.7 equiv.), toluene (1 mL), 80˚C.

Another isomerising method involving the palladium(I) dimer ([μ-bromo(tri-*tert*-butylphosphine)palladium(I)]$_2$), **4.17**, as also reported previously by our group.[22] [μ-Bromo(tri-*tert*-butylphosphine)palladium(I)]$_2$ is very air and moisture unstable, it is very readily decomposable, therefore the complex should be prepared fresh and not be stored for a long period of time prior to use. The substrate should be azeotropically dried with anhydrous toluene 3 times. The palladium dimer was synthesised following the reported

procedure.[30] Dibromo(1,5-cyclooctadiene)palladium(II) ([$PdBr_2$(cod)], **4.18**) was reacted with tri-*tert*-butylphosphine (P^tBu_3, **4.19**) in a ratio of 1: 9 to obtain the highest yield of [μ-bromo(tri-*tert*-butylphosphine)palladium(I)]$_2$, **4.17**, (Scheme 4.9). The dark green solid was obtained in 84% yield and stored at -20˚C in the glovebox for less than two weeks. The phosphorous NMR of the pure compound is shown in Figure 4.6.



Scheme 4.9. Synthesis of bromo(tri-*tert*-butylphosphine)palladium(I).

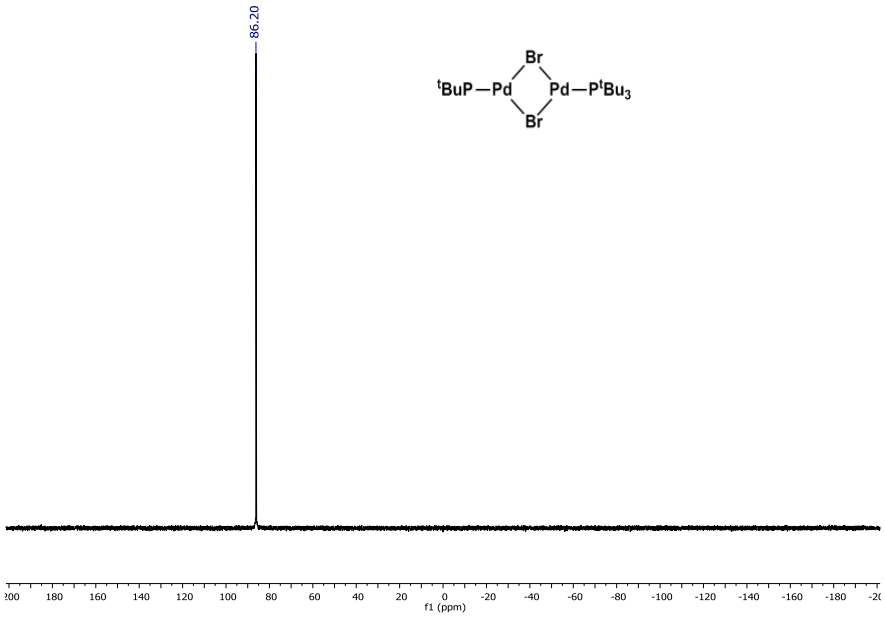
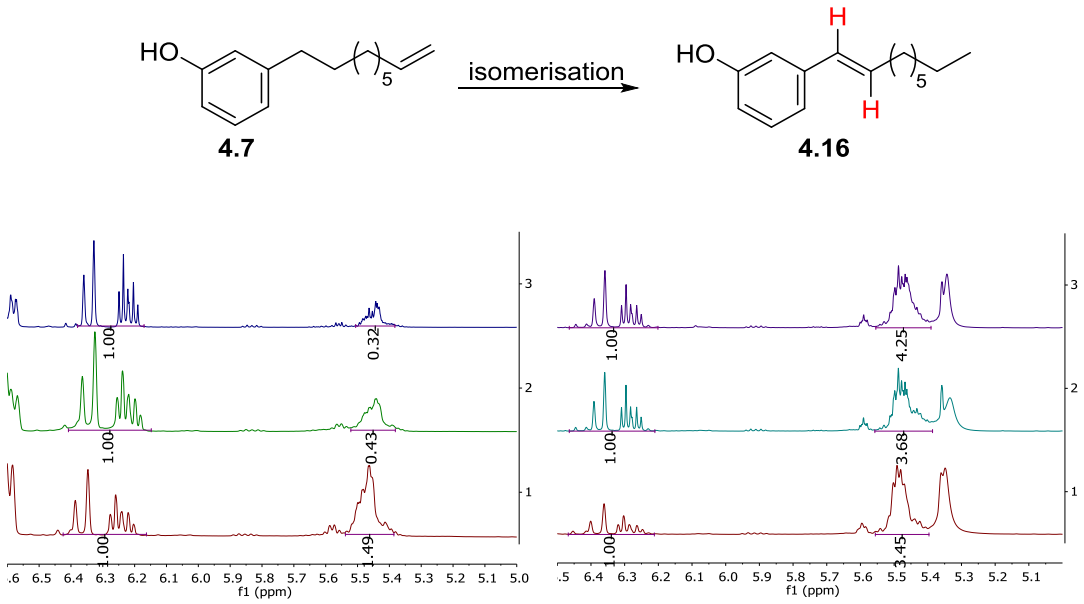


Figure 4.6. ^{31}P NMR of bromo(tri-*tert*-butylphosphine)palladium(I) dimer.

Isomerisation reactions in different solvents were first studied, when the terminal alkene was isomerised using **4.17** in d-DCM at 50 °C, 3-(non-1-en-1-yl)phenol was observed in about 21% yield after 16 hours, whist when the same isomerising reaction was carried out in d-THF, 70% yield of 3-(non-1-en-1-yl)phenol, **4.16**, was obtained after the same reaction time. THF is a preferred solvent in the isomersation reaction. Increasing the reaction time in both cases did not improve the yield of the styrene,

confirming that the equilibrium position had been reached. The reactions were monitored by NMR analysis and the results are shown in Figure 4.7. The peaks at around 6.3 ppm belong to the styrene protons (coloured in red) which were used to calculate the percentage of benzylic alkene over the other alkenes (with the other alkene protons at around 5.4 ppm).



(A) (B)

Figure 4.7. Metathesis with Pd dimer. Spectrum 1 was taken after 2 h; Spectrum 2 was taken after 16 h, and spectrum 3 was taken after 48 h. (A) Reaction carried out in *d*-THF (B) Reaction carried out in *d*-DCM.

The crude product from the isomerisation step was filtered over a plug of silica before being subjected to the metathesis reaction. HG1 catalyst was chosen for the metathesis because of its extraordinary performance on the ethenolysis of cardanol (Table 4.2, Entry 3). However, 3-vinylphenol, **4.12**, was not obtained after the metathesis of the crude reaction mixture containing 3-(non-1-en-1-yl)phenol, **4.16**.

The major difference between the ethenolysis of cardanol, **4.3**, and 3-(non-1-en-1-yl)phenol, **4.16**, was the position of the double bond. A test metathesis reaction was then carried out using *trans*-β-methyl styrene, **4.20**, as a model compound as it has the double bond at the benzylic position which mimics 3-(non-1-en-1-yl)phenol, **4.16**. The optimisations of *trans*-β-methyl styrene metathesis are summarised in Table 4.4. Reactions with HG2, **4.14**, and M1, **4.21,** catalysts gave better results compared to the

reactions with G1, G2, HG1 and M2 (Table 4.4, Entry 1-6). When THF was used as the solvent, slightly lower yield was obtained compared to the reaction performed in DCM (Table 4.4, Entry 5 vs 7). Increasing the reaction temperature did not have a significant impact on the results (Table 4.4, Entry 4 vs 10; Entry 5 vs 15). Different catalyst loadings were tested for both catalyst HG2, **4.14**, and M1, **4.21** (Table 4.4, Entry 8-19), it turned out that 2 mol% catalyst loading of M1, **4.21**, gave the highest yield (Table 4.4, Entry 19).

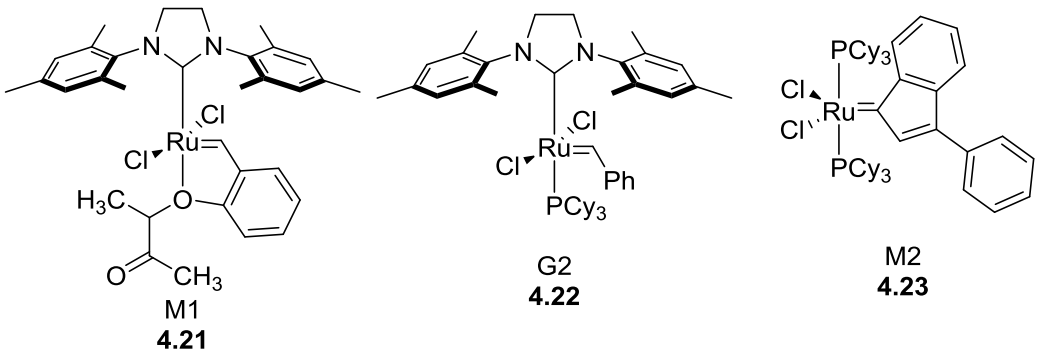
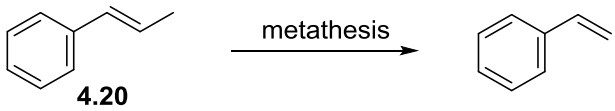


Figure 4.8. Structures of metathesis catalysts.

Table 4.4. Test metathesis reaction on methyl styrene.

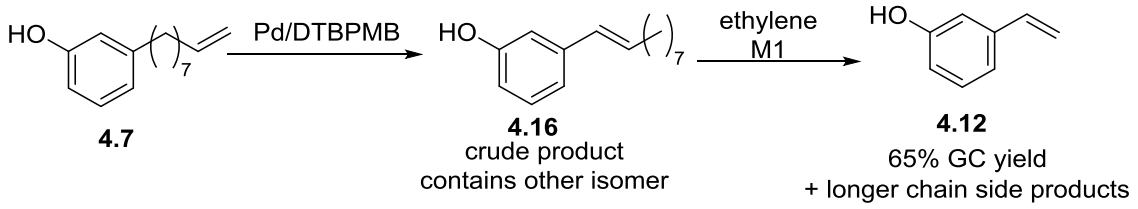


Entry	Catalyst	Catalyst loading (mol%)	solvent	Temperature (˚C)	Yield (%)
1	G1, **4.15**	0.05	DCM	25	3.3
2	G2, **4.22**	0.05	DCM	25	9.8
3	HG1, **4.13**	0.05	DCM	25	3
4	HG2, **4.14**	0.05	DCM	25	18.3
5	M1, **4.21**	0.05	DCM	25	18.2
6	M1, **4.21**	0.05	DCM	25	5.4
7	M1, **4.21**	0.05	THF	25	8.7
8	M1, **4.21**	0.025	DCM	25	8.2

9	M1, **4.21**	0.1	DCM	25	28.5
10	HG2, , **4.14**	0.05	DCM	50	17
11	HG2, **4.14**	0.1	DCM	50	34.7
12	HG2, **4.14**	0.5	DCM	50	84.8
13	HG2, **4.14**	1	DCM	50	95.8
14	HG2, **4.14**	2	DCM	50	98.5
15	M2, **4.23**	0.05	DCM	50	16
16	M1, **4.21**	0.1	DCM	50	32
17	M1, **4.21**	0.5	DCM	50	54.8
18	M1, **4.21**	1	DCM	50	61.6
19	**M1, 4.21**	**2**	**DCM**	**50**	**99.6**

[(a)]Conditions: *trans*-β-Methylstyrene (0.25 mmol), solvent (1 mL), catalyst (0.025-2.0 mol%), ethylene (5 bar), 20 h. GC yield using dodecane as internal standard by calculated response factor.

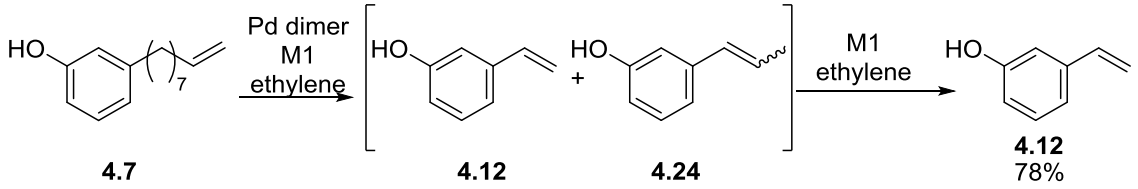
The optimised metathesis conditions were used for the crude product from the isomerisation step (70% of **4.16**, Table 4.3, Entry 2). The crude product was metathesised using M1 catalyst, and 3-vinylphenol was obtained in 65% yield by GC-FID together with alkenyl phenols with longer chain lengths (Scheme 4.10). However, the separation of the desired product and the longer chain side products was very difficult because of their similar polarity.



Scheme 4.10. Synthesis of 3-vinylphenol in two steps.

The one-pot isomerising metathesis would remove the problem of the incomplete isomerising reaction, as the double bond is isomerised and metathesised at the same time continuously, which avoided the formation of multiple isomers. The isomerisation with palladium dimer was complete in 16 hours, and so is the metathesis reaction with M1 catalyst, therefore, a one-pot isomersing metathesis was studied using palladium dimer, **4.17**, and M1 catalyst, **4.21**. Combining both isomerising catalyst and the

metathesis catalyst into the reaction containing 3-(non-8-enyl)phenol, and after heating at 50 °C for 16 hours under 5 bar of ethylene gas, a mixture of 3-vinylphenol, **4.12**, and 3-(prop-1-en-1-yl)phenol, **4.24**, was obtained. After filtering through a plug of silica, and metathesising again with M1 catalyst, the desired 3-vinylphenol was obtained in 78% isolated yield which is consistent with the literature results (Scheme 4.11).[22]

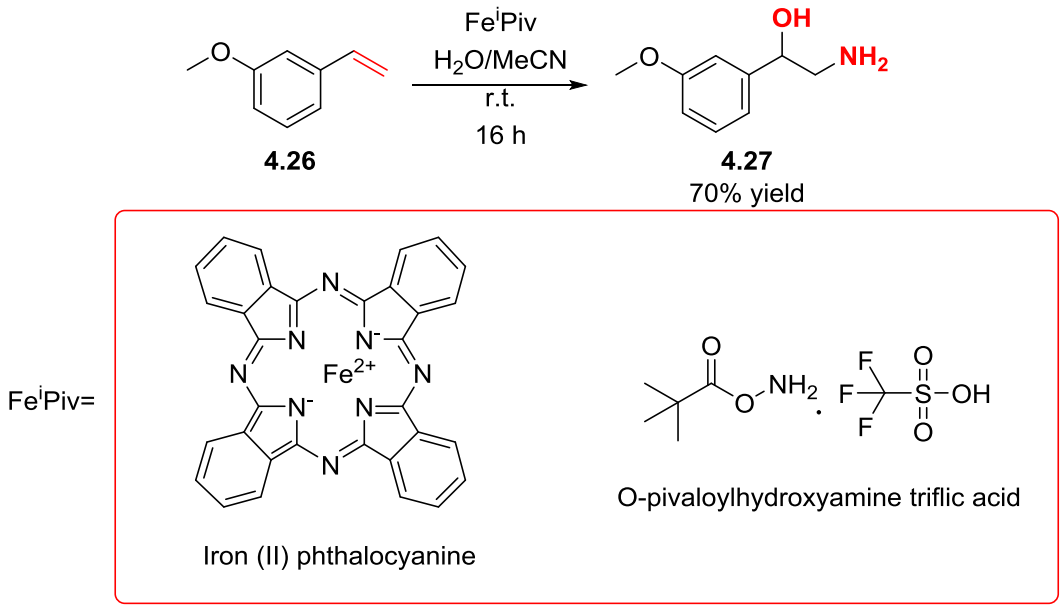


Scheme 4.11. Synthesis of 3-vinylphenol by palladium dimer and M1 catalyst.

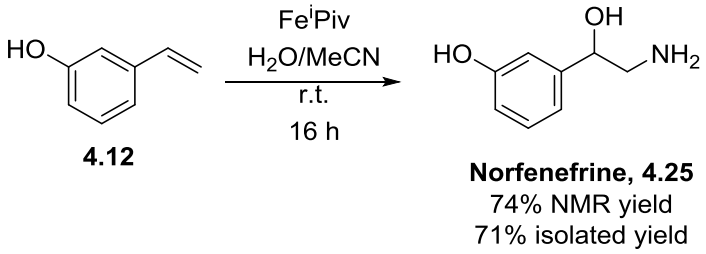
4.2.2.2 Synthesis of Norfenefrine

Norfenefrine, **4.25**, is an adrenergic agent used as a sympathomimetic drug, which is pharmaceutically active in its racemic form. It is marketed in Europe, Japan, and Mexico with brand names including A. S. COR, Energona and Novadral. Norfenefrine, **4.25**, plays a role as a minor neurotransmitter in the brain and regulates blood pressure in acute hypotensive states.[31] It is also used as an adjunct in treatment of cardiac arrest and hypotension.

As presented in Scheme 4.7, 3-vinylphenol, **4.12**, which was successfully obtained from waste CNSL, could possibly be used as an intermediate for the synthesis of norfenefrine, **4.25**, by a hydroxyamination reaction on the double bond. A reaction of this kind which converts 1-methoxy-3-vinylbenzene, **4.26**, to 2-amino-1-(3-methoxyphenyl)ethan-1-ol, **4.27**, was successfully achieved with 70% yield using an iron catalyst (Scheme 4.12).[32] We employed a similar method using 3-vinylphenol, **4.12**, as substrate, and the desired norfenefrine, **4.25**, which is also known as 3-(2-amino-1-hydroxyethyl)phenol, was obtained in 71% isolated yield (Scheme 4.13).



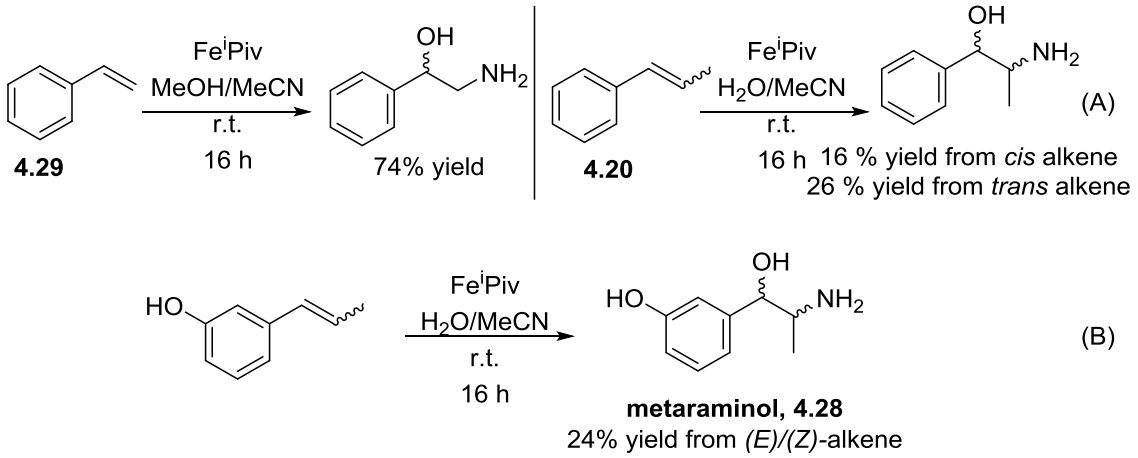
Scheme 4.12. Literature hydroxyamination of 1-methoxy-3-vinylbenzene, **4.26**. [32]



Scheme 4.13. Synthesis of norfenefrine, **4.25**, from 3-vinylphenol, **4.12**.

4.2.2.3 Synthesis of Metaraminol

Metaraminol, **4.28**, which is used in the prevention and treatment of hypotension,[33] has a very similar structure as norfenefrine, **4.25**. It is interesting to investigate if the hydroxyamination reaction used for the synthesis of norfenefrine, **4.25**, would work when using 3-(prop-1-en-1-yl)phenol, **4.24**, as substrate. From the literature, hydroxyamination of styrene, **4.29**, occurs in 74% yield, while using β-methyl styrene, **4.20**, as substrate gave around 20% yield (Scheme 4.14, Reaction A).[32] The extra methyl group on the side chain led to a dramatic decrease of the yield. The same hydroxyamination conditions were carried out on 3-(prop-1-en-1-yl)phenol, **4.24**. The desired racemic metaraminol, **4.28**, was obtained in 24% NMR yield in this case (Scheme 4.14, Reaction B). This is in line with the results from literature.

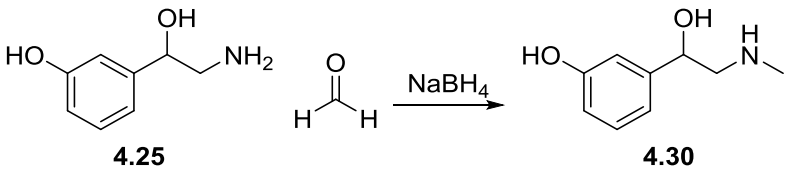


Scheme 4.14. Synthesis of metaraminol, **4.28**, and literature results.

4.2.2.4 Synthesis of *racemic* Phenylephrine

Phenylephrine which has a similar structure as norfenefrine, is a sympathomimetic, vasoconstrictor, mydriatic and cardiotonic agent. It can be used as a decongestant, pupil dilator, vasopressor and in the treatment of hemorrhoids and priapism, to dilate the pupil or to increase the blood pressure. It has a wide range of brand names such as Neophyrn, Neosynephrine, Fenox, Simitab and Adrianol.[31]

Reductive amination is a common method for the selective introduction of alkyl groups on nitrogen over hydroxyl groups with an aldehyde and a hydride. In this case, formaldehyde was used as the methyl source. Commercial formaldehyde is usually sold as a solution in water, however, when reacting norfenefrine with formaldehyde in water in the presence of sodium borohydride, a rather complex mixture was obtained after the reaction, which was difficult to analyse. Another source of formaldehyde was from paraformaldehyde, in this case, the formaldehyde is obtained in the absence of water. Paraformaldehyde was cracked in methanol under reflux to form a solution of formaldehyde in methanol. The reductive amination of norfenefrine was carried out again with the cracked formaldehyde in methanol, and only trace amount of phenylephrine was observed in this case (Scheme 4.15).



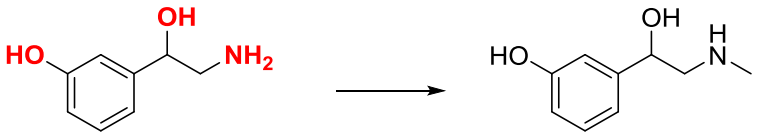
4.25 4.30

Scheme 4.15. Reductive amination of nofenefrine.

Another method to introduce a methyl group onto nitrogen is by direct methylation. Selective methylation of norfenefrine, **4.25**, could result in the formation of racemic phenylephrine, **4.30**. However, there are three active sites for the direct alkylation, both of the hydroxy groups and the amine groups are readily available for the reaction. When reacting norfenefrine, **4.25**, with methyl iodide in the presence of a base, a rather complicated mixture of products was obtained, which might be because of methylation on alcohol, mono- and dimethylated products, and selective methylation was not achieved by this method (Table 4.5, Entry 1 and 2).

It has been reported that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is a good solvent for the selective alkylation of amines, with a high proportion of mono-alkylated products over di-alkylated products.[34] Methylation of norfenefrine with methyl iodide in HFIP in the absence of base gave very poor conversion, and low yield of the desired phenylephrine (Table 4.5, Entry 3). Whilst changing the methylation agent from methyl iodide to methyl triflate, much higher conversation was observed, and the desired phenylephrine, **4.30**, was obtained in 79% yield (Table 4.5, Entry 4).

Table 4.5. Methylation of norfenefrine.[a]



4.25 4.30

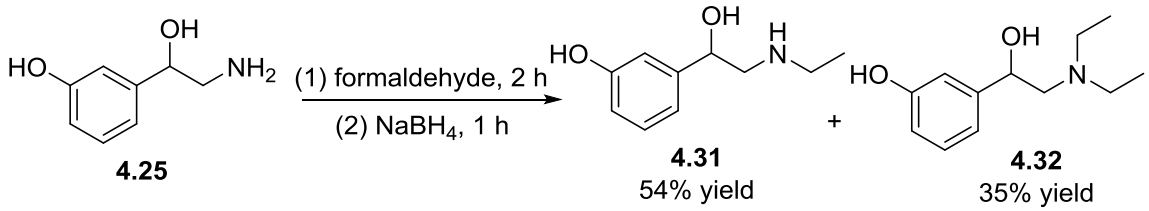
Entry	MX	Solvent	T (°C)	t (h)	Conv. (%)[b]	Yield (%)[b]
1[c]	MeI	Acetone	60	2	100	n.d.
2[c]	MeI	DMSO	100	16	100	n.d
3	MeI	HFIP	25	24	4	2
4	MeOTf	HFIP	25	1	84	79

[a]Conditions: norfenefrine (1 mmol), MeX (1.5 mmol), HFIP (1 mL). [b]Conversions and yields were calculated by ^{1}H NMR spectroscopy. [c]KOH (2 equiv.).

4.2.2.5 Synthesis of Etilefrine

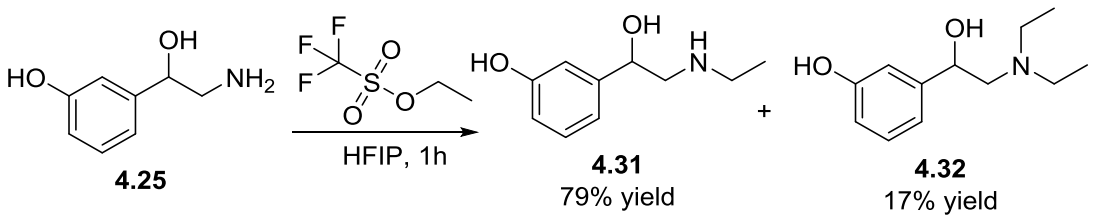
Another drug with a similar structure as norfenefrine, **4.25**, is etilefrine, **4.31**, which is a cardiac stimulant, and is used as an antihypotensive. Etilefrine can increase cardiac output, stroke volume, venous return and blood pressure by intravenous infusion.[35] It is also an analeptic and sympathomimetic agent. It is marketed with brand names such as Circupon. Apocretin, Eftortil, Palsamin, Kertasin, Pressoton, Effoless and Sanlephrin in different countries.[31]

Reductive amination was used for the selective alkylation of nitrogen over the oxygen. When reacting norfenefrine, **4.25**, with acetaldehyde in the presence of sodium borohydride, both the desired etilefrine, **4.31**, and the side diethylated product **4.32** were obtained, and they were easily separated by flash column chromatography. The expected etilefrine, **4.31**, was obtained in 54% yield, and the diethylated product was obtained in 35% yield.



Scheme 4.17. Synthesis of Etilefrine, **4.31**, from norfenefrine, **4.25**.

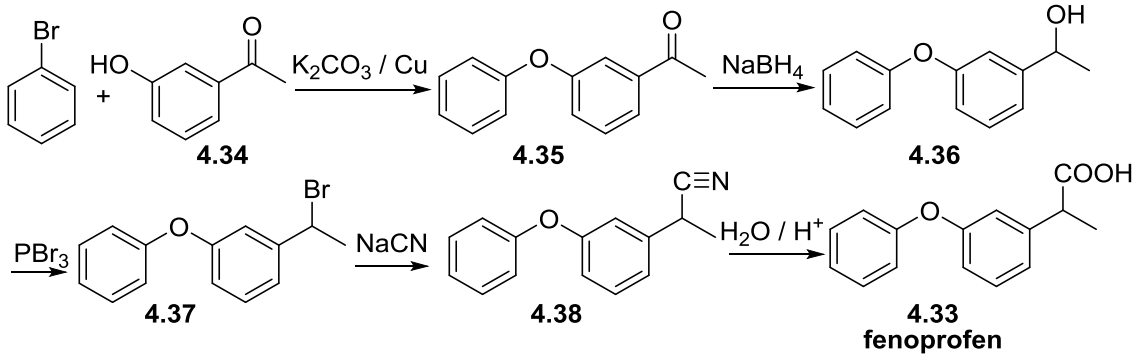
Due to the success of the methylation procedure for the selective mono-methylation of norfenefrine, we employed these conditions in the synthesis of etilefrine using ethyl triflate as an ethyl source. The ethylation of norfenefrine with ethyl triflate in HFIP led to a higher yield of the desired etilefrine (79%) compare to the reductive amination, together with 17% of the diethylated product after 1 hour at room temperature (Scheme 4.18).



Scheme 4.18. Ethylation of norfenefrine with ethyl triflate.

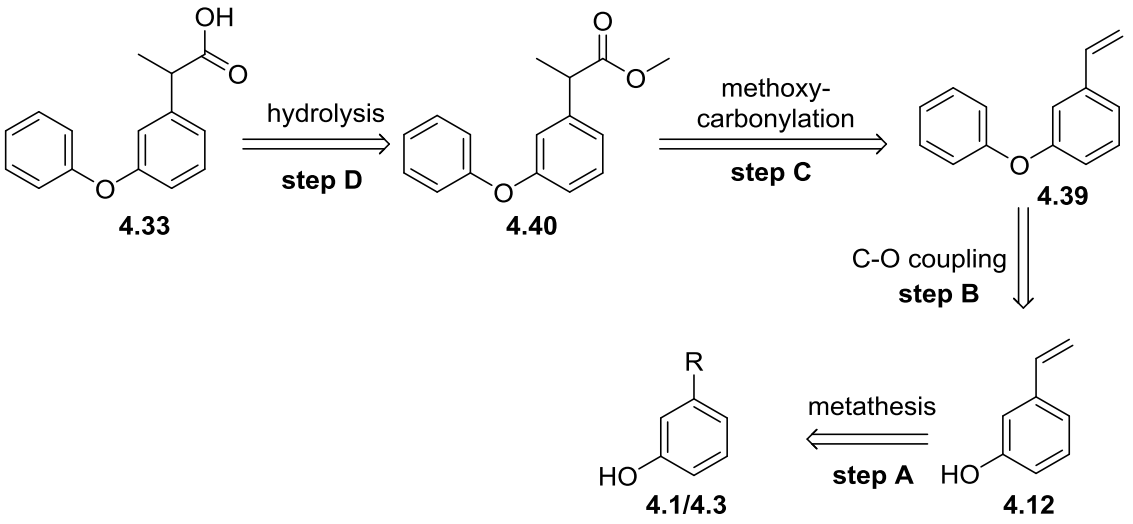
4.2.2.6 Synthesis of Fenoprofen

Another drug, which contains a *meta*-hydroxy phenyl group similar to CNSL, is fenoprofen, **4.33**. Fenoprofen, **4.33**, is a nonsteroidal anti-inflammatory drug (NSAID) and is marketed in the USA as Nalfon. The current cost for its oral capsule (400 mg) is around $256 for a supply of 90 capsules.[36] It is effective for the treatment of fever, pain and swelling caused by inflammation. Fenoprofen calcium is used for symptomatic relief for rheumatoid arthritis, osteoarthritis, and mild to moderate pain. Fenoprofen, **4.33**, is traditionally synthesised in 5 steps from 3-hydroxyacetophenone, **4.34**, which is then C-O coupled by bromobenzene using potassium carbonate and copper catalyst to 3-phenoxyacetophenone, **4.35**. Ketone, **4.35**, is then reduced using sodium borohydride to the corresponding alcohol, **4.36**, which is brominated to 1-(1-bromoethyl)-3-phenoxybenzene, **4.37**, by phosphorous tribromide. The bromide is then converted to nitrile group using sodium cyanide. Finally, 2-(3-phenoxyphenyl)propionitrile, **4.38**, is hydrolyzed to the desired fenoprofen, **4.33** (Scheme 4.19).[37]



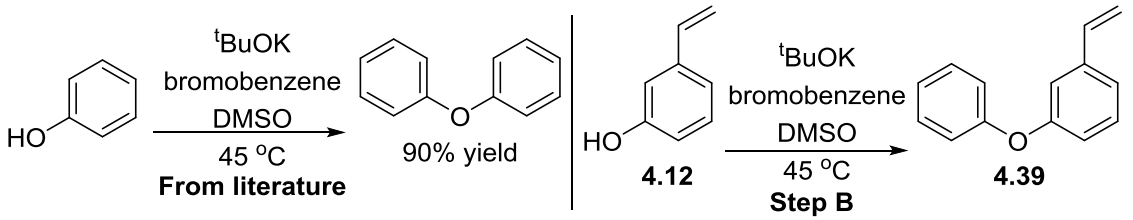
Scheme 4.19. Original synthesis of fenoprofen.[37]

This well-known reaction pathway requires stoichiometric conditions in most of the steps, which is environmentally unfriendly. It also involves sodium cyanide, which is dangerous to deal with. Our method skipped the unpleasant cyanide step and converted waste CNSL into fenoprofen. The initial retrosynthesis is shown in Scheme 4.20 which involves the conversion of the anacardic acid, **4.1**, or cardanol, **4.3**, to 3-vinylphenol, **4.12**, followed by C-O coupling to diphenyl ether, **4.39**, which can then undergo branch selective methoxycarbonylation to the corresponding ester **4.40**, and a final hydrolysis step could afford the desired drug **4.33**.



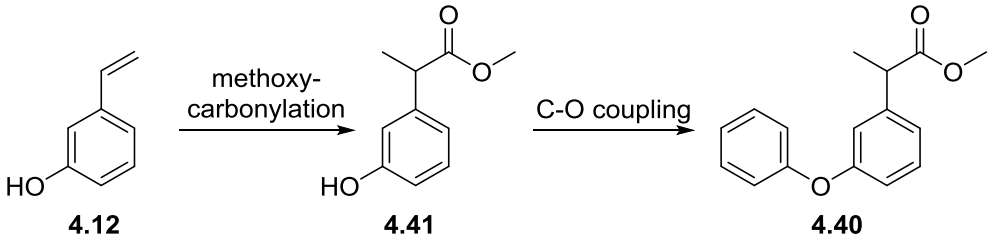
Scheme 4.20. Retrosynthesis of Fenoprofen from cashew nut shell liquid and derivatives.

Step A has been successfully studied and discussed in Session 4.2.2.1, it is then moved on to Step B (C-O coupling). From the literature, it has been found that C-O coupling between phenol and bromobenzene can be achieved in the presence of potassium *tert*-butoxide to the corresponding O-Ph product in a good yield (90%) (Scheme 4.21).[38] However, when the same reaction conditions were applied using 3-vinylphenol, **4.12**, as substrate, the expected product **4.39** was not obtained (Scheme 4.21). The starting material was fully converted to a complicated mixture of products, which was difficult to analyze.



Scheme 4.21. C-O coupling between alcohol and bromobenzene.

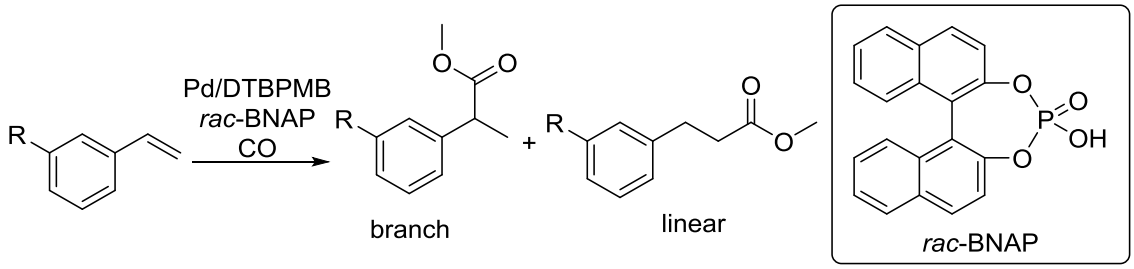
This is probably because of the instability of the styrene, and the second plan was to start with methoxycarbonylation of 3-vinylphenol for the synthesis of methyl 2-(3-hydroxyphenyl)propanoate, **4.41**, to get rid of the double bond, and make the material more stable (Scheme 4.22).



Scheme 4.22. Second plan for the synthesis of fenoprofen.

Therefore, methoxycarbonylation was then studied. The conditions for branched selective methoxycarbonylation were initially optimised using styrene, **4.29**, as a model compound with conditions adopted from literature.[39] The branched product, methyl 2-phenylpropanoate, **4.42**, was obtained in 91% selectivity over the linear methyl 3-phenylpropanoate, **4.43** (Table 4.6, Entry 1). Although in the literature,[39] $[Pd(dba)_2]$ was used as the catalyst, similar results were obtained when using $[Pd_2(dba)_3]$ (Table 4.6, Entry 2). In the absence of racemic BINOL-phosphoric acid (*rac*-BNPA) no conversion of styrene was observed (Table 4.6, Entry 3).

Table 4.6. Methoxycarbonylation of 3-vinylphenol.[a]



Entry	R	Catalyst	Yield[b] (%)	Sel. Branch: linear[b] (%)
1	H	$[Pd(dba)_2]$	93 (92)	90.9 : 9.1
2	H	$[Pd_2(dba)_3]$	92	91.4: 8.6
3[c]	H	$[Pd(dba)_2]$	0	-
4	OH	$[Pd(dba)_2]$	92[d] (89)	89.9 : 10.1

[(a)]Substrate (1 mmol), catalyst (0.5 mol%), DTBPMB (2 mol%), *rac*-BNPA (7.5 mol%), anhydrous MeOH (0.25 mL), anhydrous DCM (0.75 mL), CO (5 bar), rt, 20 h. [(b)] Yield and selectivity was calculated by GC-FID based on calculated response factor, yield was a sum of linear and branch products. Numbers in parentheses are isolated yield. [(c)]no *rac*-BNPA. [(d)]NMR yield using 1,4-dinitrobenzene as internal standard.

After optimising the methoxycarbonylation conditions, the reaction was carried out using 3-vinylphenol, **4.12**, as substrate, and 92% yield was obtained with 90% selectivity to the desired branched product, methyl 2-(3-hydroxyphenyl)propanoate, **4.41**, over the linear one, methyl 3-(3-hydroxyphenyl)propanoate, **4.44**, (Table 4.6, Entry 4). The isolated regioisomeric mixture was then used in the next C-O coupling step (Scheme 4.22) with bromobenzene. However, the expected O-Ph ester **4.40** did not form while a very complicated mixture was obtained instead, and its composition was difficult to analyse by GCMS, GC or NMR. This could possibly be explained by the nature of the starting material, methyl 2-(3-hydroxyphenyl)propanoate, **4.41**, which has more than one active side for the deprotonation (Figure 4.9). The proton adjacent to the carbonyl (coloured in red) could also be deprotonated by potassium *tert*-butoxide in the C-O coupling step, and therefore could lead to the formation of side products.

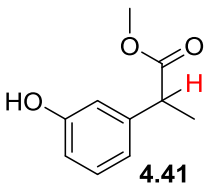
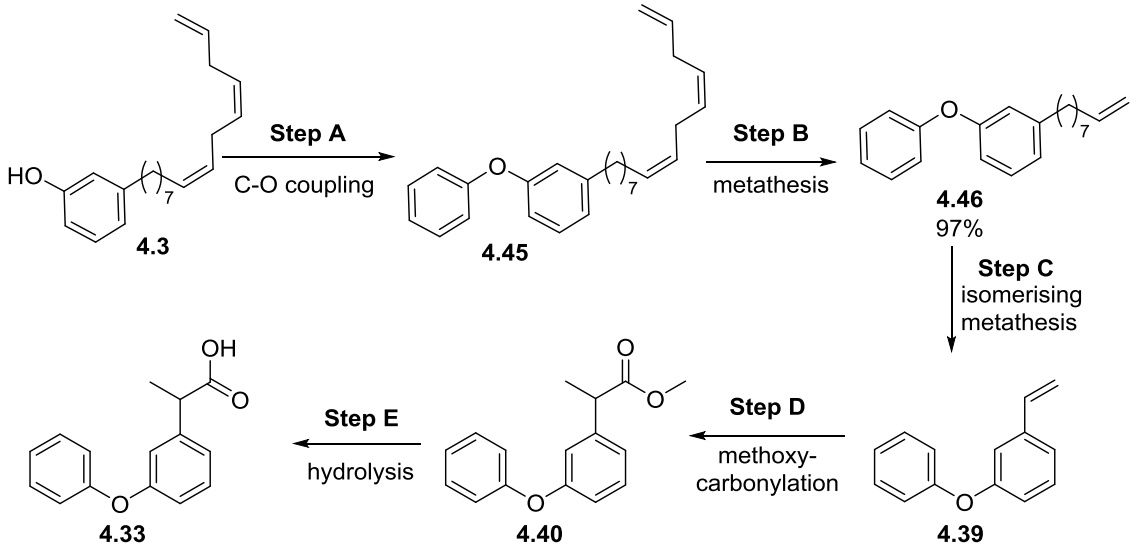


Figure 4.9. Structure of methyl 2-(3-hydroxyphenyl)propanoate.

Another plan was to convert cardanol to the O-Ph cardanol, **4.45**, firstly, which could in theory avoid the complexity of the C-O coupling with unstable intermediates (Scheme 4.23).



Scheme 4.23. A third plan for the synthesis of fenoprofen.

Cardanol, **4.3**, was therefore reacted with bromobenzene first under literature conditions for the C-O coupling of the phenol.[38] Only about 30% of cardanol was converted to the O-Ph product, **4.45,** at 45°C (Figure 4.10). Increasing the temperature increased the conversion, and at 100 °C, the starting material was fully converted. Preparative scale gave similar results, and the O-Ph cardanol, **4.45**, was successfully synthesised in 82% yield.

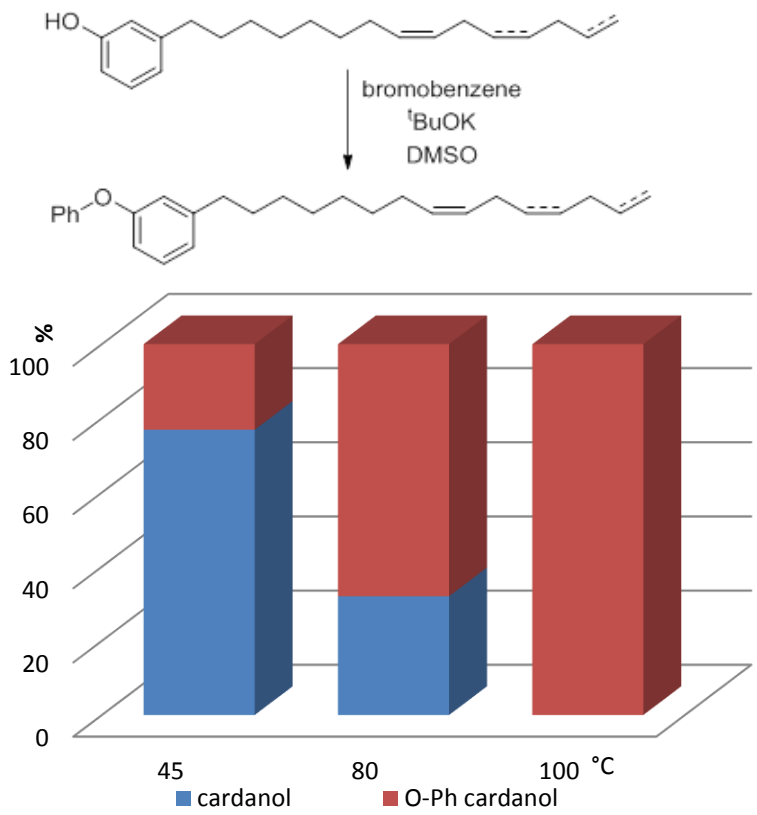
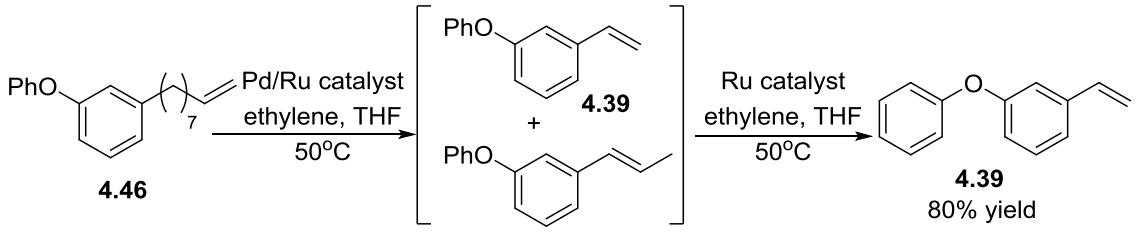


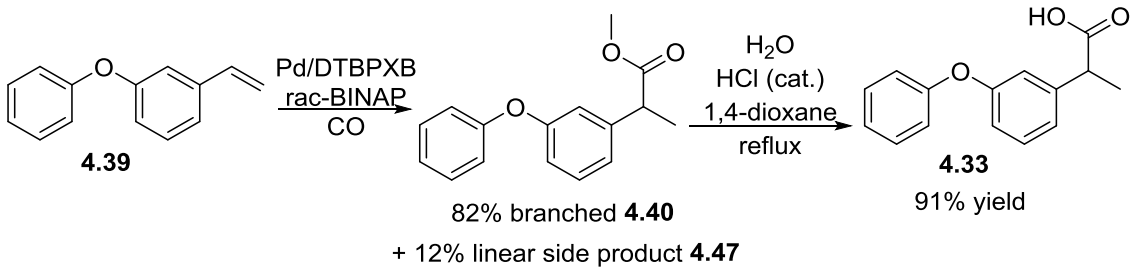
Figure 4.10. The percentage ratio (calculated by uncalibrated GC-FID) between the O-Ph cardanol and cardanol.

After obtaining O-Ph cardanol, **4.45**, 1-phenoxy-3-vinylbenzene, **4.39**, can be synthesised in two steps (Step B and C in Scheme 4.23). Firstly, the O-Ph cardanol, **4.45,** was metathesised to the corresponding 1-(non-8-en-1-yl)-3-phenoxybenzene, **4.46**, using HG1 catalyst in high yield (97%) with octene as the side product. 1-(Non-8-en-1-yl)-3-phenoxybenzene, **4.46**, was then converted to 1-phenoxy-3-vinylbenzene by isomerising metathesis reaction with palladium dimer and M1 catalysis, as discussed in Section 4.2.2.1. A one-pot isomerisation metathesis of 1-(non-8-en-1-yl)-3-phenoxybenzene, **4.46**, first afforded a mixture of 1-phenoxy-3-vinylbenzene, **4.39**, and 1-phenoxy-3-(prop-1-en-1-yl)benzene, and the crude mixture was filtered through a plug of silica, and metathesised again with M1 catalyst. The desired 1-phenoxy-3-vinylbenzene, **4.39**, was as successfully obtained in 80% yield (Scheme 4.24).



Scheme 4.24. Synthesis of 1-phenoxy-3-vinylbenzene by isomersing metathesis.

The next step is the synthesis of the branched ester **4.40** (Step D, Scheme 4.23), branch selective methoxycarbonylation with Pd/DTBPXB system in the presence of *rac*-BNPA afforded the desired product **4.40** in 82% yield (66% isolated yield plus 16% NMR yield in a mixture with linear product), together with 12% of the linear product, methyl 3-(3-phenoxyphenyl)propanoate, **4.47** (Scheme 4.25). Hydrolysis of the ester, **4.40**, afforded fenoprofen, **4.33**, in 91% yield. With this method, waste biomass is successfully converted to fenoprofen drug in good yield (47.5% overall yield from cardanol).



Scheme 4.25. Synthesis of fenoprofen from 1-phenoxy-3-vinylbenzene.

4.3 Conclusions

Waste cashew nut shell liquid has been successfully converted to important and expensive medicinal drugs, such as norfenefrine, phenylephrine, etilefrine and fenoprofen in good yields. Our methods avoided the stoichiometric steps and unpleasant reagents in the original syntheses. In further work, the synthesis of metaraminol requires more optimisation to get higher yields and it would be interesting to attempt chiral syntheses of single enantiomers.

4.4 Experimental

4.4.1 General methods

All the commercially available reagents were used without further purification unless specified otherwise. m-Cresol, *rac*-BNPA, 3-hydroxybenzaldehyde, 3-phenoxybenzaldehyde, methyltriphenylphosphonium bromide and ethyltriphenylphosphonium bromide were purchased from Alfa Aesar; Hoveyda-Grubbs catalyst 1st generation, Hoveyda-Grubbs catalyst 2nd generation, Grubbs catalyst 1st generation, Grubbs catalyst 2nd generation, dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]{[2-(1-methylacetoxy)phenyl]methylene}ruthenium(II), bis(dibenzylideneacetone)palladium(0) ([Pd(dba)$_2$]), anhydrous DMSO, potassium *tert*-butoxide, bromobenzene, n-BuLi, dichloro(1,5-cyclooctadiene)palladium(II), tri-*tert*-butylphosphine solution (1.0 M in toluene), pivalic anhydride and sodium borohydride were purchased from Sigma Aldrich; Tris(dibenzylideneacetone)dipalladium(0) ([Pd$_2$(dba)$_3$]) and *tert*-butyl hydroxycarbamate were purchased from Fluorochem. Iron phthalocyanine and styrene were purchased from Acros. Bis(ditertiarybutyl-phosphinomethyl)benzene was obtained from Digital Specialty Chemical Inc. Potassium *tert*-butoxide was freshly sublimed before use. Air sensitive or moisture sensitive reactions were carried out under argon in a fume hood using standard Schlenk techniques with oven-dried glassware. Flash column chromatography was performed manually using silica gel (pore size 60 Å, 70-230 mesh particle size, 40-63 μm particle size). Analytical TLC was performed on pre-coated polyester sheets of silica (60 F254 nm) and visualised by short-wave UV light at 254 nm. Permanganate TLC stain was used for compounds with no UV visible chromophore. Ninhydrin stain was also used for primary and secondary amines, which gave a dark purple spot for primary amines, and a yellow/orange spot for secondary amines. For the reactions carried out in microwave vials, Biotage 10 mL and 30 mL glass microwave vials were used. Mass spectra were recorded on a Micromass LCT with a TOF mass spectrometer coupled to a Waters 2795 HPLC and a Waters 2996 detector. NMR spectra were recorded on Bruker Avance II 400 and Bruker Avance II 500 spectrometers, ^{13}C spectra were measured with ^{1}H decoupling. Residual protio peaks from deuterated solvents were used as reference with TMS at 0 ppm. GCMS was carried out using a Thermo electron Corporaton DSQ

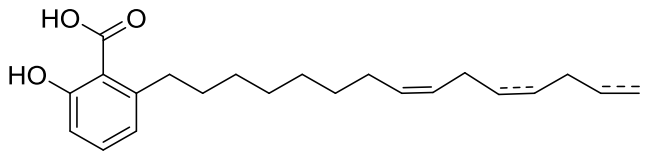
II for the GC, and Trace GC ULTRA Thermo Electron Corporation mass spectrometer for the MS with a THERMO TR-5 (5% Phenyl Methylpolysiloxane) column. Method: 50-300 °C, ramp rate 15 °C/min, hold for 20 mins.

4.4.2 Experimental procedures

4.4.2.1 Extraction of cashew nut shell liquid

Cashew nut shell liquid was extracted from cashew nut shell using a the procedure adopted from literature.[27] Clean dry shells (200 g) were soaked in petroleum ether (2 L) for four days. The shells were then separated from the solution by decantation followed by filtration to remove other solid particles. In order to increase the yield, the same procedure was repeated to extract any remaining CNSL from the shells, and the cashew nut shell was further soaked in petrol ether for another 4 days, filtration and concentration under reduced pressure afored cashew nut shell liquid as a brown oil (28 g, 14%).

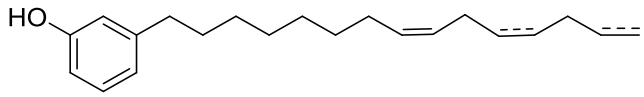
Anacardic acid, 4.1



The isolation of anacardic acid from CNSL was performed using a literature procedure reported by Santos.[27] The CNSL (20 g) was dissolved in aqueous methanol (5%, 120 mL), calcium hydroxide (10 g) was then added into the solution in portions. The pinkish solution was heated at 50 °C for 3 hours. The calcium anacardate precipitated, was filtered and washed thoroughly with 5% methanol (3 × 30 mL). The crushed cake was then transferred into a flask containing HCl (6 M, 100 mL) and ethyl acetate (150 mL), and stirred for 1 hour. The organic layer was separated, washed with distilled water (3 × 50 mL), and dried over magnesium sulphate. Filtration and concentration under reduced pressure afforded anacardic acid as a brown oil (11 g, 55%). δ_H (500 MHz, $CDCl_3$) 0.88-0.96 (4H, m, CH_3/CH_2), 1.14-1.43 (27.9H, m, CH_2), 1.52-1.66 (4.3H, m, CH_2), 1.93-2.11 (6.6H, m, CH_2), 2.18-2.20 (2.3H, m, CH_2), 2.72-2.87 (4H, m, CH_2), 2.91-3.15 (3.6H, m, CH_2), 4.90-5.11 (1.6H, m, CH), 5.25-5.48 (6H, m, CH), 5.73-5.85 (0.8H, m,

CH), 6.74-6.89 (3.6H, m, Ar-H), 7.35 (1.8H, t, *J* = 7.9 Hz), 11.1 (1.6H, br s, OH); δ_C (126 MHz, $CDCl_3$) 14.0, 14.3, 22.8, 22.9, 25.7, 25.8, 27.3, 27.4, 29.1, 29.3, 29.4, 29.5, 29.6, 29.8, 29.9, 31.7, 31.9, 32.1, 34.6, 36.6, 110.6, 112.4.8, 116.0, 122.9, 127.0, 127.7, 128.1, 128.3, 129.4, 130.0, 130.1, 130.3, 130.5, 135.4, 137.0, 147.8, 147.9, 163.7, 176.1. The uneven integral numbers in the proton NMR arise because anacardic acid is a mixture of saturated (3.9%), mono-ene (51.6%), di-ene (7%) and tri-ene (37.5%) compounds. *The spectroscopic properties of this compound were consistent with literature data*.[23]

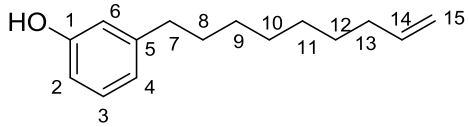
Cardanol, 4.3



Heating anacardic acid (5 g, 14.4 mmol) at 200 °C afforded the cardanol as brownish oil in a 98.6% yield (4.3 g, 14.2 mmol). δ_H (400 MHz, $CDCl_3$) 0.88-0.97 (4H, m, CH_3/CH_2), 1.26-1.48 (24.4 H, m, CH_2), 1.60 (4H, quint, *J* = 7.3 Hz), 1.96-2.14 (6.4H, m, CH_2), 2.52-2.61 (3.9H, m, CH_2), 2.73-2.90 (2.9H, m, CH_2), 4.97-5.14 (2.7H, m, CH), 5.24-5.51 (5.5H, m, CH), 5.76-5.93 (0.5H, m, CH), 6.63-6.71 (3.6H, m, Ar-H), 6.78 (1.9H, d, *J* = 7.5 Hz), 7.16 (1.8H, t, *J* = 7.7 Hz); δ_C (126 MHz, $CDCl_3$) 13.9, 14.3, 22.8, 22.9, 25.7, 25.8, 27.3, 29.1, 29.4, 29.5, 29.7, 29.8, 29.9, 31.4, 31.6, 31.9, 35.9, 112.6, 114.8, 115.4, 121.1, 127.0, 127.7, 128.1, 128.3, 129.4, 129.5, 130.0, 130.1, 130.3, 130.5, 155.5. The uneven integral numbers in the proton NMR arise because cardanol is a mixture of saturated, mono-ene, di-ene and tri-ene compounds. *The spectroscopic properties of this compound were consistent with literature data*.[23]

4.4.2.2 Synthesis of 3-vinylphenol

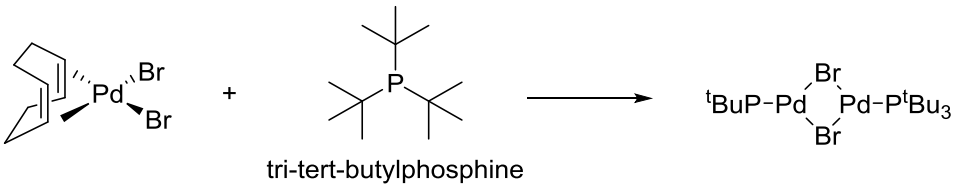
3-(non-8-en-1-yl)phenol, 3-(non-8-enyl)phenol, **4.7**



Reaction conditions adopted from literature.[22] In the glove box, Hoveyda-Grubbs 1st generation catalyst (21.6 mg, 36 μmol, 0.5 mol%) was weighed into a 30 mL

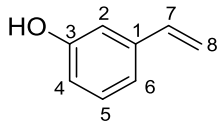
microwave vial fitted with a stirrer bar. The microwave vial was sealed and removed from the glove box. Under a flow of Ar, cardanol (2.5 mL, 7.3 mmol, 1 equiv.) and anhydrous DCM (20 mL) were introduced to the microwave vial by syringes. The microwave vial was introduced into a pre-purged 250 mL Hastelloy autoclave, and the cap of the microwave vial was removed under Ar flow. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (10 bar). The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was concentrated under reduced pressure. The product was obtained as a yellow oil (0.69 g, 96% yield) by flash column chromatography (20% ethyl acetate/ petroleum ether). δ_H (500 MHz, $CDCl_3$) 1.24-1.43 (8H, m, $H_{9\text{-}12}$), 1.60 (2H, qui, J = 7.3 Hz, H_8), 2.00-2.07 (2H, m, H_{13}), 2.56 (2H, t, J = 7.4 Hz, H_7), 4.81 (1H, s, OH), 4.91-4.96 (1H, m, H_{15}), 4.97-5.03 (1H, m, H_{15}), 5.82 (1H, ddt, J = 6.7, 10.1, 16.9, H_{14}), 6.62-6.69 (2H, m, ArH), 6.76 (1H, d, J = 7.5 Hz, ArH), 7.14 (1H, J = 7.7 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 29.1, 29.2, 29.4, 29.5, ($C_{9\text{-}12}$), 31.4 (C_8), 33.9 (C_{13}), 35.9 (C_7), 112.6, 114.3, 115.4, 121.1, 129.5 (ArC, C_{15}), 139.4 (C_{14}), 145.1 (C_5), 155.5 (C_1). *The spectroscopic properties of this compound were consistent with literature data.*[22]

Bromo(tri-tert-butylphosphine)palladium(I) dimer, 4.17



Reaction conditions adopted from literature.[30] A Schlenk flask was charged with [Pd(cod)$(Br)_2$] (375.5 mg, 1.0 mmol) and anhydrous toluene (2.5 mL), a solution of P^tBu_3 (1 M in toluene, 1.5 mL, 1.5 mmol) was added to the suspension. The reaction mixture was stirred at room temperature under Ar for 2 hours. Then anhydrous MeOH (7.5 mL) was added and the green reaction mixture stirred for another 20 minutes. The resulting green solid was isolated by filtration under argon, washed with anhydrous MeOH (5 × 2.5 mL) and dried *in vacuo* to afford the product as a dark green solid (325 mg, 84%). δ_H (400 MHz, C_6D_6) 1.32 (t, J = 6.2 Hz, 36H); $\delta_{P\ \{H\}}$ (162 MHz, C_6D_6) 86.2. It was stored under argon in a fridge and used within 14 d.

3-vinylphenol, 4.12



Method 1: Metathesis of 3-(non-8-en-1-yl)phenol

Reaction conditions adopted from literature.[22] In the glove box, Bromo(tri-tert-butylphosphine)palladium(I) dimer (5 mg, 6.5 μmol, 1.3 mol%) and **M1** (6.6 mg, 10 μmol, 2 mol%) were weighed into a 10 mL microwave vial fitted with a stirrer bar. 3-(Non-8-en-1-yl)phenol (125 mg, 0.5 mmol) in anhydrous THF (2 mL) was also added into the microwave vial. The microwave vial was sealed, removed from the glove box, and introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (5 bar). The reaction mixture was stirred at 50 °C for 16 hours. After cooling to -78 °C, the pressure was slowly released. The reaction mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. Under inert atmosphere, **M1** (6.6 mg, 10 μmol, 2 mol%), crude product and THF (2 mL) were added into a microwave vial with two needles in an autoclave, the autoclave was charged with ethylene gas again (5 bar). The reaction mixture was stirred at 50 °C for another 16 hours. Purification by flash column chromatography (20% ethyl acetate/ petroleum ether) afforded the product as a pale yellow oil (47 mg, 78% yield).

Method 2: Wittig reaction

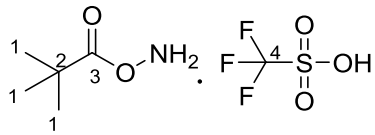
Reaction conditions adopted from literature.[40] A Schlenk flask was charged with methyltriphenylphosphonium bromide (3.57 g, 10 mmol, 2 equiv.) and THF (50 mL, 0.2 M). The suspension was cooled to 0 °C and n-BuLi (4 mL, 10 mmol, 2.5 M in hexanes, 2 equiv.) was added dropwise. The yellow solution was then stirred for 2 h at 0 °C. Subsequently, 3-hydroxybenzaldehyde (0.61 g, 5 mmol, 1 equiv) in THF (4 mL, 1.25 M) was added dropwise, while a white precipitate started appearing. After allowing the solution to warm to room temperature, it was stirred for further 16 hours. The solvent was evaporated under reduced pressure to afford the crude product, which was

then purified by flash column chromatography (33% ethyl acetate/cyclohexane) to afford the desired 3-vinylphenol as a pale yellow oil. (0.552 g, 92% yield).

δ_H (400 MHz, $CDCl_3$) 5.12 (1H, br s, OH), 5.26 (1H, dd, *J* = 0.8, 10.9 Hz, $H_{8\ cis\ to\ 7}$), 5.73 (1H, dd, *J* = 0.9, 17.5 Hz, $H_{8\ trans\ to\ 7}$), 6.67 (1H, dd, *J* = 10.9, 17.6 Hz, H_7), 6.75 (1H, ddd, *J* = 0.9, 2.6, 8.0 Hz, H_4), 6.90 (1H, dd, *J* = 1.6, 2.6 Hz, H_2), 7.00 (1H, ddt, *J* = 0.6, 1.5, 7.7 Hz, H_6), 7.21 (1H, t, *J* = 7.9 Hz, H_5); δ_C (101 MHz, $CDCl_3$) 112.9 (C_2), 114.5 (C_8), 115.0 (C_4), 119.3 (C_6), 129.9 (C_5), 136.5 (C_7), 139.5 (C_1), 155.7 (C_3). *The spectroscopic properties of this compound were consistent with literature data.*[40]

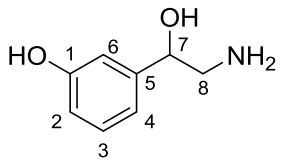
4.4.2.3 Synthesis of Norfenefrine

O-pivaloylhydroxyamine triflic acid



Reaction conditions adopted from literature.[41] Pivalic anhydride (3.66 mL, 18.02 mmol, 1.2 equiv.) was added to a solution of *tert*-Butyl hydroxycarbamate (2.00 g, 15.02 mmol, 1 equiv.) in chloroform (40 mL). The reaction mixture was refluxed for 16 hours. The mixture was then quenched with sat. $NaHCO_3$ and diluted with DCM. The organic phase was washed 3 times with sat. $NaHCO_3$ after which it was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The white solid obtained (3.77 g, 17.4 mmol) was dissolved in diethyl ether (40 mL) and triflic acid (1.54 mL, 17.4 mmol, 1 equiv.) was added dropwise at 0 °C. The reaction was allowed to reach room temperature and it was diluted with petroleum ether (40 mL) to precipitate the product. The mixture was filtered to obtain the desired product as a white solid (2.75 g, 69% over 2 steps). δ_H (500 MHz, d^6-DMSO) 1.22 (9H, s, H_1); δ_C (126 MHz, d^6-DMSO) 26.5 (C_1), 37.8 (C_2), 120.6 (1C, q, *J* = 322.8 Hz, C_4), 175.0 (C_3); δ_F (471 MHz, d^6-DMSO) -77.8. *The spectroscopic properties of this compound were consistent with literature data*.[41]

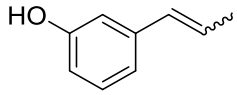
3-(2-amino-1-hydroxyethyl)phenol, 4.25



Reaction conditions adopted from literature.[42] A microwave vial fitted with a stirring bar was charged with iron (II) phthalocyanine (14.2 mg, 0.025 mmol), and degassed for 20 minutes with Ar. O-pivaloylhydroxyamine triflic acid (0.33 g, 1.25 mmol) was dissolved in acetonitrile (1 mL) and water (0.5 mL), and degassed for 5 minutes. 3-Vinylphenol (60 mg, 0.5 mmol) in degassed acetonitrile (0.2 mL) and the solution of O-pivaloylhydroxyamine triflic acid were added to the microwave vial containing the iron catalyst simultaneously. The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was diluted with methyl *tert*-butyl ether (15 mL), extracted with HCl solution (1 M, 3 × 15 mL). The combined water phases were concentrated under reduced pressure to afford the amine salt. 1,4-Dioxane was used as internal standard for an NMR yield in deuterated water (74% yield). The free amine was obtained by dissolving the chloride salt in triethyl amine (1 equiv. to the salt) and DCM, and purified by flash column chromatography (100: 15 :1.5 of DCM: MeOH: Et_3N). The desired product was obtained as a pale yellow oil (54 mg, 71%). δ_H (500 MHz, d^6-DMSO) 2.52-2.2.56 (1H, m, H_8), 2.61-2.66 (1H, m, H_8), 4.33-4.38 (1H, m, H_7), 5.23 (1H, br s, OH), 6.58-6.62 (1H, m, ArH), 6.69-6.74 (2H, m, ArH), 7.05-7.10 (1H, m, ArH); δ_C (126 MHz, d^6-DMSO) 50.0 (C_8), 74.2 (C_7), 112.8 (ArC), 113.7 (ArC), 116.6 (ArC), 128.9 (ArC), 145.9 (C_5), 157.1 (C_1). *The spectroscopic properties of this compound were consistent with literature data*.[43]

4.2.2.4 Synthesis of Metaraminol

3-(prop-1-en-1-yl)phenol, 4.24

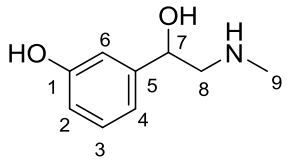


Reaction conditions adopted from literature.[40] A Schlenk flask was charged with ethyltriphenylphosphonium bromide (3.71 g, 10 mmol, 2 equiv.) and THF (50 mL, 0.2

M). The suspension was cooled to 0 °C and n-BuLi (4 mL, 10 mmol, 2.5 M in hexanes, 2 equiv.) was added dropwise. The yellow solution was then stirred for 2 h at 0 °C. Afterwards, 3-hydroxybenzaldehyde (0.61 g, 5 mmol, 1 equiv) in THF (4 mL, 1.25 M) was added dropwise. A white precipitate started appearing. After allowing the solution to warm to room temperature, it was stirred for further 16 hours. The solvent was evaporated under reduced pressure to afford the crude product, which was then purified by flash column chromatography (33% ethyl acetate/ cyclohexane) to afford the desired 3-vinylphenol as colourless oil. (0.63 g, 94% yield).

A mixture of *E*- and *Z*- isomers were obtained. δ_H (400 MHz, $CDCl_3$) 1.84-1.94 (6H, m), 5.68 (2H, br s, OH), 5.77-5.85 (1H, m), 6.17-6.26 (1H, m), 6.31-6.42 (2H, m), 6.68-6.75 (2H, m), 6.80-6.86 (2H, m), 6.88-6.95 (2H, m), 7.14-7.25 (2H, m); δ_C (101 MHz, $CDCl_3$) 14.8, 18.6, 112.6, 113.6, 113.9, 115.8, 118.8, 121.7, 126.5, 127.4, 129.5, 129.5, 129.8, 130.65, 139.4, 139.8, 155.2, 155.6. *The spectroscopic properties of this compound were consistent with literature data.*[22,44]

4.4.2.5 Synthesis of racemic Phenylephrine, 4.30

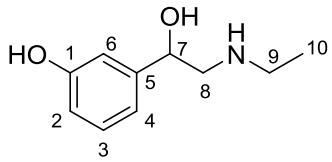


Reaction conditions adopted from literature.[34] Methyl triflate (164 ml, 1.5 mmol, 1.5 equiv.) was added to a solution of norfenefrine (153 mg, 1 mmol, 1 equiv.) in HFIP (1 mL) under stirring at room temperature. After 1 h, the reaction mixture was quenched by an aq. sol. of HCl 2 N (1 mL) and the reaction mixture was concentrated under reduced pressure. Dodecane was used as internal standard for an NMR yield in deuterated methanol (79% yield). A sample of the free amine for analysis was obtained by dissolving the chloride salt in triethyl amine and DCM, and purified by prep-TLC (100: 10: 1 of DCM: MeOH: aq. NH_3). δ_H (500 MHz, MeOD) 2.39 (3H, s, H_9), 2.67 (1H, dd, J = 4.5 Hz, 12.1 Hz, H_8), 2.77 (1H, dd, J = 8.6 Hz, 12.1 Hz, H_8), 4.60 (1H, dd, J = 4.5 Hz, 8.6 Hz, H_7), 6.44 (1H, d, J = 7.4 Hz, ArH), 6.51-6.55 (1H, m, ArH), 6.62-6.63 (1H, m, ArH), 6.96 (1H, t, J = 7.7 Hz, H_3); δ_C (126 MHz, MeOD) 36.0 (C_9), 60.0 (C_8),

73.9 (C_7), 112.7 (C_6), 117.6 (C_2), 119.5 (C_4), 129.9 (C_3), 144.8 (C_5), 168.3 (C_1). *The spectroscopic properties of this compound were consistent with literature data.*[45]

4.4.2.6 Synthesis of Etilefrine

3-(2-(Ethylamino)-1-hydroxyethyl)phenol; etilefrine, **4.31**



Method 1: Reductive amination

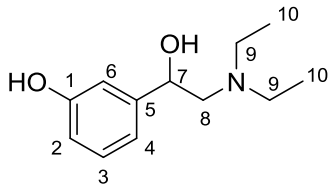
Reaction conditions adopted from literature.[32] Acetaldehyde (0.23 mL, 4 mmol, 4 equiv.) was added to a solution of norfenefrine (153 mg, 1 mmol, 1 equiv.) in EtOH (10 mL), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to 0 °C in an ice bath before the slow addition of $NaBH_4$ (158.8 mg, 4.2 mmol, 4.2 equiv.), and stirred at 0°C for 1 hour. The reaction was quenched with water, and the reaction mixture was concentrated under reduced pressure before being dissolved in DCM. The organics was washed with sat. $NaHCO_3$ (60 mL), and the aqueous layer was extracted with a mixture of 3:1 chloroform: isopropanol (3×60 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Methanol: dichloromethane: aq. NH_3 = 10: 90: 1) to a colourless oil (98 mg, 54%). δ_H (500 MHz, MeOD) 1.18 (3H, t, J = 7.2 Hz, H_{10}), 2.71-2.90 (4H, m, $H_{8,9}$), 4.74 (1H, dd, J = 5.4, 7.7 Hz, H_7), 6.67-6.72 (1H, m, ArH), 6.79-6.90 (2H, m, ArH), 7.16 (1H, t, J = 8.0 Hz, ArH); δ_C (126 MHz, MeOD) 13.8 (C_{10}), 44.4 (C_9), 57.0 (C_8), 72.4 (C_7), 113.8, 115.7, 118.0, 130.5 (ArH), 145.6 (C_5), 158.8 (C_1). *The spectroscopic properties of this compound were similar to those of* etilefrine. *HCl.* [46]

Method 2: Ethylation

Reaction conditions adopted from literature.[34] Ethyl triflate (190 ml, 1.5 mmol, 1.5 equiv.) was added to a solution of norfenefrine (153 mg, 1 mmol, 1 equiv.) in HFIP (1 mL) under stirring at room temperature. After 1 h, the reaction mixture was quenched by an aq. sol. of HCl (2 N, 1 mL) and the reaction mixture was concentrated under

reduced pressure. Dodecane was used as internal standard for an NMR yield in deuterated methanol (79%).

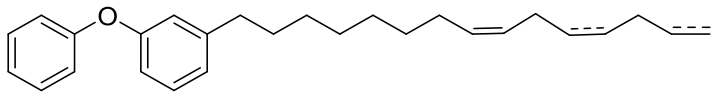
3-(2-(Diethylamino)-1-hydroxyethyl)phenol, 4.32



Reaction conditions adopted from literature.[32] **4.32** was obtained as a side product during the synthesis of 3-(2-(ethylamino)-1-hydroxyethyl)phenol (etilefrine) by reductive amination. The crude product was purified by flash column chromatography (methanol: dichloromethane: aq. NH_3 = 10: 90: 1) to a colourless oil (73 mg, 35%). δ_H (500 MHz, MeOD) 1.08 (6H, t, *J* = 7.2 Hz, H_{10}), 2.59-2.78 (6H, m, $H_{8,9}$), 4.68 (1H, dd, *J* = 4.1, 8.7 Hz, H_7), 6.66-6.70 (1H, m, ArH), 6.79-6.85 (2H, m, ArH), 7.14 (1H, t, *J* = 8.0 Hz, ArH); δ_C (126 MHz, MeOD) 11.6 (C_{10}), 48.4 (C_9), 62.2 (C_8), 71.9 (C_7), 113.9, 115.3, 118.2, 130.4 (ArH), 146.3 (C_5), 158.6 (C_1).

4.4.2.7 Synthesis of Fenoprofen

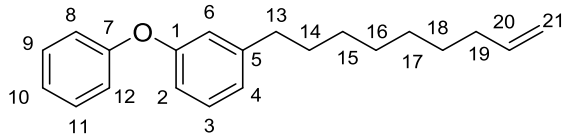
O-Phenyl Cardanol, 4.45



Anhydrous dimethyl sulfoxide (10 mL) was added into a microwave vial containing cardanol (3.03 g, 10 mmol, 1 equiv.) and bromobenzene (2.1 mL, 20 mmol, 2 equiv.). The solution was stirred for 5 minutes before introducing anhydrous potassium *tert*-butoxide (2.8 g, 25 mmol, 2.5 equiv.) portionwise. The microwave vial was sealed, and the reaction mixture was heated to 100°C for 8 hours. The reaction mixture was then added into water (50 mL) and extracted with DCM (4 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a brown oil. The crude material was purified by flash column chromatography (20% DCM / Hexane) to afford the desired product as a yellow oil (3.1 g, 82% yield). δ_H (500 MHz, $CDCl_3$) 0.83-0.94 (4H, m, CH_3/CH_2), 1.10-1.38

(15.9 H, m, CH_2), 1.57-1.64 (2H, m, CH_2), 1.98-2.06 (3.8H, m, CH_2), 2.53-2.62 (1.9H, m, CH_2), 5.29-5.40 (1.4H, m, CH), 6.79-6.84 (1H, m, Ar-H), 6.84-6.87 (1H, m, CH), 6.91-6.95 (1H, m, CH), 6.99-7.04 (2.7H, m, ArH), 7.06-7.13 (1.7H, m, ArH), 7.18-7.25 (1.4H, m, ArH), 7.30-7.37 (3.5H, m, ArH); δ_C (126 MHz, $CDCl_3$) 14.3, 22.8, 27.3, 27.4, 29.1, 29.4, 29.5, 29.6, 29.9, 31.5, 31.9, 36.0, 116.3, 118.8, 119.0, 119.2, 123.1, 123.3, 123.6, 129.5, 129.8, 129.9, 130.0, 130.1, 145.2, 157.2, 157.6. The uneven integral numbers in the proton NMR arise because *O*-phenyl cardanol is a mixture of saturated, mono-ene, di-ene and tri-ene compounds. HRMS: (EI+) Mono-ene: Found: [M]+ 378.2921, $C_{27}H_{38}O$ requires 378.2923; Tri-ene: Found: [M]+ 374.2595, $C_{27}H_{34}O$ requires 374.2610; Saturated: Found: [M]+ 380.3071, $C_{27}H_{40}O$ requires 380.3079;

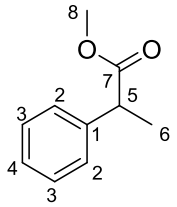
1-(Non-8-en-1-yl)-3-phenoxybenzene, 4.46



Reaction conditions adopted from literature.[22] In the glove box, Hoveyda-Grubbs 1st generation catalyst (3.0 mg, 5 μmol, 0.5 mol%) was weighed into a 30 mL microwave vial fitted with a stirrer bar. The microwave vial was sealed and removed from the glove box. Under a flow of Ar, degassed O-phenyl cardanol (0.38 g, 1 mmol, 1 equiv.) and anhydrous DCM (3 mL) were introduced into the microwave vial by syringes. The microwave vial was introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (10 bar). The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was concentrated under reduced pressure. The product was obtained as a colourless oil (0.284 g, 97% yield) by flash column chromatography (1% acetone/ pentane). δ_H (500 MHz, $CDCl_3$) 1.28-1.41 (8H, m, H_{15-18}), 1.61-1.71 (2H, m, H_{14}), 2.05-2.15 (2H, m, H_{19}), 2.63 (2H, t, J = 7.8 Hz, H_{13}), 4.95-5.08 (2H, m, H_{21}), 5.80-5.92 (1H, m, H_{20}), 6.85-6.89 (1H, m, ArH), 6.90-6.92 (1H, m, ArH), 6.96-6.99 (1H, m, ArH), 7.04-7.08 (2H, m, ArH), 7.12-7.16 (1H, m, ArH), 7.26-7.30 (1H, m, ArH), 7.35-7.40 (2H, m, ArH); δ_C (126 MHz, $CDCl_3$) 29.0, 29.1, 29.3, 29.4 (C_{15-18}), 31.3 (C_{14}), 33.9 (C_{19}), 35.9 (C_{13}), 114.2, 116.2, 118.8, 119.1, 123.0, 123.5,

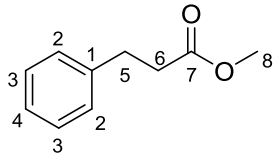
129.5, 129.7, 139.2, 145.1, 157.1, 157.5 ($C_{1,7}$). HRMS: (ASAP+) Found: [M+H]+ 295.2061, $C_{21}H_{27}O$ requires 295.2062.

Methyl 2-phenylpropanoate, 4.42



Reaction conditions adopted and modified from literature.[39] In the glovebox, [Pd(dba)$_2$] (2.9 mg, 5 μmol, 0.5 mol%), bis(ditertiarybutyl-phosphinomethyl)benzene (DTBPMB) (7.9 mg, 20 μmol, 2 mol%), *rac*-BNPA (26 mg, 75 μmol, 7.5 mol%) were weighed and added into a 10 mL microwave vial. The microwave vial was sealed and removed from the glovebox. Under a flow of Ar, anhydrous DCM (0.75 mL), distilled MeOH (0.25 mL), and styrene (115 μL, 1.0 mmol, 1 equiv.) were added into the microwave vial. The vial was then introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with CO gas (~5 bar), and charged with CO (5 bar). The reaction mixture was stirred at room temperature for 24 hours. The b : l ration was determined by GC-FID (91 : 9). The yield was determined by GC-FID with dodecane as internal standard (93% yield). The crude product was purified by flash column chromatography (5% ethyl acetate/ cyclohexane), the regioisomeric compounds were obtained as a colourless oil (0.15 g, 92% yield). δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, J = 7.2 Hz, H_6), 3.69 (3H, s, H_8), 3.77 (1H, q, J = 7.2 Hz, H_5), 7.29-7.39 (5H, m, $H_{1\text{-}4}$); δ_C (101 MHz, $CDCl_3$) 18.7 (C_6), 45.5 (C_5), 52.1 (C_8), 127.2, 127.6, 128.7 ($C_{2\text{-}4}$), 140.6 (C_1), 175.1 (C_7).

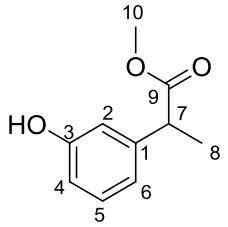
*Minor signals for linear regioisomer, **4.43**:*



δ_H (400 MHz, $CDCl_3$) 2.68 (2H, dd, *J* = 7.2, 8.5 Hz, H_6), 3.00 (2H, t, *J* = 7.8 Hz, H_5), 3.71 (3H, s, H_8), aromatic region was not assigned because of the overlap; δ_C (101 MHz, $CDCl_3$) 31.0 (C_5), 35.8 (C_6), 51.7 (C_8), 126.4, 128.3, 128.6 ($C_{2\text{-}4}$), 140.5 (C_1), 173.4 (C_7).

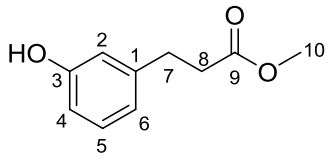
The spectroscopic properties of this compound were consistent with literature data.[39]

methyl 2-(3-hydroxyphenyl)propanoate, 4.41



Reaction conditions adopted and modified from literature.[39] In the glovebox, [$Pd(dba)_2$] (2.9 mg, 5 μmol, 0.5 mol%), bis(ditertiarybutyl-phosphinomethyl)benzene (DTBPMB) (7.9 mg, 20 μmol, 2 mol%), *rac*-BNPA (26 mg, 75 μmol, 7.5 mol%) were weighed and added into a 10 mL microwave vial. The microwave vial was sealed and removed from the glovebox. Under a flow of Ar, anhydrous DCM (0.75 mL), distilled MeOH (0.25 mL), and 3-vinylphenol in anhydrous DCM (1 mL, 1.0 mmol, 1 equiv., 1 M stock solution) were added into the microwave vial. The vial was then introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with CO gas (~5 bar), and charged with CO (5 bar). The reaction mixture was stirred at room temperature for 24 hours. The b : l ratio was determined by GC-FID (91 : 9). The crude product was purified by flash column chromatography (20% ethyl acetate/ petroleum ether), the regioisomeric compounds were obtained as a colourless oil (0.16 g, 89% yield of both branched and linear products). δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* = 7.2 Hz, H_8), 3.67 (3H, s, H_{10}), 3.69 (1H, q, *J* = 7.2 Hz, H_7), 6.48 (1H, br s, OH), 6.74-6.78 (1H, m, H_6), 6.81-6.86 (2H, m, $H_{2,4}$), 7.14-7.21 (1H, m, H_5); δ_C (101 MHz, $CDCl_3$) 18.5 (C_8), 45.4 (C_7), 52.5 (C_{10}), 114.4, 114.5 ($C_{2,4}$), 119.8 (C_6), 130.0 (C_5), 142.0 (C_1), 156.3 (C_3), 175.9 (C_9).

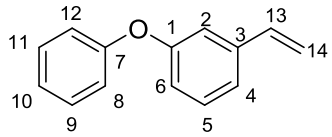
*Minor signals for linear regioisomer, **4.44**:*



δ_H (400 MHz, $CDCl_3$) 2.63 (2H, dd, *J* = 7.2, 8.4 Hz, H_8), 2.89 (2H, t, *J* = 7.8 Hz, H_7), 3.68 (3H, s, H_{10}), 3.69 (1H, q, *J* = 7.2 Hz, H_7), 6.28 (1H, br s, OH), aromatic region was not assigned because of the overlap; δ_C (101 MHz, $CDCl_3$) 30.9 (C_7), 35.7 (C_8), 52.0 (C_{10}), 113.5, 115.4 ($C_{2,4}$), 120.5 (C_6), 129.8 (C_5), 142.2 (C_1), 156.0 (C_3), 174.2 (C_9).

The spectroscopic properties of these compounds were consistent with literature data.[47]

1-phenoxy-3-vinylbenzene, 4.39



Method 1: Metathesis of 3-(non-8-en-1-yl)phenol

Reaction condition adopted from literature.[22] In the glove box, bromo(tri-tert-butylphosphine)palladium(I) dimer (5 mg, 6.5 μmol, 1.3 mol%) and **M1** (6.6 mg, 10 μmol, 2 mol%) were weighed into a 10 mL microwave vial fitted with a stirrer bar. 1-(Non-8-en-1-yl)-3-phenoxybenzene (147 mg, 0.5 mmol) in anhydrous THF (2 mL) were also added into the microwave vial. The microwave vial was sealed, removed from the glove box, and introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (5 bar). The reaction mixture was stirred at 50 °C for 16 hours. After cooling to -78 °C, the pressure was slowly released. The reaction mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. Under inert atmosphere, **M1** (6.6 mg, 10 μmol, 2 mol%), crude product and anhydrous THF (2 mL) were added into a microwave vial with two needles in an autoclave, the autoclave was purged and charged with ethylene gas again (5 bar). The reaction mixture was stirred at 50 °C for another 16 hours. Purification by flash column chromatography

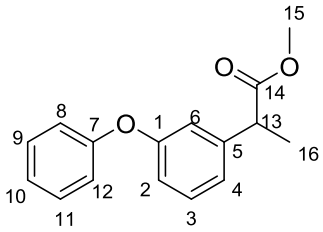
(20% ethyl acetate/ petroleum ether) afforded the product as a colourless oil (79 mg, 80% yield).

Method 2: Wittig reaction

Reaction conditions adopted from literature.[40] A Schlenk flask was charged with methyltriphenylphosphonium bromide (10.71 g, 30 mmol, 2 equiv.) and anhydrous THF (150 mL, 0.2 M). The suspension was cooled to 0 °C and n-BuLi (12 mL, 30 mmol, 2.5 M in hexanes, 2 equiv.) was added dropwise. The yellow solution was then stirred for 2 h at 0 °C. Afterwards, 3-phenoxybenzaldehyde (2.6 mL, 15 mmol, 1 equiv) in anhydrous THF (12 mL, 1.25 M) was added dropwise. After allowing the solution to warm to room temperature, it was stirred for a further 16 hours. The solvent was evaporated under reduced pressure to afford the crude product, which was then purified by flash column chromatography (20% ethyl acetate/ petroleum ether) to afford the desired 1-phenoxy-3-vinylbenzene as a colourless oil. (1.7 g, 58% yield).

δ_H (400 MHz, $CDCl_3$) 5.27 (1H, dd, *J* = 0.8, 10.9 Hz, $H_{14\ cis\ to\ 13}$), 5.73 (1H, dd, *J* = 0.8, 17.6 Hz, $H_{14\ trans\ to\ 13}$), 6.69 (1H, dd, *J* = 10.9, 17.6 Hz, H_{13}), 6.92 (1H, ddd, *J* = 1.0, 2.5, 8.1 Hz, H_2), 6.99-7.06 (2H, m, ArH), 7.08-7.20 (3H, m, ArH), 7.27-7.41 (3H, m, ArH); δ_C (101 MHz, $CDCl_3$) 114.8 (C_{14}), 116.6, 118.4, 119.0, 121.5, 123.4, 129.8 129.9 (ArC), 136.4 (C_{13}), 139.6 (C_3), 157.3, 157.6 ($C_{1,\ 7}$). *The spectroscopic properties of these compounds were consistent with literature data.*[48]

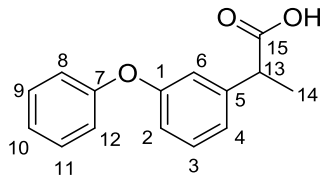
methyl 2-(3-phenoxyphenyl)propanoate, 4.40



Reaction conditions adopted and modified from literature.[39] In the glovebox, $[Pd(dba)_2]$ (2.9 mg, 5 μmol, 0.5 mol%), bis(ditertiarybutyl-phosphinomethyl)benzene (DTBPMB) (7.9 mg, 20 μmol, 2 mol%), *rac*-BNPA (26 mg, 75 μmol, 7.5 mol%) were weighed and added into a 10 mL microwave vial. The microwave vial was sealed and removed from

the glovebox. Under a flow of Ar, anhydrous DCM (0.75 mL), distilled MeOH (0.25 mL), and 1-phenoxy-3-vinylbenzene (0.196 g, 1.0 mmol, 1 equiv.) were added into the microwave vial. The vial was then introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with CO gas (~5 bar), and charged with CO (5 bar). The reaction mixture was stirred at room temperature for 24 hours. The b : l ratio was determined by GC-FID (89 : 11). The crude product was purified by flash column chromatography (10% ethyl acetate in petroleum ether) and the regioisomeric compounds were obtained as a colourless oil (0.24 g, 94% yield in total, 82% branched, 12% linear product by isolation and NMR analysis of the mixture). δ_H (500 MHz, $CDCl_3$) 1.49 (3H, d, *J* = 7.2 Hz, H_{16}), 3.67 (3H, s, H_{15}), 3.70 (1H, q, *J* = 7.2 Hz, H_{13}), 6.86-6.89 (1H, m, ArH), 6.97-7.05 (4H, m, ArH), 7.09-7.13 (1H, m, ArH), 7.27 (1H, t, *J* = 7.9 Hz, ArH), 7.32-7.37 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 18.6 (C_{16}), 45.4 (C_{13}), 52.3 (C_{15}), 117.4, 118.2, 119.1, 122.4, 123.5, 129.9, 130.0 (ArC), 142.6 (C_5), 157.1, 157.5 ($C_{1,7}$), 174.8 (C_{14}). *The spectroscopic properties of this compound were consistent with literature data*.[49]

2-(3-phenoxyphenyl)propanoic acid; Fenoprofen, 4.33



Methyl 2-(3-phenoxyphenyl)propanoate (50 mg, 0.2 mmol, 1 equiv.) was introduced into a round bottomed flask. 1,4-Dioxane (5 mL), distilled water (5 mL), and hydrochloric acid (36% in water, 2 drops) were added and the mixture was heated under relux overnight until TLC indicated the full consumption of the ester. After cooling, dilute HCl (1M) was added to the reaction mixture to a pH of 1, and extracted 3 times with DCM (20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% ethyl acetate/ petroleum ether) to a colourless oil (43 mg, 91%). δ_H (500 MHz, $CDCl_3$) 1.51 (3H, d, *J* = 7.2 Hz, H_{14}), 3.72 (1H, q, *J* = 7.2 Hz, H_{13}), 6.87-6.91 (1H, m, ArH), 7.00-7.04 (3H, m, ArH), 7.05-7.08 (1H, m, ArH), 7.09-7.14 (1H, m,

ArH), 7.29 (1H, t, *J* = 7.9 Hz, ArH), 7.32-7.36 (2H, m, ArH); δ_C (126 MHz, $CDCl_3$) 18.2 (C_{14}), 45.3 (C_{13}), 117.6, 118.4, 119.1, 122.5, 123.5, 129.9, 130.0 (ArC), 141.8 (C_5), 157.0, 157.6 ($C_{1,7}$), 180.4 (C_{15}). *The spectroscopic properties of this compound were consistent with literature data*.[50]

4.4 References

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Chapter 5 Conclusions and future plans

Conversion of renewable feedstocks from industrial waste (such as tall oil and cashew nut shell liquid) into value-added materials to replace fossil fuel based materials has been successfully achieved.

Value-added esters, such as methyl oleate, can easily be obtained from tall oil fatty acid by esterification. Methoxycarbonylation of methyl oleate using $[Pd_2(dba)_3]$ catalyst and DTBPMB ligand can afford dimethyl 1,19-dimethyl nonadecanedioate as a polymer precursor. This difunctional ester, dimethyl 1,19-dimethyl nonadecanedioate, can then be hydrogenated to diols, *N*-substituted diamines and primary diamines with ruthenium catalysts in the presence of water, amine or aqueous ammonia (2 steps *via* the diol) respectively. Diols and diamines are useful precursors for the synthesis of polyesters and polyamides to replace petroleum-based polymers.

Lactams such as ε-caprolactam, which is also a useful polymer precursor for the synthesis of nylon 6, is also obtained by hydrogenation of adipic acid/adipate estesr together with aqueous ammonia in the presence of a ruthenium catalyst.

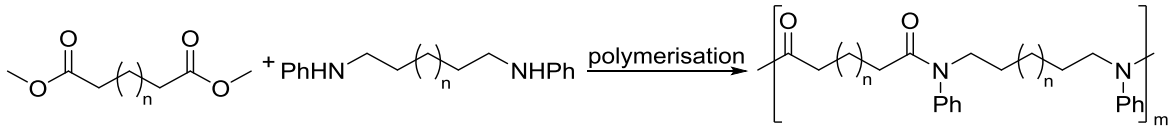
A new simple and selective route to the synthesis of *N*-phenyl heterocycles, which are important building blocks for the synthesis of drug molecules, has also been developed from the hydrogenation of diesters with shorter chain length (4-7 carbon chains) in the presence of aniline and a Ru/triphos catalyst.

Synthesis of medicinal drugs, such as norfenefrine, *rac*-phenylephrine, etilefrine and fenoprofene, were successfully achieved from renewable cashew nut shell liquid (CNSL). Our methods started from waste materials, and avoided unpleasant reagents in the original syntheses of those drugs, for example, cyanide is no longer needed for the synthesis of fenoprofene.

Future plans

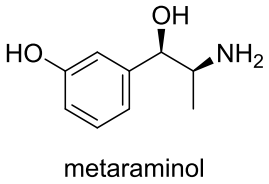
The first plan is to test the polymerisation reaction with long chain linear *N*-phenyl diamines to synthesise *N*-phenyl polyamide, since *N*-phenyl polyamide based materials

have the potential to be more fire resistant and more stable than other polyamides. (Scheme 5.1).



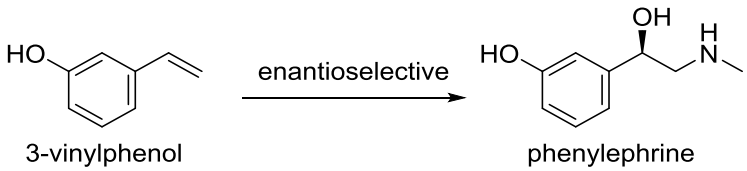
Scheme 5.1. Polymerisation between diester and *N*-phenyl diamine.

Another plan is to optimise the synthesis of drugs from CNSL. Presently, metaraminol was only obtained as a racemic mixture in 21% yield from norfenefrine. The future plan is to optimise the reaction conditions to obtain a higher yield of this reaction, and if possible, metaraminol should be synthesised in the enantiopure form by using chiral ligands (Scheme 5.2).



Scheme 5.2. Structures of metaraminol and phenylephrine.

The final future plan is to do a chiral resolution of *rac*-phenylephrine to give the pure form of phenylephrine. Otherwise, enantioselective synthesis of phenylephrine from 3-vinylphenol is also desirable (Scheme 5.3).



Scheme 5.3. Enantioselective synthesis of phenylephrine.