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REDUCTIVE APPROACH TO POLYOLS

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ABSTRACT OF MASTER'S THESIS

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The study discusses production of cyclohexane-1,2-dimethanol, cyclohexane-1,3-dimethanol, and cyclohexane-1,2,4-trimethanol using catalytic hydrogenation. The literature review discusses the hydrogenation of benzenepolycarboxylates and cyclohexanepolycarboxylates, and hydrogenation catalysts and their properties, supports and catalyst preparation methods. Catalysts to reduce aromatic esters and benzenepolycarboxylates are reviewed, in addition to catalysts to reduce esters, carboxylic acids and acid anhydrides.

In the experiments, aromatics were hydrogenated with 2% ruthenium on carbon. Dimethyl phthalate was hydrogenated at 80–100 bar and 120 °C neat, with ethanol, acetic acid and ethanol-acetic acid mixture, in 74–79% yield and 94.5–97.1% selectivity. The only solvent effect observed was that 90% of product was *cis* diastereomer with and 80% without acetic acid. Dimethyl isophthalate was hydrogenated with 2% Ru/C in ethanol at 80–95 bar and 120 °C to give a 66% yield of hexahydroisophthalates. Solvolysis gave a product mixture with 85% dimethyl hexahydroisophthalate and 13% other hexahydroisophthalates, or 98% in total. At 140 °C, hydrogenolysis occurred and the selectivity to hexahydroisophthalates was only 59%. Trimethyl trimellitate hydrogenation with 2% Ru/C at 88–97 bar and 120 °C in ethanol stopped at 39% conversion. Hydrogenation of phthalide with 2% Ru/C at 82–87 bar and 140 °C gave a 46% yield of hexahydrophthalide in 65% purity. There was 4% hexahydrophthalan and rest was products of hydrogenolysis and decarboxylation.

Dimethyl phthalate was reduced to cyclohexane-1,2-dimethanol with lithium aluminum hydride in tetrahydrofuran in 84% yield. Quench with the 1-2-1 method (1, 2, 1 parts water, 20% NaOH, and water) facilitated the filtration of the salts, but quench with minimal water followed by sodium sulfate decahydrate did not.

Dimethyl hexahydrophthalate hydrogenation to cyclohexane-1,2-dimethanol was unsuccessfully attempted with copper chromite, 2% ruthenium-1.5% tin on carbon and 2% ruthenium-0.7% platinum-0.4% tin on carbon. Hexahydrophthalide was the main intermediate, and dehydration to hexahydrophthalan readily occurred. Copper chromite was used at 95–98 bar. First 23 hours of hydrogenation at 150 °C resulted in little reaction, and then after 23 h at 200 °C, there was still 74% starting material of which 82% *cis* isomer, and the rest was 8% hexahydrophthalide, 6% cyclohexane-1,2-dimethanol of which 35% *cis* isomer, 1.5% hexahydrophthalan, 9% unidentified compounds and 1.5% lights. RuSn/C, which was the most effective catalyst, was used at 84–94 bar and 240 °C. After 31 h, there was 38% unidentified light compounds, 39% hexahydrophthalan, 5% hexahydrophthalide, and 0.2% *trans*-cyclohexane-1,2-dimethanol remained. It was evident that diester hydrogenation had occurred, but it was followed by dehydration to hexahydrophthalan. RuPtSn/C was used at 175–230 °C for 95 h in total, but the reaction did not proceed after 7 h at 230 °C. In the end, there was 66% starting material, 9% hexahydrophthalide and 25% unidentified compounds.

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Diplomityön aihe on sykloheksaani-1,2-dimetanolin, sykloheksaani-1,3-dimetanolin ja sykloheksaani-1,2,4-trimetanolin valmistaminen katalyyttisellä hydrogenaatiolla. Kirjallisuusosa käsittelee bentseenipolykarboksylaattien ja sykloheksaanipolykarboksylaattien hydrogenaatiota sekä vedytyskatalyyttejä ja niiden ominaisuuksia, sekä kantaja-aineita ja katalyyttien valmistusmenetelmiä. Lisäksi käsitellään katalyyttejä aromaattisten estereiden ja bentseenipolykarboksylaattien pelkistykseen sekä katalyyttejä esterien, karboksyylihappojen ja happoanhydridien pelkistämiseen.

Kokeellisessa osassa aromaatteja pelkistettiin 2 % rutenium-hiilellä. Dimetyyliftalaatti pelkistettiin 80–100 bar paineessa ja 120 °C:ssa 74–79 % saannolla ja 94,5–97,1 % selektiivisyydellä ilman liuotinta, etanolissa, etikkahapossa ja etanoli-etikkahapposeoksessa. Liuottimen ainoa vaikutus oli se, että 80 % tuotteesta oli *cis*-diastereomeeria ilman etikkahappoa ja 90 % etikkahapon kanssa. Dimetyyli-isoftalaatti pelkistettiin 2 % Ru/C:lla etanolissa 80–95 bar paineessa ja 120 °C:ssa dimetyyliheksahydroisoftalaateiksi 66 % saannolla. Solvolyysi tuotti seoksen, jossa oli 85 % dimetyyli-isoftalaattia ja 13 % metyylietyyli-isoftalaattia, eli yhteensä 98 %. 140 °C:ssa hydrogenolyysiä tapahtui ja selektiivisyys heksahydroisoftalaattien suhteen oli vain 59 %. Trimetyylitrimellitaatin pelkistys 2 % Ru/C:lla 88–97 bar paineessa ja 120 °C:ssa pysähtyi 39 % konversioon. Ftalidin pelkistys 2 % Ru/C:lla 82–87 bar paineessa ja 140 °C:ssa antoi 46 % saannon heksahydroftalidia, jonka puhtaus oli 65 %. Seoksessa oli lisäksi 4 % heksahydroftalaania ja loppu oli hydrogenolyysi- ja dekarboksylaatiotuotteita.

Dimetyyliftalaatti pelkistettiin sykloheksaani-1,2-dimetanoliksi 84 % saannolla litiumalumiinihydridillä tetrahydrofuraanissa. Suodatus onnistui, kun sammutus tehtiin 1-2-1 -menetelmällä (1, 2, 1 osaa vettä, 20 % NaOH-liuosta ja vettä), mutta epäonnistui, kun sammutus tehtiin pienellä määrällä vettä ja natriumsulfaattidekahydraatilla.

Dimetyyliheksahydroftalaatin pelkistystä sykloheksaani-1,2-dimetanoliksi yritettiin siinä onnistumatta kuparikromiitilla, 2 % rutenium-1.5 % tina-hiilellä ja 2 % rutenium-0.7 % platina-0.4 % tina-hiilellä. Heksahydroftalidi oli tärkein välituote, ja dehydraatio heksahydroftalaaniksi tapahtui helposti. Kuparikromiittia käytettiin 95–98 bar paineessa. Reaktiota tapahtui vain vähän ensimmäisenä 23 tuntina 150 °C:ssa, ja kun lämpötila nostettiin 200 °C:seen 23 tunniksi, lähtöainetta, josta 82 % oli *cis*-isomeeria, oli edelleen 74 % jäljellä. Loppu oli 8 % heksahydroftalidia, 6 % sykloheksaani-1,2-dimetanolia, josta 35 % *cis*-isomeeria, 1.5% heksahydroftalaania, 9 % tuntemattomia ja 1.5 % kevyitä sivutuotteita. RuSn/C:a, joka oli tehokkain katalyytti, käytettiin 84–94 bar paineessa ja 240 °C:ssa. 31 h jälkeen tuloksena oli 38 % kevyitä tuntemattomia aineita, 39 % heksahydroftalaania, 5 % heksahydroftalidia ja 0,2 % *trans*-sykloheksaani-1,2-dimetanolia. Diesterin siis pelkistyi, mutta tuote dehydrautui heksahydroftalaaniksi. RuPtSn/C:a käytettiin 175–230 °C:ssa yhteensä 95 h ajan, mutta reaktio ei edistynyt enää 7 h sen jälkeen, kun lämpötila oli nostettu 230 °C:seen. Lopussa reaktioseos oli 66 % lähtöainetta, 9 % heksahydroftalidia ja 25 % tuntemattomia yhdisteitä.

Foreword

The literature search and experimental part of this work were done at the Perstorp Oy, Porvoo site, from 2 April to 1 October, 2008. Additionally, NMR spectra measurements and database searches were conducted at Helsinki University of Technology facilities.

I present my heartfelt thanks to the instructor, Dr. Tech. Esko Karvinen, and supervisor, Professor Reija Jokela for persistence and interest in the topic and my ideas.

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1 Introduction

Reduction is generally defined as a chemical reaction where an atom gains electrons. In organic chemistry, reduction refers to reactions where hydrogen, a less electronegative element, forms a bond with an atom, reducing its formal oxidation state. Reduction occurs at any element that forms multiple bonds with an identical element or single or multiple bonds with a more electronegative element. Starting materials for reduction are for example alkenes, aromatics and esters, with products being alkanes, cyclohexanes, and alcohols or alkanes, respectively. In this work, polyols are defined as alcohols that have more than one alcohol functional group, including diols and triols.

A reductive approach to polyols is a strategy where reduction is used to transform oxidized and unsaturated compounds into saturated polyols. Reactions that realize this strategy include catalytic hydrogenation, hydrogenolysis and the use of stoichiometric reagents that deliver a hydride equivalent. The reduction can be approached by reducing each type of functional group in a separate reaction step, or in a single step using a bifunctional catalyst.

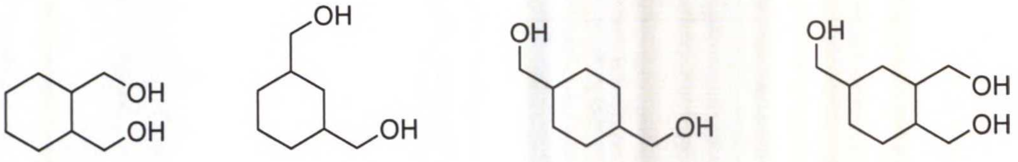
Polyols are speciality chemicals and their industrial applications include solvents in paints, lubricants, monomers for plastics, and production of dimeric or oligomeric ethers. Polyols are esterified with acids to polyesters, such as polyethylene terephthalate; esterified with phosgene to polycarbonates; and reacted with isocyanates to produce polyurethanes. Polyols are derivatized by alkylation to give ethers, or by reaction with epoxides to produce polyether polyols. Some polyols lend themselves to dehydration into cyclic ethers that are polymerized into polyether polyols, such as polytetrahydrofuran, which are derivatized like polyols. Uses for these plastics include elastomers for shoe soles, foams for insulation and for mattresses, adhesives, and elastan (Spandex, Lycra) for clothing. [1] Cyclohexane-1,4-dimethanol, for example, is used as a performance-enchancing additive in polymerization reactions, *e.g.* in polyethylene terephthalate, or as a precursor to chemicals such as flame retardants, antioxidants [1] and plasticizers. [1, 2, 3] Pentaerythritol is a cross-linker monomer in alkyd resins. [1] Sugar alcohols, such as the sweetener xylitol, are also polyols, produced by hydrogenation of the aldehyde function in sugars.

This thesis includes a literature survey of the chemistry of hydrogenation of carbonyl compounds, particularly carboxylates, and aromatic compounds, particularly aromatic carboxylates. Furthermore, practical laboratory scale experiments have been done to test catalysts and to synthesize compounds. Reactions that are studied experimentally are ring hydrogenations with ruthenium on carbon and ester hydrogenations with RuSn, RuPtSn and copper chromite. Ruthenium on carbon was used for the following ring hydrogenations: dimethyl phthalate into dimethyl hexahydrophthalate, followed by reduction into cyclohexane-1,2-dimethanol using lithium aluminum hydride, dimethyl isophthalate into dimethyl hexahydrophthalate, trimethyl trimellitate hydrogenation with low conversion, and phthalide into hexahydrophthalide with only moderate selectivity. RuSn, RuPtSn and copper chromite are tried for ester hydrogenation with variable, but poor results.

2 Literature survey

2.1 Scope

The subject of the investigation is finding syntheses for cyclohexanes bearing two or more methanol groups. In particular, cyclohexane-1,2-dimethanol **1**, cyclohexane-1,3-dimethanol **2**, and cyclohexane-1,2,4-trimethanol **4** are synthesis targets. Cyclohexane-1,4-dimethanol **3** is an analogous compound. For reasons of industrial applicability, catalytic reactions are preferred.



1 **2** **3** **4**

Figure 1. Target polyols.

2.2 Background

There are several routes for the industrial production of polyols, with examples given in Schemes 1–4: [1]

1. 1,2-diols by ring-opening of epoxides, produced by epoxidation of alkenes. (See Scheme 1)

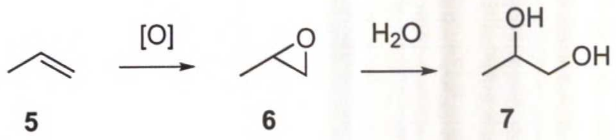
2. 1,3-diols, particularly *β*-methanol alcohols, by aldol addition of formaldehyde to an aldehyde, followed by the reduction of the aldehyde function either by catalytic hydrogenation or by Cannizzarro reaction using excess base and formaldehyde. (See Scheme 2) At equilibriating conditions, aldol addition to the *β* position continues until it has been quaternized.

3. 1,3-diols by hydration of an *α*,*β*-unsaturated aldehyde, followed by catalytic hydrogenation of the aldehyde function. (See Scheme 3)

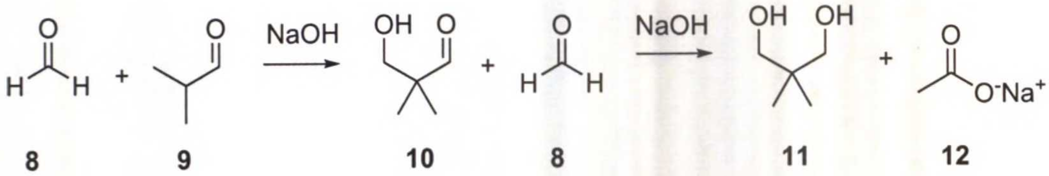
4. 1,3-diols by hydroformylation of epoxides into 3-hydroxy aldehydes, followed by aldehyde hydrogenation. (Scheme 4)

5. Primary diols by catalytic hydrogenolysis of esters, carboxylic acids or derivatives.

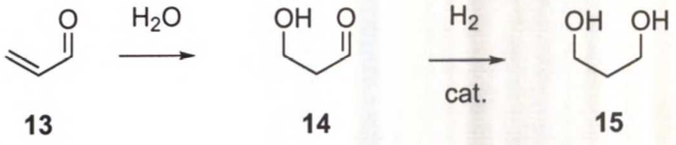
6. Cyclohexanediols by hydrogenation of phenols.



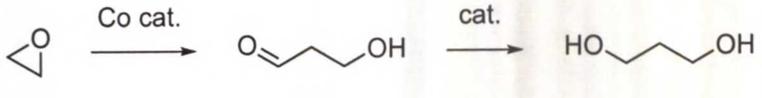
Scheme 1. Production of propane-1,2-diol **7** by epoxidation followed by hydrolysis.



Scheme 2. Production of neopentyl glycol **11** by aldol addition of formaldehyde **8** to isobutyraldehyde **9** followed by a Cannizzarro reaction.



Scheme 3. Production of 1,3-propanediol **15** by hydration of acrolein **13** followed by reduction of the aldehyde **14**.



16 **14** **15**

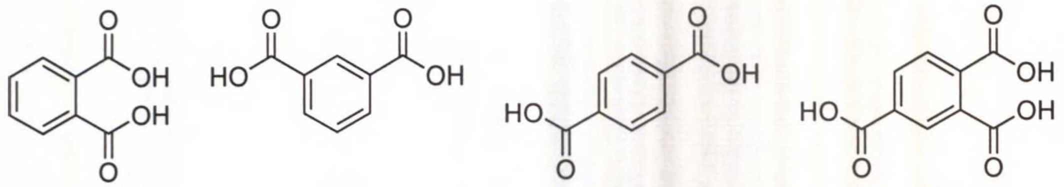
Scheme 4. Hydroformylation of ethylene oxide into 3-hydroxypropanal **14** followed by hydrogenation into 1,3-propanediol **15**.

2.3 Applicable methods

2.3.1 Selection

The targets are all cyclohexanedimethanols or trimethanols. Diol **1** and triol **4** are 1,4-diols, and the isomeric diols **2** and **3** are 1,5-, and 1,6-diols, respectively. Thus, methods relating to 1,2-, or 1,3-diols are not applicable. Similarly, the targets are primary diols, such that methods relating to cyclohexanols or other secondary diols also are not applicable. Thus, catalytic hydrogenolysis of carboxylate derivatives remains.

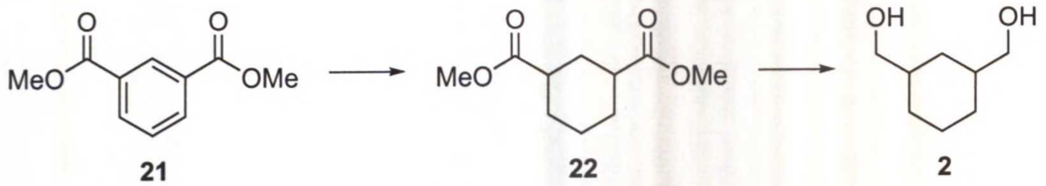
The other functional group in the targets is the cyclohexyl part. Cyclohexyl compounds are industrially manufactured by hydrogenation of aromatics. This leads us to aromatic dicarboxylates, also known as phthalates, as precursors. Phthalic acid has three isomers: *ortho-, meta-, and para*-phthalic acids (**17**, **18**, **19** respectively, Figure 2), commonly known as phthalic, isophthalic and terephthalic acids. Furthermore, trimellitic acid **20** corresponds to the triol **4**.



17 **18** **19** **20**

Figure 2. The three phthalic acids and trimellitic acid.

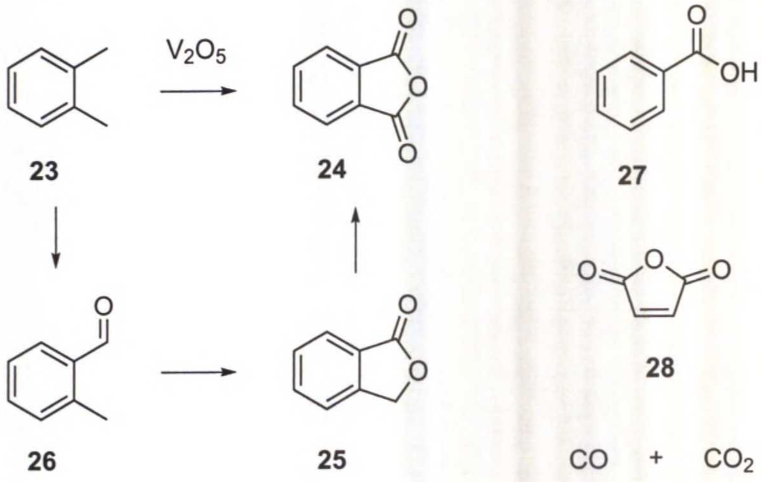
Phthalates and trimellitates are high-volume intermediates that are used as plastic monomers or plasticizers. A reaction sequence that could be used as shown in Scheme 5, where the ring and then the ester groups are hydrogenated in dimethyl isophthalate **21** to give hexahydroisophthalate **22** and then cyclohexane-1,3-dimethanol **2**.



Scheme 5. Example hydrogenation sequence with dimethyl isophthalate **21**.

2.3.2 Manufacture of precursors

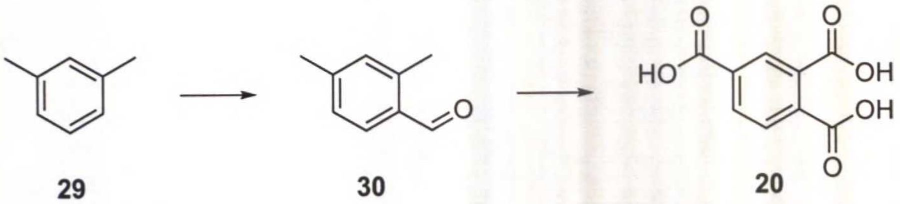
Phthalic anhydride **24** is industrially produced by catalytic oxidation of *o*-xylene **23** on vanadium pentoxide on TiO_2 (Scheme 6). The benzene ring activates the benzylic hydrogens towards oxidation to give water and aromatic carbonyl compounds. Intermediates that are also found as byproducts include phthalide **25** and *o*-tolualdehyde (**26**). Destructive oxidation produces benzoic acid **27**, maleic anhydride **28**, CO and CO_2. The selectivity is 70–80% to phthalic anhydride **24**. [4] In the production of aromatic esters for plasticizer applications, full oxidation to an anhydride is necessary. To produce the corresponding diol, the reaction could be stopped to the phthalide stage.



Scheme 6. Oxidation of *o*-xylene.

Xylene oxidation is also used for the production of isophthalic acid from *m*-xylene and terephthalic acid from *p*-xylene. Terephthalic acid can also be produced by disproportionation of potassium benzoate. [4]

Trimellitic anhydride is also produced by oxidation (precursor pseudocumene *i.e.* 1,2,4-trimethylbenzene), but Mitsubishi has a process where the third carbon is added by formylation (Scheme 7). Dimethylbenzaldehyde **30** is produced by a reaction of *m*-xylene with CO, catalyzed by HF/BF_3. The methyls are then oxidized to give trimellitic acid **20**. [4, p. 378] The challenges of hydrogenation remain similar.

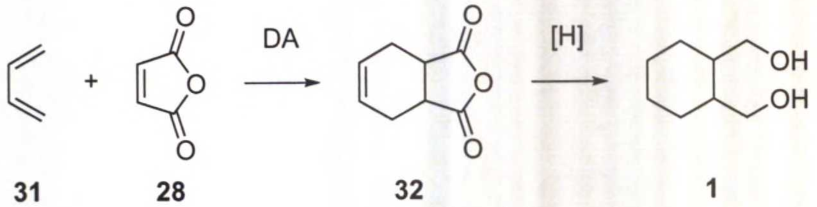


Scheme 7. Trimellitic acid production by *m*-xylene formylation.

2.3.3 Alternative Diels-Alder strategy

2.3.3.1 Hexahydrophthalyl alcohol

Diol **1** could be made by a Diels-Alder reaction of butadiene with a 2,3-unsaturated 1,4-dioxygenated compound. Indeed, an alternative strategy is to form the cyclohexane by Diels-Alder reaction of butadiene **31** and maleic anhydride **28**, followed by reduction of the alkene and the anhydride functional groups to give a fully saturated diol (Scheme 8). The alkene would be hydrogenated with *e.g.* platinum [5] [6] and the anhydride with *e.g.* nickel [7] or promoted palladium or ruthenium. [8]



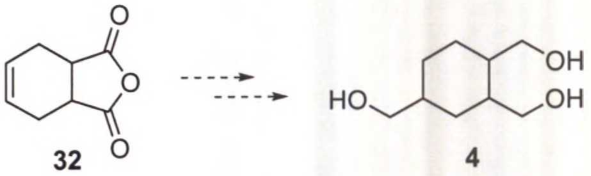
Scheme 8. Diels-Alder reaction of butadiene followed by hydrogenation.

This Diels-Alder reaction is used industrially. Butadiene is one of the products from the steam cracking process and a common intermediate in petrochemical processes, and maleic anhydride is produced by oxidation of n-butane. The produced tetrahydrophthalic anhydride **32** is used as a monomer. [4]

The highly oxygenated starting material maleic anhydride is necessary, because in an ordinary Diels-Alder reaction such as this, the diene has to be electron-rich and the dienophile electron-poor. The alkene bond in maleic anhydride has two carbonyls that make it electron-poor and thus an effective dienophile. The oxygenation, however, comes at a cost of hydrogen consumption in the overall process to manufacture a diol. In effect, n-butane would be oxidized to a dicarboxylate and then reduced.

2.3.3.2 Hexahydrotrimellitic alcohol

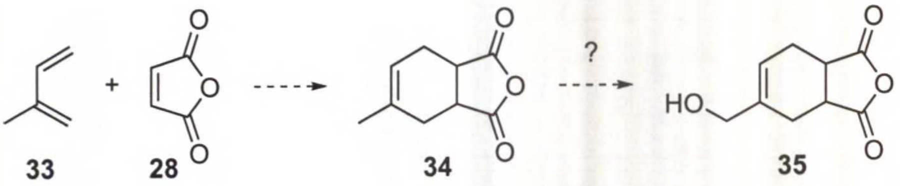
For triol **4**, the same intermediate **32** could be used, if the alkene was hydroformylated and the carbonyls reduced (Scheme 9).



Scheme 9. Hydroformylation of Diels-Alder product, hydrogenation to alcohol.

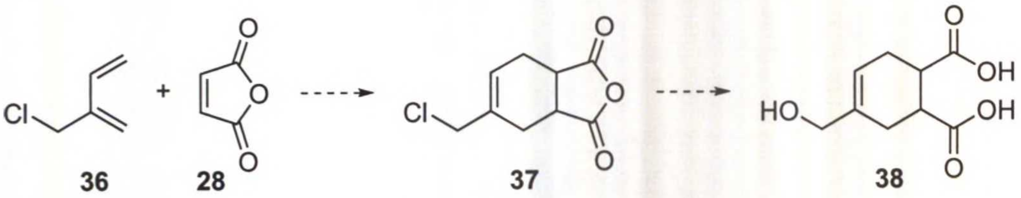
Another possibly Diels-Alder route to **4** is the use of isoprene **33** as the ultimate precursor, analogously to butadiene in Scheme 8. Isoprene is a common industrial chemical, produced from C_1–C_4 petrochemicals or by cracking of naphtha and used mainly to produce synthetic rubber. [9]

However, the synthesis of precursors and reduction to a diol will not be so straightforward. The first route (Scheme 10) would start with maleic anhydride **28** and isoprene **33** to give a methylcycloalkene **34**, after which the allylic methyl would be oxidized to give the alcohol **35**. However, the allylic methyl is not as favorably activated as a methyl conjugated with an aromatic ring, and there are also two allylic positions on the ring that are subject to oxidation. Quantitative oxidants with homogeneous catalysts would be necessary to oxidize directly into the alcohol oxidation level. These methods suffer from toxicity of the metals, stoichiometric oxidants or nongenerality, thus they are unlikely to scale up. [10] Furthermore, all of the methods are selective towards oxidation at the ring – including molecular oxygen. [11] Hydrogen peroxide will not give the desired alcohol either. [12]



Scheme 10. Route 1: Diels-Alder, then allylic oxidation of a methylcyclohexene

The second route (Scheme 11) would start with an oxidized isoprene, such as an organochloride. Oxidation should occur before the Diels-Alder reaction, because allylic oxidations of cyclohexenes have the precisely opposite selectivity than desired, *i.e.* the ring position is oxidized. A possible process would be to chlorinate isoprene to chloroisoprene **36**, perform a Diels-Alder reaction with maleic anhydride **28** and hydrolyze the resulting allyl chloride **37** to the alcohol **38**. Incidentally the anhydride would also be hydrolyzed, but it could be for example esterified with excess methanol and then hydrogenated. The opposite order, hydrogenation of anhydride before hydrolysis, would probably suffer competetive dehydrochlorination. Again, there would be a quantitative oxidant, chlorine, but this chemistry is more likely to scale up. Selective chlorination of isoprene is a patented process and the patent mentions use as a monomer. [13] Also, allyl alcohol is analogously produced from allyl chloride for industrial uses. [14]



Scheme 11. Route 2: Diels-Alder reaction of chloroisoprene and hydrolysis of the organochloride.

2.4 Hydrogenation and hydrogenolysis

Catalytic hydrogenation adds hydrogen into an unsaturated compound and converts alkenes into alkanes, aromatics into cyclohexanes and aldehydes into alcohols. The reaction requires a catalyst and possibly high pressures and elevated temperatures, depending on the catalyst and the substrate, and may be run with reagents in the gas or liquid phase. Reduction of aromatics requires a particularly active catalyst. Catalysts used are transition metals, especially platinum metals, such as platinum, palladium, rhodium, ruthenium, and nickel. The metals can be used as is or dispersed onto a support material. Although hydrogenations are usually conducted at elevated temperatures and pressures, the reaction does not thermodynamically require this, and by using a large amount of active catalyst, hydrogenations occur even at ordinary conditions.

Catalytic hydrogenolysis, while occurring in similar conditions to hydrogenation, cleaves a carbon-carbon or carbon-heteroatom bond. The term was first mentioned by Carleton Ellis referring to C−C bond cleavage, and applied to esters by Homer Adkins. [15] The catalytic conversion of a carboxylate derivative, such as ester, lactone, acid or acid anhydride, into two alcohols is a "lysis" by hydrogen, *i.e.* hydrogenolysis, but is usually called hydrogenation. Catalysts used for reduction of esters are copper, promoted copper such as copper-zinc, copper-manganese and especially copper chromite, rhenium, ruthenium-tin, and platinum-tin, or trimetallic combinations such as platinum-ruthenium-tin or platinum-rhenium-tin. The reaction is operationally similar to hydrogenation but requires more severe conditions.

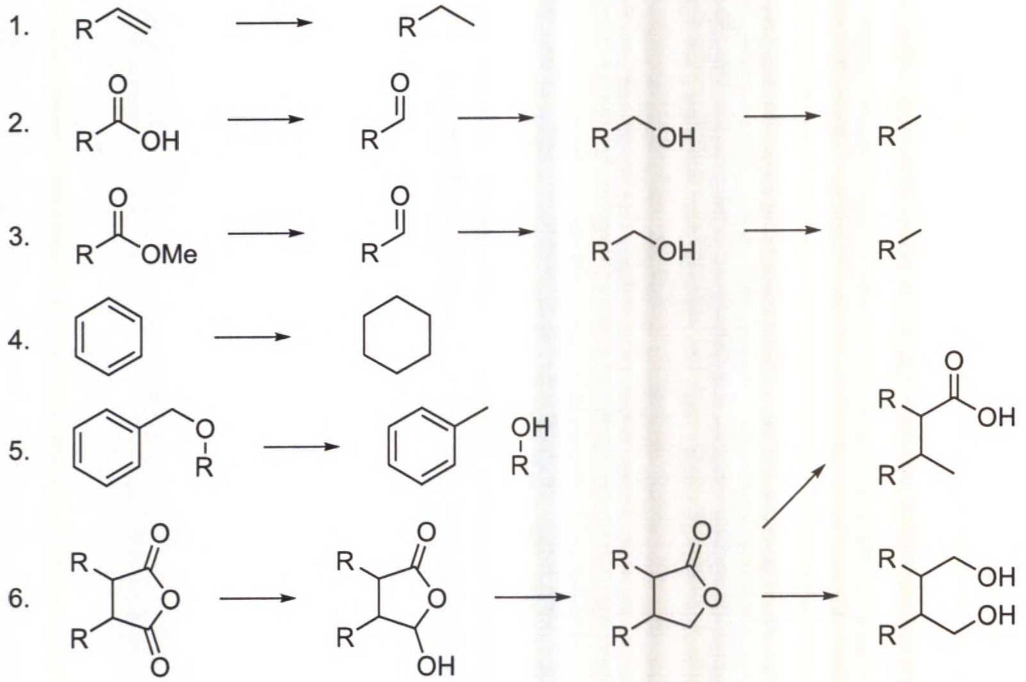
Hydrogenolysis also occurs to alcohols, which give alkanes. The precise name for this reaction is hydrodeoxygenation, but is commonly referred to as hydrogenolysis. Hydrodeoxygenation is an undesirable side reaction when the alcohol is the intended product.

Hydrogenation was pioneered by Sabatier with a gas-phase reduction on nickel and copper. [16] Ipatieff performed the first liquid-phase hydrogenation of aromatics, and incidentally also attempted hydrogenation of phthalic anhydride. [17] Adkins developed the hydrogenolysis reaction of esters with copper chromite, [18, 19] a material first described by Gröger in 1908. [20] Adams developed the Adams catalyst, PtO_2 reduced *in situ*, and with this catalyst, it was discovered that the rate increases with pressure. [21]

2.4.1 Substrates and products

Hydrogenation applies to varied unsaturated groups, for example nitriles give amines, but the following (Scheme 12) are within the scope of this work:

1. Alkene → alkane
2. Carboxylic acid → aldehyde → alcohol → alkane
3. Ester → aldehyde → alcohol → alkane
4. Benzene → cyclohexane
5. Benzyl ether → toluene + alcohol
6. Cyclic anhydride → hemiacylal → lactone → dimethanol / hydrogenolysis



Scheme 12. Hydrogenations of alkenes, carboxylates, esters, aromatics and acid anhydrides.

Although all of these reactions occur under hydrogenation conditions, the same functional group can undergo three kinds of reactions: hydrogenation, hydrogenolysis, and hydrodeoxygenation. The simplest example is the hydrogenation of an alkene (1). The hydrogenations of carboxylic acids (2) and esters (3) cleave a carboxylate into an alcohol and alcohol or water, and are thus called hydrogenolysis reactions. They go via an aldehyde intermediate that is easily hydrogenated further. Aromatics are usually hydrogenated directly to cyclohexane (4). The hydrogenation of an alcohol is also a hydrogenolysis that can be called hydrodeoxygenation. Benzylic positions are strongly activated towards hydrodeoxygenation (5). Cyclic anhydrides are somewhat analogous to acids, but are readily half-reduced into hemiacylals [22] and then lactones, which are more difficult than other esters to hydrogenate further to diols (6). Lactones can undergo a side reaction that is another kind of hydrogenolysis: the cleavage of the C–O bond in the alcohol moiety of the ester, *e.g.* phthalide into *o*-toluic acid. [23]

2.4.2 Sensitivity to hydrogenation

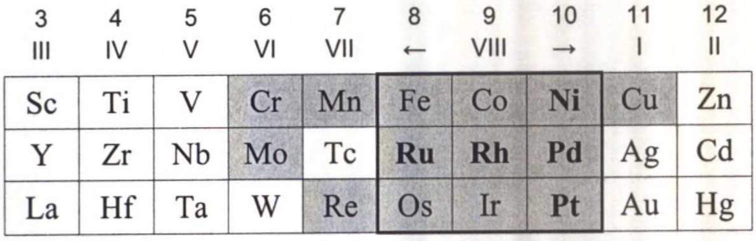
The precise ordering of hydrogenation reactivity depends on the catalyst, but an approximation is:

aldehyde > alkene > ketone > benzyl alcohol > ester > aromatics

Thus, for example, conditions that promote ester hydrogenation usually reduce the intermediate aldehyde. However, different catalysts have different selectivity. Benzylic alcohols are readily hydrogenolyzed by palladium but not platinum, rhodium or ruthenium. [24, p. 624] Carboxylic acids are also more difficult to hydrogenate than esters, but this is catalyst-dependent: for example, ruthenium under high pressure reduces acids but not esters.

2.4.3 Catalysts

In general, industrial hydrogenation is catalyzed by transition metals, particularly from the platinum group.



3	4	5	6	7	8	9	10	11	12
III	IV	V	VI	VII	←	VIII	→	I	II
Sc	Ti	V	Cr	Mn	Fe	Co	**Ni**	Cu	Zn
Y	Zr	Nb	Mo	Tc	**Ru**	**Rh**	**Pd**	Ag	Cd
La	Hf	Ta	W	Re	Os	Ir	**Pt**	Au	Hg

Figure 3. Transition metals with platinum metals highlighted, with active hydrogenation catalysts shaded and the most used catalysts in bold.

The metals nickel, ruthenium, rhodium, palladium and platinum are particularly useful. Other metals have lower activity and require more forcing conditions. Iridium, iron, cobalt and osmium are rarely used and are confined to special applications. Other transition metals with notable hydrogenating activity are copper, chromium, rhenium, molybdenum and cobalt. Copper has a low activity but good selectivity. Copper chromite is a catalyst that is used to reduce esters to alcohols. [25] Rhenium is an expensive precious metal that has also some, but not exclusive selectivity towards carbonyls. [26] Metal catalysts can be homogeneous or heterogeneous. Heterogeneous catalysts are preferred in large-scale industrial settings, because separating and recycling a homogeneous catalyst introduces complications with separation of the catalyst from product.

2.4.3.1 Platinum

Platinum is an active catalyst that is actually promoted by exposure to oxygen. [27] Platinum is also compatible with acidic conditions. Adams developed a platinum oxide catalyst (PtO_2, Adams platinum [27, 28, 29]) that reduces into platinum *in situ*. [25] Effectively, the oxide is the support and promoter for the formed platinum black. Oxygen promotes the catalyst. [29] Adams' catalyst was previously in common use in organic synthesis. Platinum is an expensive precious metal.

Platinum hydrogenates various groups such as aromatics, [27] anhydrides, alkenes and ketones. [30] In the laboratory, with an excess of catalyst, low temperatures and pressures (<70 °C and 3–4 atm [31]) are sufficient. Increasing the pressure to 70–120 atm hydrogenates aromatics rapidly. Aromatic hydrogenation requires an acidic environment. The solvent can be AcOH or EtOH acidified with HCl or other acids. [32] Platinum is promoted by Lewis acids such as $FeCl_2$ and $SnCl_2$ and poisoned by reduced sulfur.

Platinum does not hydrogenate acids or esters. [31] Pt does not cause benzylic hydrogenolysis, and olefin isomerization is only slight. [30]

2.4.3.2 Palladium

Palladium has lower activity, but also a lower cost. Its activity towards aromatic hydrogenation is low, but despite requiring high pressures, Pd is used industrially for ring hydrogenation. [4] Pd reliably hydrogenolyzes benzylic ethers. Indeed, in the laboratory, Pd/C is used to remove benzylic ether protecting groups. Pd also isomerizes alkenes. It does not hydrogenate carboxylates. [33] Pd requires no activation and is in fact deactivated by the formation of the non-stoichiometric interstitial compound palladium hydride. [34]

2.4.3.3 Rhodium

Rhodium is an active precious metal catalyst commonly used for aromatic hydrogenation. Its activity towards aromatics is specific — it is less reactive towards alkenes. Rh causes very little hydrogenolysis, for example aromatic ethers are ring-hydrogenated. [31] Acids can be hydrogenated as a side reaction at ordinary conditions and quantitatively with RhO_2 at 138 bar and 150 °C. [35] The 3:1 mixture of RhO_2/PtO_2 (the Nishimura catalyst [36]) is a better catalyst for aromatic hydrogenation that Rh alone; it is five times more active. [37] Rhodium can be dispersed on a support or tethered. [38]

2.4.3.4 Nickel

Nickel is a base metal that is often used as massive metal, without a support. Nickel hydrogenates various groups such as anhydrides, aromatics, alkenes and ketones. [39] At very high pressure (350 atm) it can hydrogenate acids and esters. However, nickel also has hydrogenolyzing activity, and benzylic compounds give toluene. [39]

Raney nickel (RaNi) is a form prepared by reacting nickel-aluminum alloy with sodium hydroxide, which removes most of the aluminum, leaving fine grains of nickel-aluminum alloy. Several grades of RaNi are produced with different activity (W1–W8, see [31, p. 243]) by different preparation methods. Since different phases are produced by different Ni/Al ratios, different reactivities with sodium hydroxide and thus different porosities result. Urushibara nickel is produced by reducing a nickel chloride solution with zinc (or aluminum) dust, then digesting the precipitated nickel with acid, alkali, or both. [31]

2.4.3.5 Ruthenium

Ruthenium is a precious metal that is useful for selective aromatic hydrogenation and also for carbonyl compounds. Characteristically ruthenium requires a high pressure (up to 150 atm) for sufficient hydrogen adsorption. Ru also requires activation by heating in hydrogen, typically overnight. The activated catalyst cannot be stored, because the activity lasts for a day, according to literature. [40] However, it has a good selectivity for hydrogenation of compounds sensitive to hydrogenolysis. [30] For example, phenols give cyclohexanols without hydrodeoxygenation into cyclohexane. [31] Ruthenium also hydrogenates carbonyl compounds, such as ketones, aldehydes and at high pressures, carboxylic acids. Water is a promoter for ruthenium; [41] even alkenes insoluble in water are hydrogenated faster. [31] Heterosubstituted [42] and benzylic compounds are selectively reduced by ruthenium (as *e.g.* RuO_2). [43] Ru/Al_2O_3 can be regenerated by heating in nitrogen. [44]

2.4.3.6 Rhenium

Rhenium is a rare precious metal that is selective in reduction of acids and esters. However, branched-chain acids are difficult to hydrogenate. [31] It has only moderate activity towards groups easily reduced by platinum or nickel. [26] As a catalyst, rhenium is used as rhenium heptoxide Re_2O_7 reduced *in situ*. Rhenium has a high selectivity towards esters and low hydrogenolysis activity. For example, ethyl benzoate is hydrogenated into benzyl alcohol, avoiding the benzylic hydrogenolysis of the product to toluene. [26]

Both rhenium and its oxides can function as hydrogenation catalysts. The catalytic species is rhenium black in EtOH or dioxane, and ReO_2 in H_2O or AcOH. Prereduction in EtOH or dioxane gives coarse rhenium black, AcOH gives partly colloidal black, but H_2O gives shiny flakes with low activity. Prereduction can be seeded with ruthenium or platinum (0.01 equivalents). [26]

Smith Broadbent systematically screened the compounds of rhenium: Re_2S_7, [45] ReS_2, [45] Re_2Se_7, [46] Re_2O_7, [26] Re_2O_3, [47] $Re_2O_7 \cdot$tetrahydropyran, [48] $ReO_2 \cdot 2\frac{1}{2} H_2O$, [49] ReO_3, [50] $ReO \cdot 2 H_2O$, [51] and found that Re_2O_7 is best. Re_2S_7 is slow to hydrogenate aromatics and causes hydrogenolysis, [45] ReS_2 is not any better, [45] Re_2Se_7 is not an improvement either, [46] Re_2O_3 is similar to Re_2O_7, [47] and $ReO \cdot 2 H_2O$ hydrogenolyzes benzyl alcohol to toluene. [51] However, Re_2O_3 (rhenium(VI) oxide) non-hygroscopic and not air sensitive, but otherwise like Re_2O_7. [50] In the original study, it did not reduce aromatics, but did not cause hydrogenolysis either. Tetrahydropyran and rhenium heptoxide form a solid complex, which hydrogenates aromatics, unlike other forms of rhenium. [48]

2.4.3.7 Other metals

Other metals with hydrogenation activity (see Figure 3), or iridium, iron, cobalt, osmium, copper, chromium, manganese and molybdenum have lower activities and are rarely used. Catalysts with low activity may be useful for their selectivity, however. For example, iridium promoted by Fe^{3+} or Ge^{4+} is selective towards the hydrogenation of the aldehyde function in α,β-unsaturated aldehydes, *e.g.* citral into geraniol and nerol (isomeric allylic alcohols). [52] The iron(III) functions a Lewis acid promoting carbonyl hydrogenation. Iridium on TiO_2 also catalyses the same transformation as a transfer hydrogenation of isopropanol at a 47-60% selectivity. [53]

Nickel(II) compounds $NiCl_2$ and NiB_2 are rather inactive. [54] Also, iron functions as a catalyst for alkene hydrogenation, but is of little interest in this case. An iron compound, *e.g.* $FeCl_2$, is activated with reagents such as $LiAlH_4$, DIBALH or ^{s}BuLi. [55, p. 61] It has a low activity, and will not necessarily hydrogenate dienes. More importantly, electrophiles such as ketones, nitriles, imines or nitro groups react with the activation reagent or activated catalyst, rendering the catalyst inactive.

[55, p. 65] This implies a lack of activity in aromatic ester hydrogenation.

2.4.4 Catalyst modifiers

Catalysts can be modified by bases, Lewis acids, and metals with specific activities. Iron and tin are examples of Lewis acids that promote carbonyl hydrogenation. For example, the addition of Sn produces catalysts like RuSn and PtSn that are selective towards hydrogenation of carbonyls (carboxylic acids, anhydrides, esters and lactones). [16] However, tin may occur as a metal and thus the catalyst is discussed as a multimetallic catalyst (section 2.4.5.4, p. 20).

Iron and tin also reduce catalyst poisoning in the hydrogenation of aldehydes with Pt. [30] Iron as $FeCl_2$ is known to reduce alcohol hydrogenolysis on platinum. [56]

Platinum catalysts are usually produced by reduction of chloroplatinic acid (H_2PtCl_6). However, acidic residues remain; it is very difficult to reach halogen levels lower than 0.1%. Addition of a base, such as Li_2O, to the mix can suppress side reactions caused by acids. [57]

2.4.5 Bimetallic and multimetallic catalysts

Bimetallic catalysts are used in for example reforming (PtRe) or in ring hydrogenation (Nishimura's RhPt [36]). Although multimetallic catalysts are widely used, it is difficult to find information on them on the open literature, [58] except for patents, which are strictly technical and contain the minimum of scientific analysis.

Addition of an inert metal paradoxically increases the activity of the main metal and decreases hydrogenolysis activity, for example, gold in PtAu or PdAu and copper in NiCu. [59, 16, 60] The metals can also have complementary roles in reducing reaction intermediates and removing poisons and coke, [16] or protecting the catalyst from oxidation, as with ruthenium-copper. [60]

For example, a pyridine derivative was hydrogenated with a RhPd catalyst (0.5% Rh, 4.5% Pd) with better activity and *cis*-selectivity than either metal alone. Similar synergy has been observed in PdRu, PtRu, NiPt, and PtPd. PdRu has 10 times the activity of Pd in butynediol hydrogenation. PtRu is optimal at 1:1 atomic ratio for benzene hydrogenation. PdPt is more resistant to sulfur poisoning than Pd or Pt. [16]

Not all metal pairs, however, form solid solutions, and if they do, not necessarily in all mixing ratios. Even if coprecipitated, they may occur separately or layered on the support. Complete formation of an alloy, which has different electronic properties, occurs only with selected metal pairs. Rather, alloys often form incompletely or not at all. However, the formation of an alloy is not necessary to change selectivity or activity. The second metal may block sites on the surface [60] or change the dispersion of the parent metal, *e.g.* PtRe. [61] The second metal changes the electron density of the active site, which can be compared to the modification of electronic properties of complexes by different ligands. [60]

In "true" multimetallic catalysts, the metals occur on "clusters", *i.e.* sites with multiple different atoms. In a cluster, the electronic environment and thus the chemistry is changed by the interaction of the metal atoms. The concept of a cluster, a site consisting of a few atoms, is different from an alloy in bulk, as metals that do not form an alloy in bulk may form clusters. Coprecipitation or sequential precipitation forms clusters, which are chemically and electronically different from the same atoms occurring in separate crystals. Physically mixing two catalyst preparations produces a different result. Dispersion has also an effect, *e.g.* with Ru particles, deactivation by Cu occurs less readily on smaller particles. [60]

Metals can be precipitated together or in a specific order. In some cases, this affects their performance. This is consistent with the observation that individuals sites are responsible for catalysis. If a metal modifies a site, then it also modifies reactivity. Particularly, it has been found that tin has to be precipitated with or on platinum. [58]

2.4.5.1 Copper chromite

Copper chromite is a complex compound containing copper, chromium and oxygen and in industrial use, it is typically promoted by barium oxide. The barium reduces poisoning by sulfate and reduction of the catalyst. [62] It can contain other modifiers such as silica, but is essentially unsupported catalyst. It is used in the oxidized form.

Characteristically copper chromite is entirely inactive towards alkenes, but reduces esters. However, it requires high pressures and temperatures, up to 350 atm and 300 °C. [25] It is a well-known and reliable catalyst. The compound was described by Gröger in 1908, [20] and as a catalyst by Adkins in 1931. [18, 19]

2.4.5.2 Platinum-rhenium

Platinum-rhenium (PtRe) is of interest in catalytic reforming, an industrial process rather different from hydrogenation. Catalytic reforming occurs at high temperatures and the main reactions are isomerization into cyclohexanes and their dehydrogenation into aromatics. However, the dehydrogenation of cyclohexanes is the reverse of aromatic hydrogenation, and a catalyst must catalyse the reverse reaction equally. [63] Methylcyclohexane dehydrogenation has been used as a model reaction for reforming. [61] Thus, research concerning PtRe is relevant to hydrogenation.

Platinum and rhenium are not mutually soluble in bulk. [60] In the PtRe catalyst, Pt, Re and PtRe alloy are all present. However, Pt and PtRe have the same activity and Re has no activity in methylcyclohexane dehydrogenation. Thus, unit activity is not increased. However, the area of PtRe is larger than that of Pt; Re disperses the metal particles. [61] Re in PtRe does not adsorb hydrogen, only carbon monoxide. In activation, Pt is reduced to a metal, but in the presence of water, Re is found mainly as rhenium(IV) oxide (ReO_2). By removing water at 400–450 °C, Re is also reduced to the metallic form. [60]

In catalytic reforming, coking of PtRe is less severe than with Pt alone. In the dehydrogenation of methylcyclohexane, when there is no hydrogen to hydrogenolyze coke, Pt loses half of its activity in 1 h and is completely coked in 6 h. For PtRe, half-life is 12 h and even after 24 h, PtRe still has about 20–25% of its activity. The resistance to coking is explained by two main reasons. The first reason is the inertness of Re, which, unlike Pt, is not complexed strongly to methylcyclohexane. In PtRe, the Pt sites are separated as islands, which inhibits the formation of polymer mats on the metal. Secondly, Re has a high hydrogenolytic activity, unlike Pt. [61] In industrial conditions, there is a low pressure of hydrogen in the stream to inhibit coking.

There are also patent by Pollitzer (1970 and 1975) about platinum-rhenium as a hydrogenation catalyst. [57, 64] Rhenium significantly helps with aromatic hydrogenation: activity increases, coking decreases and poisoning by sulfur is reduced. Lithium oxide is also added to suppress the effects of acidic residues left from the reduction of H_2PtCl_6. In the patent examples, alumina is used as the carrier in hydrogenation of benzene.

2.4.5.3 Platinum-rhenium-tin

A further development is the trimetallic catalyst ReSnPt with a lithium oxide promoter, for aromatic hydrogenation. An example composition is 0.5% Sn, 0.25% Re, 0.375% Pt, 0.5% Li. [65] It appears that the coke is deposited on SnO, not the noble metal. The tin has to be deposited after the platinum, or it does not slow deactivation. The best order is Pt-Sn-Re; in contrast, Pt-Re-Sn does not work. [58]

2.4.5.4 Ruthenium-tin

Ruthenium-tin (RuSn) has a different selectivity than Ru itself: RuSn hydrogenates esters and acids. RuSn was described by Deshpande *et al.* in 1990 [66] and by Mizukami in 1992. [67] Mizukami used the sol-gel method, and also found that chloride decreases selectivity. Tahara impregnated the metals by regular methods, and hydrogenated abietic acid at 98 bar and 260 °C. [68]

Tin(II) does function as a Lewis acid, because adding $SnCl_2$ to the reaction mixture produces the same result as coimpregnation. [69] However, the role of tin is more complex than this. Tin specifically blocks sites that promote alkene hydrogenation. [69] The tin precursor affects the yield. Tin(II) chloride ($SnCl_2$) resulted in only 53% selectivity and 42% yield, but stannates (K_2SnO_3, $NaSnO_3$) gave 81–88% conversion and 95% selectivity at the same conditions. [68] Chlorine prevents tin from being reduced to a low valent state. Hara and Endou found that platinum — to give the trimetallic PtRuSn — reduces tin (even as chloride) and also drastically increases the rate. [70] Hara also reduced terephthalate to 1,4-cyclohexanedimethanol at 85 bar and 230 °C with RuPtSn/C.

2.4.5.5 Platinum-tin and platinum-iron

The effect of tin on platinum and palladium is the same as that on ruthenium. Platinum-tin is selective towards carbonyls, platinum towards alkenes. A small amount of tin increases reactivity, but at 1.2–1.3 equivalents of Sn per Pt, platinum is deactivated. [71] As before, tin increases the electron density of platinum. [72] To prepare PtSn, it is best to impregnate the tin compound in the absence of air. A Pt-Sn complex is formed, which process is evidently disturbed by oxygen. A dehydrocyclization catalyst prepared in air deactivates 2–3 times faster than a catalyst prepared under inert gas. [73]

Platinum is promoted also by iron for carbonyl hydrogenation. Iron(III) as $FeCl_3$ increases the rate and reduces deactivation. The mechanism is that aldehydes oxidize platinum, and iron inhibits this reaction. [74]

2.4.6 Supports and catalyst preparation

Catalysts can be used as is or on a support, and they can be prepared in different manners that affect reactivity. Modern industrial catalysts are usually on a support, with Raney nickel and copper chromite as noteworthy exceptions. The specific surface area of a catalytic metal is increased by dispersion onto a support. [16]

Generally, the dispersion of a catalyst onto a support increases its specific activity. The reactions occur preferentially on coordinatively unsaturated, irregular sites, denser in smaller particles. [16] The smaller the metal loading is, the smaller the crystallites, and the higher the specific activity. For example, palladium black has an area of 5–10 m^2/g, but 10% palladium on carbon has 100-200 m^2/g. The area increases exponentially with decreasing metal loading. The metal is also stabilized by the support. [30]

Dispersion also affects the selectivity of the catalyst. Hydrogenation is not very sensitive to particle size; it can be changed by an order of magnitude without affecting the rate of benzene hydrogenation. However, hydrogenolysis activity is higher on larger particles. [60] Thus, hydrogenolysis is best avoided by using smaller particles, and avoiding calcination that causes sintering.

The surface atoms of a metal become mobile at temperatures far below the melting point. [63] Heating of a catalyst changes its surface structure and may be behind the necessity to activate for example ruthenium by heating under hydrogen.

2.4.6.1 Unsupported catalysts

Originally catalysis was observed on a metal mesh, which has a very low surface area. Colloidal metals were also previously used, but this method is obsolete. [30] Another old method is the preparation of a metal black, a fine precipitated powder, which is still used in some specific cases. Platinum black and reduced platinum oxide were previously much used. Palladium black is another example. [16]

Since only the surface reacts, it is preferable to maximize surface area. In massive metal, most of the metal does not contribute to catalysis. This becomes expensive with precious metals. However, unsupported base metal catalysts are still in wide industrial use. Relevant examples are Raney and Urushibara nickel and copper chromite.

2.4.6.2 Supported catalysts

The most common method of catalyst preparation is to disperse it onto a support as microcrystalline metal particles. A support is a porous material with a high surface area. Commonly used supports are carbon, alumina, and silica, and special supports include zeolites, titania, zirconia, calcium carbonate, barium sulfate, molecular sieves, carbon molecular sieves, polymers and organic materials (e.g. nylon and silk). [16] The metal is added by impregnating the support with a metal salt solution and reducing the metal, either with hydrogen or other methods.

The choice of support affects the selectivity of the catalyst. This is because the area and the tortuosity of the support affects the rate of diffusion. A high surface area increases activity. A low surface area decreases the residence time of the reactants, which is important when the products may react further. In this case, a high surface area can lead to increased hydrogenolysis of product alcohols. Another disadvantage of porous supports is that they are susceptible to pore plugging caused by the formation of polymeric products, which can deactivate the catalyst severely. [16]

The size of pores also affects performance. Micropores (< 2 nm), mesopores (2–50 nm) and macropores (>50 nm) are distinguished. [16] The size of micropores is comparable to the size of molecules. Scarlett (see section 2.6.4.2, p. 50) claims in a patent that catalysts with macropores are better for ester hydrogenation than catalysts with mesopores, with other variables such as microporosity and surface area being controlled. [75]

Acidic supports, such as alumina, increase the hydrogenation rate of unsaturated hydrocarbons on platinum or palladium. [16] This is similar to the general promoting effect of Brønsted acids on aromatic hydrogenation.

Carbon has a high surface area (500–1000 m^2/g). [30] Carbon is supplied as a powder or granules, and is activated by oxidation with an oxidizing atmosphere or an oxidizing acid. Carbon is often used with precious metal catalysts. A low loading can be impregnated onto granular carbon, but with higher loadings, the result is a powder. Carbon-supported precious metals are easy to recycle by burning the carbon off. Carbon has the disadvantages of high-area supports mentioned above.

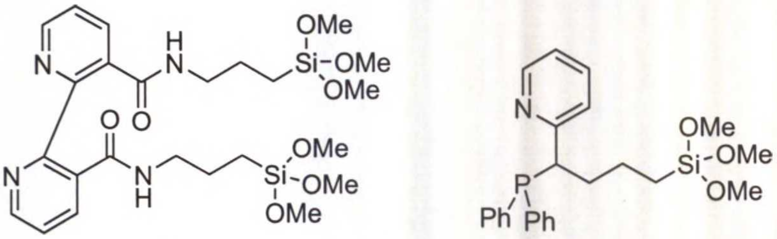
Alumina (Al_2O_3) has a lower surface area (75–350 m^2/g). [30] Alumina occurs in various phases, particularly α-, and γ-alumina. γ-alumina is hygroscopic and soluble to strong acids and bases. In contrast, α-alumina, also known as corundum, is generated by heating into 800–1000 °C, and is only very slightly soluble in acids and bases. Activated alumina is obtained by heating the material to dehydrate it. Alumina is a Lewis acid, and also functions as a Lewis acid catalyst in high-temperature reactions such as reforming. It is best used in processes where the reactants are gases, because alumina leaches easily into liquid phase with the help of acids or chelating ligands. The resistance of alumina can be increased by changing the crystal structure into an insoluble spinel. This has been patented for phthalic ester hydrogenation. [76]

Silica (SiO_2) has an area similar to alumina (100–300 m^2/g), [30] and has the advantage over alumina that in hydrocarbon hydrogenation, polymerization is reduced. Silica is also acid-resistant. Titania (titanium dioxide, TiO_2) and zirconia (zirconium dioxide, ZrO_2) are similar, also stable to acid and chelating ligands and not sensitive to pore plugging. [16]

Calcium carbonate ($CaCO_3$) is a basic material with a low surface area, and it prevents C−O hydrogenolysis. Another example of a low surface area material is barium sulfate ($BaSO_4$). $BaSO_4$ is used in the Rosenmund reduction, which is a synthesis of aldehydes from acid chlorides catalyzed by palladium on $BaSO_4$. $BaSO_4$ poisons the palladium and has a low surface area. Additionally, the catalyst is poisoned by pyridine, reducing its activity further.

2.4.6.3 Tethered homogeneous catalysts

Heterogeneous catalysts are preferred, because they have a higher stability and lower cost, and homogeneous catalysts suffer from ligand degradation, ion leakage and complications in the separation of catalyst and product, and their activity is low. Tethering a homogeneous catalyst (tethered catalyst on supported metal, TCSM) has been applied by Angelici *et al.* for terephthalate ring hydrogenation at mild conditions, 4 atm and 70 °C. [38] Angelici's catalyst comprises a Pd/SiO_2 catalyst, where a rhodium complex has been tethered. The chelating ligand is either the bipyridyl **39** or the pyridylphosphine **40** with an organosilicon group (Figure 4). The organosilicon is reacted with the silanol groups on a silica surface, tethering the ligand onto the surface.



39 **40**

Figure 4. Tethering ligands for Angelici rhodium.

The catalysts are 10–32 times more active than either the rhodium complex or heteregeneous palladium alone — the specific activition requires both. The palladium possibly activates the rhodium complex because it adsorbs atomic hydrogen. For dimethyl terephthalate ring hydrogenation, the turnover frequency was 76 mol/mol Rh/h with pyridylphosphine and 270 mol/mol Rh/h with bipyridyl as the ligand. The substrate-to-catalyst mass ratio 5.1:1 gave 100% conversion in 25 h. This was 1–2 orders of magnitude slower than with other substrates, such as benzoates. The catalyst did not deactivate in 100 h at a 50000:1 ratio and no Rh leakage (<0.1 ppm) could be detected. The greatest advantage that this kind of catalyst would have compared to conventional heterogeneous catalysts are the mild conditions, which allow for sensitive substrates.

2.4.6.4 Nanoparticles

A new method for preparing heterogeneous catalysts is the thermolysis of polymetallic clusters to polymetallic nanoparticles. Polymetallic clusters are organometallic clusters, usually carbonyl complexes, with metal-metal bonds. Although they do function as homogeneous hydrogenation catalysts, their hydrogenation activity is low. Instead, a heterogeneous catalyst is synthesized by impregnating a support with a slurry of the complex and heating at 195 °C for 2 h. [77] The nanoparticles form upon thermolysis of the clusters. The advantage is that the size and stoichiometry of the particles can be controlled exactly, unlike in a conventional method based on crystallization, where a complex mixture of monometallic crystals and intermetallic compounds is produced. [78]

The specific activity is high because in a small, 1–1.5 nm particle, essentially all metal atoms are exposed. Also, such particles are less likely to deactivate by sintering and more resistant to sulfur poisoning. [77] They are firmly anchored to the silanol groups on the silica surface and are resistant to leaching. [79] Additionally, the activity of bimetallic particles is higher than that of monometallic particles. [78]

Research on this method was motivated by the discovery of bimetallic catalysts for petroleum reforming. However, the nanoparticle catalysts are highly active also in hydrogenation. [78] The nanoparticle method is a recent research topic and the heteronuclear precursors are not commercially available. The polymetallic clusters are usually synthesized starting from carbonyl complexes. [78]

Nanoparticles of the exact atomic composition Ru_5PtSn on SiO_2 have been demonstrated for single-step hydrogenation of dimethyl terephthalate into 1,4-cyclohexanedimethanol. [80] The nanoparticle was synthesized by a multistep procedure (Scheme 13). The combination RuSn has also been synthesized as Ru_6Sn particles. [81]

$$\mathrm{RuCl_3 \cdot nH_2O} \xrightarrow{\mathrm{CO}} \mathrm{Ru_3(CO)_{12}} \xrightarrow{\mathrm{C_2H_4}} \mathrm{Ru_6C(CO)_{17}} \xrightarrow{\mathrm{CO}} \mathrm{Ru_5C(CO)_{15}}$$

$$\xrightarrow{\mathrm{Na_2CO_3}} [\mathrm{Ru_5C(CO)_{14}}]^{2-} \xrightarrow{\mathrm{Pt(COD)Cl_2}} \mathrm{PtRuC(CO)_{14}(COD)} \xrightarrow{\mathrm{CO}} \mathrm{PtRuC(CO)_{16}}$$

$$\xrightarrow{\mathrm{Ph_3SnH}} \mathrm{PtRu_5C(CO)_{15}(\mu{-}SnPh_2)}$$

Scheme 13. The seven-step synthesis of the precursor to Ru_5PtSn nanoparticles. $Ru_3(CO)_{12}$ is also commercially available. [82, 83, 84, 85]

2.4.6.5 Other methods for catalyst preparation

Hydrogenation catalysts have been prepared by atomic layer deposition. In ALD, a gaseous metal cluster is adsorbed on a surface, and flushed with inert gas to leave a monolayer. This form does not react with the surface; however, with decomposition of the cluster, the metal is fixed to the surface. The process is repeated until the desired number of layers is produced. For example, Ni/Al_2O_3 has been prepared in this manner from nickel acetoacetonate, which is fixed by calcination in air. ALD-prepared catalysts had similar catalytic activities (per gram Ni) as impregnated catalysts in toluene hydrogenation, but their rate maximum was at a higher temperature, owing to decreased adsorption of the substrate. However, it was found that the most active catalyst had 4 layers nickel deposited, demonstrating that the active site has multiple atoms — with 1–2 atoms, the activity was low. [86]

Leon has patented (ExxonMobil World Patent, 2004) the thermolysis of a cluster, particularly amine cluster, onto a support, for benzenepolycarboxylate hydrogenation. In the method, impregnation is done with an amine in the solution, and the formed amine cluster thermolyzed. Examples include *N,N*-diethanolamine for Ni/Al_2O_3 and L-arginine for Ru/SiO_2. The catalyst is better than that deposited from water solution. An aromatic ester (di-isononyl phthalate) was ring-hydrogenated by Ru/SiO_2 at 58 bar and 80 °C, or at 207 bar and 120 °C, in 90% yield. [87] There is also another patent application to the same effect. Triethanolamine was the cluster-producing compound. [88]

2.4.6.6 Characterisation of catalysts

Various physical methods are used for catalyst characterisation. The area and pore size distribution is found with the BET method, where a nitrogen monolayer probes the area. The catalyst is placed into a helium stream, cooled with a liquid nitrogen bath and a small amount of nitrogen in a stream of helium is introduced. The amount of absorbed nitrogen and desorbed nitrogen is measured for several amounts of nitrogen. Area and pore size distribution is calculated with the BET theory developed by Brunauer, Emmett and Teller. [89] Nitrogen is nonselective and the result represents the total area of the support-catalyst mixture. Area was formerly probed by infusing metallic mercury into the catalyst.

The dispersion of the metal (metal surface area per particle size) can be observed by several methods. Chemisorption with a selectively adsorbed gas, like H_2 or CO, probes the area of the metal itself. X-ray diffraction (XRD) correlates the widening of the diffraction lines with the size of the crystallites. XRD gives the average size in the range 30-1000 Å. The change caused by sintering tells about crystallites smaller than 50 Å. Electron microscopy, *i.e.* directly viewing the catalyst, requires a lot of images in order for the average to be reliable. Temperature programmed desorption (TPD) probes the distribution of adsorbing sites and the total surface concentration.

There are also several physical methods to probe the surface structure: low energy electron diffraction (LEED), ion scattering spectroscopy (ISS), Auger electron spectroscopy (AES), secondary ion mass spectrometry (SIMS), bombardment light emission (BLE) and electron spectroscopy for chemical analysis (ESCA) with photoelectrons produced with X-rays (XPS, X-ray photoelectron spectroscopy) or ultraviolet (UPS, ultraviolet photoelectron spectroscopy). [30]

2.4.7 Reaction mechanisms

According to the contemporary view, catalytic hydrogenation follows the Horiuti-Polanyi mechanism. [90] The mechanism, (Figure 5) which was proposed originally in 1934, is still widely accepted. [16] Since the concerted addition of H_2 to an alkene is a forbidden transition, the addition must happen in two steps. [30]

The mechanism begins with the chemisorption of the alkene on the catalyst to give a metal-alkene intermediate. (1) Hydrogen is adsorbed dissociatively as hydrogen atoms, which react with the chemisorbed alkene to produce a half-hydrogenated alkyl intermediate in a reversible reaction. (2) Another chemisorbed hydrogen reacts with the intermediate to produce an alkane in a reaction irreversible under hydrogenating conditions. (3) [90]

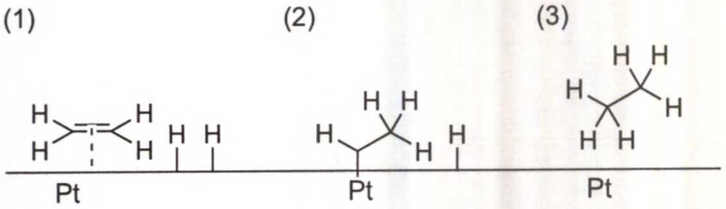


Figure 5. Horiuti-Polanyi mechanism for ethylene hydrogenation on platinum.

The same mechanism is valid also for carbonyls. Specifically, their hydrogenation does not go through an enol intermediate, which would be trapped in deuteration experiments. [56]

Hydrogenations, particularly aromatic hydrogenations, are rather insensitive to substituent effects. [56] This is expected as they are reactions of adsorbed atomic hydrogen. An exception is that conjugated alkenes are more reactive, because the alkene bond is easier to polarize. [30]

Reactions occur on special active sites on the catalyst. The amount of active sites on a catalyst is small. The sites consist of multiple atoms that include coordinatively unsaturated atoms. The sites are located in edges, crystal imperfections, etc., and less on the regular surface. [30] Furthermore, different reactions occur on different types of sites. In a metal microcrystal, several crystal planes are exposed, and they may have different selectivity. [16]

2.4.7.1 Diastereoselectivity

The mechanism may be illustrated by the observation that partial hydrogenation also isomerizes the bond, demonstrating the single-bonded intermediate. The hydrogens are added from the same side of the alkene in both reactions, which should favor *cis*-hydrogenation. However, the half-hydrogenated intermediate can rotate before being hydrogenated. This also produces *trans*-hydrogenated products.

If the molecule is cyclic and thus the hydrogenated bond is unable to rotate, only *cis*-products should form assuming that both hydrogens come from the same side of the bond. [16] However, *trans*-isomers are also produced in the reaction. This is not because of isomerization, because more than the thermodynamic equilibrium of *trans* products can be produced. An interpretation is that second hydrogen comes from solution. Indeed, in protic solvents on Pt or Pd, *trans* products are found. It is, however, possible to produce *cis* products selectively on Pt (or Ir, Os). Pd, Rh or Ni are not as inherently selective. Pressure has only a minor effect. [30]

2.4.7.2 Adsorption of hydrogen

Hydrogen is readily adsorbed onto the active hydrogenation catalysts even at room temperature. However, at over 200 °C, activated chemisorption begins and rapidly increases at over 400 °C. [91] Activated chemisorption is chemisorption with a net activation energy, with the consequence that equilibrium is attained slowly, unless temperature is increased (see Figure 6). [63] The hydrogen layer is removed only at higher temperatures, for example at 427 °C on platinum. [91]

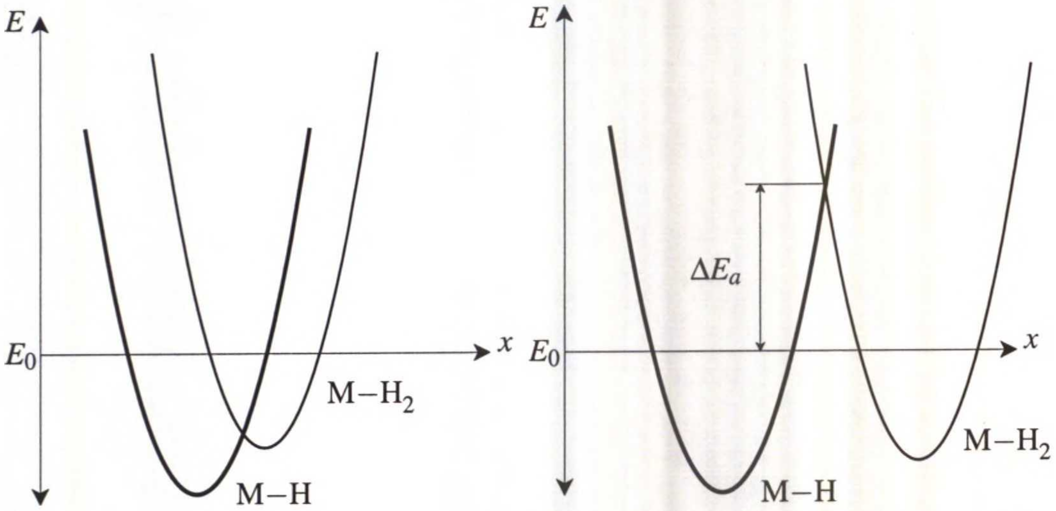


Figure 6. Unactivated chemisorption (left) vs. activated chemisorption (right). [63] Left: adsorbed $M-H_2$ readily forms $M-H$. Right: the potential wells of $M-H_2$ and $M-H$ do not overlap, the transition requiring the net activation energy ΔE_a.

The reactions occur exclusively at the surface, with hydrogen adsorbed dissociatively. The contribution of hydrogen dissolved in the metal is insignificant. [91, p. 33]

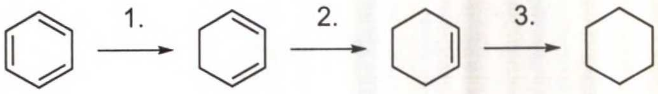
Water with $ZnCl_2$ on ruthenium promotes the production of cyclohexenes from aromatics, by decreasing hydrogen availability to the catalyst and aiding with the desorption of the cyclohexene. In fact, tetrahydrophthalate salts can be produced from the phthalate salts using ruthenium in NaOH-alkalified water at 155 bar and 140 °C. [92]

2.4.7.3 Aromatics

The hydrogenation of aromatics also follows the same mechanism to produce cyclohexadienes and cyclohexenes. However, these intermediates are more reactive than aromatics and thus are usually not produced in significant yields. [16]

Aromatic hydrogenation is effectively irreversible. This is shown by deuteration: deuterium exchange occurring with ethene does not occur with benzene. Deuteration of benzene gives $C_6H_6D_6$ only. The only exception is a small amount of monodeuterated benzene resulting from a spectator process, where benzene is adsorbed as a phenyl radical, without loss of aromaticity. [34]

The motivation for its irreversibility is that benzene hydrogenation occurs in three steps (Scheme 14).



Scheme 14. Intermediates in aromatic hydrogenation

The first step destroys aromaticity, which is thermodynamically disfavored, by 34 kcal/mol. [56] Thus, conditions sufficient to attack aromatics are more than sufficient to attack dienes. Dienes are not usually observed at all. The last intermediate, cyclohexene, is observable. Special catalysts and conditions can produce a significant yield cyclohexene, *e.g.* ruthenium with water. Ruthenium is an active aromatic hydrogenation catalyst but not as active towards alkenes. The same may occur on rhodium. [56, 30] The cyclohexene intermediate is also special in the respect that it can be disproportionated to cyclohexane and benzene over platinum. [56]

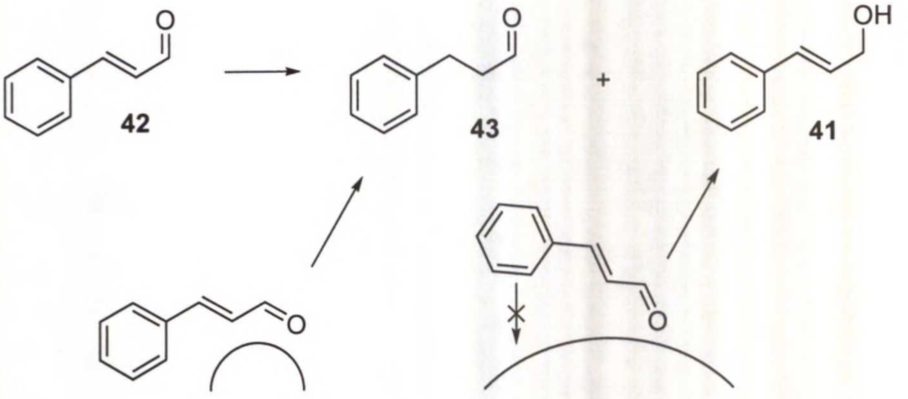
2.4.7.4 Steric effects

In hydrogenation reactions, the geometry of the reactants and the active site lead to selectivity effects. Generally for hydrogenation, an alkene is easier to hydrogenate the easier it is to be adsorbed flat, illustratively with ethene vs. propene. [93] In the hydrogenation of substituted alkenes, the rate of elementary hydrogenation reactions depends little on the substituents. However, their steric bulk can change their adsorption coefficients by six orders of magnitude, and the observed reaction rate is changed in the same manner. [16, p. 22-23] The order of alkene hydrogenation rates is terminal > *cis*-internal > *trans*-internal > trisubstituted > tetrasubstituted. [30] The effect is entropic: for more substituted alkenes, despite the larger enthalpy resulting from larger strain release, the entropy of the transition state is higher. [30]

Aromatic hydrogenation requires that the molecule is adsorbed flat. [93] If there are sterically demanding parts, then reactivity is decreased. Another effect is that very small metal particles do not have such flat surfaces, but large particles do, resulting in activity differences. This has implications for catalyst preparation, because crystal sizes are different depending on the method. In one study, particle sizes of platinum produced by different methods of preparation were: ion exchange 1.3 nm on carbon and graphite, sintering with graphite 5.0 nm, impregnation into carbon 8.0 nm, reduction of Adams platinum 2.0-6.0 nm (60 °C) and 20-200 nm (100 °C). [16]

Hydrogenolysis requires a larger site than hydrogenation. This is also aided by large crystals with large flat planes. [16] For further discussion, see section 2.6.7, p. 62.

Another example is that the selectivity of allyl alcohol production from α,β-unsaturated compounds is determined by the tilt of the molecule with respect to the surface. In cinnamaldehyde hydrogenation over Pt/C, larger particles favor aldehyde hydrogenation. Repulsion of the aromatic ring and the metal surface is greater on the flatter surfaces of larger particles. This results in the other side, or aldehyde function, contacting the catalyst (see Scheme 15). On smaller particles, the adsorption of the alkene is less hindered. [16]



Scheme 15. Steric repulsion changes the selectivity of cinnamaldehyde **42** hydrogenation from **43** to **41**.

The reaction rate and selectivity depends on the crystal plane. For example, when hydrogenating an α,β-unsaturated aldehyde (3-methylcrotonaldehyde) on platinum, mainly aldehyde was hydrogenated on the Pt(111) face, whereas Pt(110) gave fully saturated products. The geometric explanation is a difference in adsorption: the methyl groups produce a steric hindrance on the close-packed Pt(111) face, but not on the corrugated Pt(110) face. Similarly, crotonaldehyde was an order of magnitude faster to hydrogenate than methylcrotonaldehyde. [16]

The same effect has been observed also in asymmetric reactions. Cinchonidine-modified platinum hydrogenates ethyl pyruvate into ethyl lactate. Heating of the Pt/Al_2O_3 catalyst to 400 °C increased enantioselectivity significantly, because particle coalescence occurred. For reduction of platinum onto the support, sodium and potassium formiate and formaldehyde were better reducing agents compared to hydrogen, which produced high dispersions and low enantioselectivities. [94] A similar effect has been observed with rhodium: diastereoselectivity in an asymmetric reaction was better on alumina than on carbon. On alumina, rhodium appeared in flat particles. [95]

2.4.8 Properties of a metal and its reactivity

Metals were investigated earlier to try to establish a correlation between the bulk properties of metals and their catalytic activity, but results from this research, although definite, may be misleading. In contemporary understanding, reactions actually occur on specific active sites rather than on the bulk metal. Furthermore, the studied reactions or catalysts may not be entirely relevant to the practical reaction at hand. Each different molecule has different chemical and electronic characteristics. Despite attempts, the rational selection of a catalyst remains an unsolved problem in organic chemistry. [16]

2.4.8.1 Chemisorption of reagents

The differences in energy of chemisorption accounts for the selectivity differences between metals. [16] For example, when comparing different metals, the heat of adsorption of hydrogen and reaction rate is correlated (consider Figure 7). [96]

According to the Sabatier principle, there exists an optimum binding of intermediates to the metals, at which the reaction rate is at maximum. [97] Both weaker and stronger binding decrease the availability of reagents to the reaction. [91] The result may then be that for a given set of catalysts, the weakest adsorbing metal is the most active (e.g. Figure 7). [96]

2.4.8.2 The *d* character

Linus Pauling defined the quantity of *d*-character of metals as the proportion of *d* orbitals in the intermetallic bond. He found a linear correlation between percent *d*-character of metal bonds and their metallic radii. [98] The rate of ethylene hydrogenation was also correlated to percent *d*-character. [99] [96]

Also, competetive hydrogenation of benzene and toluene has been investigated. Toluene is adsorbed stronger than benzene on Pd, Rh and Ru surfaces. Toluene is a better electron donor due to its methyl group, and is used to probe the electron density of the metal. [100] Indeed, electron density on the conduction band (Fermi level) and ratios of adsorption coefficient of benzene and toluene follow the same order. [101]

Couper and Eley [102] used the conversion of *para-*, and *ortho-*hydrogen as the model reaction. These are spin isomers of hydrogen, differing in the orientation

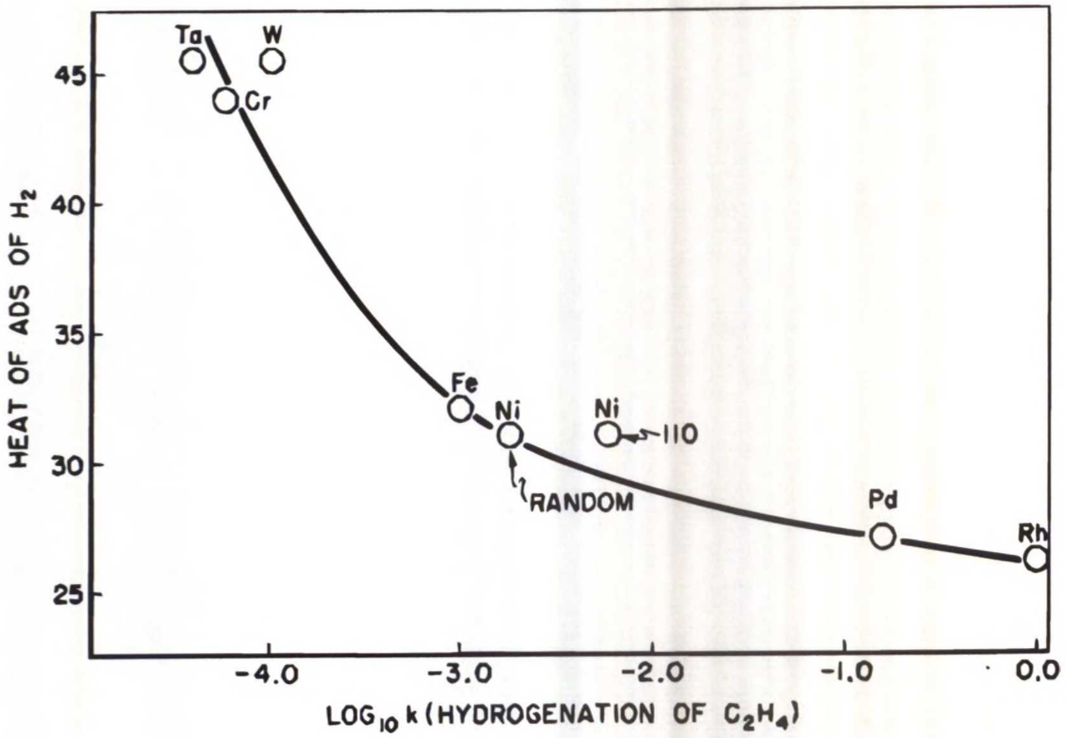


Figure 7. Rate of hydrogenation of ethene correlated with heat of adsorption of hydrogen for Ta, W, Cr, Fe, Ni, Pd and Rh. From Beeck 1950. [96]

of spins of hydrogen atoms: *ortho* same direction, *para* opposite direction. The conversion of *ortho* to *para* is an exothermic, heterogeneously catalyzed reaction. Couper and Eley found that by alloying gold to palladium, the model reaction slowed down. Their conclusion was that Au would fill the *d* orbital of Pd, thus poisoning the catalyst. [102]

A reaction of considerable interest has been the selective hydrogenation of the carbonyl in α,β-unsaturated aldehydes. Selectivity towards aldehyde hydrogenation increases in the order Pd, Rh > Ru, Pt, Ir. Adsorption of the alkene is hindered by a large *d*-band of the metal, and its size also increases in the order Pd > Pt > Ir. [16, p. 20-21]

However, the attempt to correlate bulk properties and catalytic activity did not lead to conclusions of practical interest. Kinetic measurements are very sensitive to impurities [56] and so ultra-high vacuum and specially prepared catalysts have been used. To study the role of the *d* orbital, metal pairs that form alloys have been selected. The model reactions of conversion of *para-*, *ortho*-hydrogen and ethylene hydrogenation, and the use of specially selected and prepared catalysts have little relevance to industrial bimetallic catalysts. [60] This rather abrupt conclusion is because experiments with unusual reactions and catalysts, metal wires, sputtered catalysts, ultra-high vacuum etc. had fundamentally different chemical conditions and thus different chemistry. Furthermore, the massive metal may be irrelevant to the reaction, reactions occurring on special sites. Not all metals form alloys and their interaction in a bimetallic mixture is more complex. [60]

Furthermore, hydrogenation of benzene derivatives led to different order of activity not clearly correlated with the *d*-orbital. In gas-phase hydrogenation of benzene, where the rate-determining step is hydrogen adsorption, one investigation produced the order of hydrogenation activity W > Pt > Ni > Fe > Pd, inconsisted with the correlation [34] and another with different metals Rh > Ru > Pt > Pd, consistent with the correlation. [40] Overall, this does not support a determining role for the *d* orbitals. This illustrates that other factors, like adsorption, are also important. The hydrogenation of ethene is reversible, the hydrogenation of benzene is not.

2.4.9 Catalyst inhibition

Catalyst inhibition is the reduction of catalytic activity by chemical binding to the catalyst. Catalyst poisoning is specific, permanent inhibition. Hydrogenation catalysts are generally poisoned by reduced sulfur and nitrogen. Another mechanism of deactivation is the deposition of polymeric side products or coke on the surface.

Even atmospheric oxygen and nitrogen can poison some catalysts. Oxygen forms a stable chemisorbed monolayer very quickly in even very small amounts. The only way to remove this is by prolonged heating in hydrogen. Even in these conditions, the mechanism of oxygen removal from Ru is actually plain desorption. [103] However, platinum is actually promoted by oxygen, [27] and many catalysts tolerate oxygen, because their oxides are also catalytic or because they are readily reduced to metals.

Poisons can have a drastic effect on activity even at low exposures, for example, on tungsten, when nitrogen covers only 50% of the surface, it reduces the reaction rate by 340-fold. [91] This is because multiple atoms are a part of the site, and poisoning of any of them kills the entire site.

2.4.10 Chemical kinetics

Hydrogenation is always thermodynamically favored at moderate temperatures and high pressures, but different functional groups have different free energies of hydrogenation. The rate of hydrogenation varies with temperature according to the Arrhenius equation.

$$k = k_0 e^{-\frac{E_a}{RT}} \tag{1}$$

The activation energy is usually $E_a = 8 - 12$ kcal/mol. This corresponds to a doubling of rate per every 10 °C. [16, p. 33] For aromatics, it is 12 kcal/mol for all metals. The differences between metals are entirely in the frequency factor k_0. [40]

The reaction rate is often described as $r = kC^m P_{H_2}{}^n$, where C is concentration of substrate and P_{H_2} is hydrogen pressure, but this formalism has no mechanistic significance. Experimentally, the usual observation is that for hydrogen, $n = 1$ and for the substrate, $m = 0$, which holds for both alkenes and aromatics. [40] This is consistent with hydrogen availability being the rate-determining constraint. [56] Generally the surface is saturated with the substrate, rather than hydrogen.

If the first hydrogen transfer is rate-limiting, the order should be $n = \frac{1}{2}$, but if it is the second, then it should be $n = 1$. (Also, if there was no half-hydrogenated intermediate, it should be $n = 1$.) Experimentally, the reaction order with respect to hydrogen is often between $n = \frac{1}{2}$ and $n = 1$. A reaction order of $n = 0$, *i.e.* no dependence on hydrogen pressure, indicates either very strong hydrogen adsorption or that the rate-limiting step is the adsorption of the substrate. [16]

A Langmuir-Hinshelwood mechanism is actually more approriate. This presumes that reactions occur between the adsorbed complexes of the reagents. For example, it is known that the liquid-phase ring hydrogenation of di-isononyl phthalate obeys Langmuir-Hinshelwood kinetics. [87, p. 56–57] Experimentally, the reaction rate has the form:

$$r = \frac{k[A]}{1 + k'[A] + k''([B] - [A])} \tag{2}$$

where $[A]$ is the concentration of the aromatic substrate and $[B]$ the hydrogenated product. [87, p. 56–57]

In typical experiments, the hydrogen pressure is kept constant by means of a pressure-regulating valve. Thus, only the frequency factor, which depends on amount of catalyst and temperature, determines the rate, and the reaction has linear kinetics. This has in fact been observed for the ring hydrogenation of phthalic acid. [104] For ring hydrogenation of di-isononyl phthalate, Leon claims in a patent that at below 90% conversion and constant hydrogen pressure, the reaction is zero-order, otherwise obeying Equation 2. [87, p. 56–57]

When the limiting factor is the adsorption equilibrium of hydrogen — particularly vs. starting material — faster reaction can be achieved principally with higher H_2 pressure. Ester hydrogenations often feature a massive excess of hydrogen in feed and a high liquid hourly space velocity (LHSV) for forced convection. Ester hydrogenation is an equilibrium reaction, thus having an excess of hydrogen on the catalyst surface increases the rate.

2.5 Hydride reduction

Stoichiometric hydride equivalents convert carboxylates and aldehydes into alcohols. Commonly used nucleophilic hydrides are lithium aluminum hydride, sodium borohydride and lithium borohydride. These reagents contain four hydrogen atoms, each of which is available to attack a carbonyl group by nucleophilic addition, producing an alkoxide. The alkoxide binds with the produced coordinatively unsaturated borane or alane. These compounds are also active reducing agents, and may disproportionate to tetrahydride. The reaction ultimately produces aluminates or borates of the product alcohol. Quenching with water or other acid protonates the alkoxide and precipitates solid aluminate or borate salts.

Electrophilic reagents include diborane and di-isobutylaluminum hydride. Although they deliver an equivalent of a hydride anion, they are attracted to electron-rich compounds. Thus, for example diborane readily reduces carboxylic acids in the presence of electrophilic groups such as esters and ketones and even acyl chlorides. In contrast, lithium aluminum hydride neutralizes the acid, producing an unreactive lithium carboxylate, while attacking esters and ketones. [24, p. 619] Some acids may be reduced by $LiAlH_4$, however. [106]

Stoichiometric reagents produce voluminous salts also in stoichiometric quantity. The processes are difficult to scale up, thus being limited up to the fine chemicals scale.

2.5.1 Lithium aluminium hydride

$LiAlH_4$ is a basic ionic compound that consists of AlH_4^- anions and Li^+ cations. AlH_4^- can attack carbonyls and effectively deliver the equivalent of a "H^-" anion. Li^+ is an oxygen-specific Lewis acid that functions as catalyst. $LiAlH_4$ is highly reactive and will reduce all carbonyls in the molecule, unselectively and totally, into alcohols. It is least reactive towards acids, but does reduce them also. [106] $LiAlH_4$ reactions are usually conducted in ether solvents. $LiAlH_4$ is widely used in laboratory chemistry. It is, however, corrosive, pyrophoric and produces flammable hydrogen and dangerous amounts of heat with water.

$LiAlH_4$ contains four hydride equivalents. The initial reduction produces an aluminohydride alkoxide $ROAlH_3^-$, which is at least as powerful a reducing agent and can also disproportionate into $LiAlH_4$. The reaction continues until all four hydrides have been replaced with an alkoxide. The reaction is quantitative. [107] Thus, for the case of a diester, which requires four hydride equivalents, the molar ratio 1:1 is used (Equation 3). Often a slight excess is used to account for adventituous water and air. There is, however, no reason to use massive excesses, which consume material and exacerbate the hazard. Correspondingly, the quench of four alkoxides with water consumes four protons (Equation 4), in addition to the $LiAlH_4$ excess, *i.e.* four protons per molecule of $LiAlH_4$.

$$R(CO_2Me)_2 + LiAlH_4 \longrightarrow R(CH_2O)_2(MeO)_2LiAl \tag{3}$$

$$\xrightarrow{4\,H_2O} R(CH_2OH)_2 + 2\,MeOH + LiAl(OH)_4 \tag{4}$$

$LiAlH_4$ reductions are conducted in ether solvents. Ethers are non-reducible, but slightly Lewis basic and able to complex to Lewis acids. The solubility of $LiAlH_4$ in ethers is 350 g/l in diethyl ether and 130 g/l in tetrahydrofuran. [54] Diethyl ether forms phases with water and has a low boiling point of only 34.6 °C. This is hazardously low, and furthermore, the autoignition temperature is extraordinarily low at 170 °C. Preparations are traditionally conducted in refluxing diethyl ether, so that substrate is added slowly and the heat of reaction maintains a reflux. An alternative ether is tetrahydrofuran, the cyclic C_4 ether, which has a higher boiling point (66 °C). It is, however, freely soluble with water. The consequence is that water from the quench remains in solution.

$LiAlH_4$ reductions must be quenched with an acid, but because of the high alkalinity of hydrides and alkoxides, water suffices. The reaction mixture contains excess $LiAlH_4$ and a stoichiometric quantity of lithium aluminium alkoxides. Water quenches the excess $LiAlH_4$ and protonates the alkoxides. A problem is that when hydrated, aluminium hydroxide forms. Hydrated aluminum hydroxide is gelatinous and very difficult to filter off. There is a laboratory method that avoids this and produces granular salts: in inexact terms, for each gram of $LiAlH_4$, 1 ml water, 2 ml NaOH solution (20%) and 1 ml water is added in this sequence. [108, p. 121] Ostensibly the added of NaOH forms sodium aluminate, which crystallizes and can be filtered off. A specific problem with methyl esters may be that aluminum is soluble as aluminum methoxide. With tetrahydrofuran, water should be used conservatively, and the salts would be allowed to absorb water. The salts would be extracted as is, and then, the combined solution would be dried with a desiccant, such as anhydrous Na_2SO_4.

In earlier syntheses of cyclohexane-1,2-dimethanol, $LiAlH_4$ was quenched with 20% sulfuric acid, which dissolved also the aluminum salts, and then the aqueous cyclohexane-1,2-diol solution had to be continuously extracted with diethyl ether. [109]

2.5.2 Diborane

Diborane is a reducing agent specifically for carboxylic acids. Diborane itself is the gas B_2H_6, a dimer of borane BH_3. The specificity of borane is explained by its high Lewis acidity at boron, where carboxylates attack it. The adduct $RCO_2BH_4^-$ is now reactive and by intramolecular reaction, produces an alcohol, RCH_2OH. Carboxylic acids are reduced by borane, a reactivity pattern complementary to the ester-reducing $LiAlH_4$.

Diborane itself is flammable, odorous and toxic gas, but it readily forms borane adducts with Lewis bases, particularly diethyl ether (Et_2O) and dimethyl sulfide (Me_2S), that are more convenient to handle. Both $BH_3 \cdot Et_2O$ and $BH_3 \cdot Me_2S$ reduce carboxylic acids. The $BH_3 \cdot Et_2O$ adduct is more reactive, and its maximum concentration is 1 M. The $BH_3 \cdot Me_2S$ adduct is more stable and can be purchased neat. However, dimethyl sulfide released in quantitative amounts is difficult to handle because of its odor. Gaseous diborane can be used if it is possible to handle; with ether solvents, an adduct is formed in the solution. [54]

2.5.3 Sodium borohydride

Sodium borohydride $NaBH_4$ is mildly reactive for carbonyl reduction. It can even be dissolved in water or alcohols, although hydrogen and diborane are evolved particularly from acidic solutions. It does not ordinarily reduce esters or acids at ordinary conditions. [54] However, its reactivity can be promoted by various means: heat, Lewis acids, solvolysis and derivatization *in situ* with Ca, Li, or Zr. [110]

The first method is to simply use a higher temperature. Without a pressure vessel, this requires a high-boiling solvent, such as a glyme (glycol methyl ether). An aromatic acid was reduced to a benzylic alcohol at 162 °C in diglyme. [110]

Another method is derivatization by solvolysis: protic solvents such as water and methanol react with $NaBH_4$ to produce a more reactive reductant. The initial reaction of solvolysis leads to a loss of hydride equivalents (Equation 5). However, insofar as they contain hydride, the products are more reactive than $NaBH_4$ itself because of the electron donation from oxygen.

$$NaBH_4 + MeOH \longrightarrow NaBH_3OMe + H_2 \longrightarrow \textit{etc.} \tag{5}$$

This leads to a protocol where $NaBH_4$ is dissolved in methanol and reacted. Methanol does, however, solvolyze the borohydride quite rapidly, and to moderate this, less reactive ethanol can be used to dilute the methanol. [110] Methyl esters should be reduced with $NaBH_4$/MeOH, because $NaBH_4$ catalyses ester interchange with the solvent. [54] Another, similar method is to used tetrahydrofuran as a solvent with added water for derivatization. [54]

The enchancing effect of alcohols is also produced intramolecularly. That is, hydroxyesters are reduced, *e.g.* a 3-hydroxy ethyl ester reduced into 1,3-diol in toluene at 55 °C in 3 h with $NaBH_4$. [110]

Unlike $NaBH_4$, $LiBH_4$ reduces esters and dissolves in THF. Lithium functions as an oxygen-specific Lewis acid. The reagent can be produced *in situ* from $NaBH_4$ and LiCl. Similarly, $Ca(BH_4)_2$ is made from $NaBH_4$ and $CaCl_2$; it must be made *in situ* because of poor stability. Lewis acids that promote ester reduction are $AlCl_3$, $ZrCl_4$ and LiCl (without removal of NaCl). [110] The product is, however, a borate ester. This is hydrolyzed with an aqueous acid, such as 1 M HCl at 10 °C. Cyclohexane-1,2-dimethanol **1**, however, is known to readily dehydrate with acids. Thus, if $NaBH_4$ can be applied for production of diol **1**, the hydrolysis has to be optimized.

It is also possible to generate borane *in situ* by combining $NaBH_4$ and a powerful Lewis acid, sulfuric acid, trifluoroacetic acid, catechol or I_2. Another method is to activate the carboxylic acid as an anhydride or carboxymethyleneiminium salt. [54]

2.6 Reduction of different functional groups

2.6.1 Aromatics and carboxylates hydrogenated in one step

Terephthalate hydrogenation has been of interest for producing the corresponding cyclohexyl diol for polyester monomer uses, and there has been interest in developing bifunctional catalysts. The two-step process allows tailoring conditions and catalysts separately for aromatic hydrogenation and carboxylate hydrogenation. Hydrogenation of both groups in one step requires catalyst optimization, because the fundamental requirements differ.

Demonstrated one-step catalysts are detailed below: RuSnMn for esters (section 2.6.4.4, p. 52), nanoparticles of compositions Ru_6Sn, Ru_5Pt and Ru_5PtSn for esters (section 2.6.4.5, p. 52), $RuSn/Al_2O_3$, RuSn/C and PtRuSn/C (section 2.6.5.2, p. 55) for acids, and PtRe and PtReAg (section 2.6.5.4, p. 58) for acids.

2.6.2 Hydrogenation of aldehydes

Aldehydes are intermediates in hydrogenation of esters and acids, and are usually reduced by nearly any catalyst capable of carboxylate hydrogenation, zirconia being an exception. Ru/C works even in ordinary conditions. [54] Adams PtO_2 promoted by $FeCl_2$ in EtOH works in 3 atm and room temperature. Aromatics are not hydrogenated in this reaction. Regarding the solvent, methanol has the specific problem that it tends to form an unreactive acetal with the aldehyde. [28, 111] Also, Pd, Pt and Ni reduce aldehydes. [111]

There has been research interest in reducing α,β-unsaturated aldehydes to allylic alcohols. Most catalysts have no inherent selectivity towards the alkene or the aldehyde. Tin is a promoter that changes the selectivity for aldehyde hydrogenation, for example in PdSn [112] and PtSn. [72] Tin blocks the active sites for alkene hydrogenation, rather than promoting aldehyde hydrogenation. [112] In PdSn, tin is not present as Lewis acidic Sn^{2+} ions. However, it increases the electron density of the palladium and thus decreases olefin adsorption. [112] The same phenomenon has been observed with iron particles covered with platinum: the metallic iron donates electron density to the platinum. [72]

2.6.3 Hydrogenation of aromatics

The reduction of aromatics requires an active catalyst. For aromatics, activity increases Co < Ni < Pd << Pt << Ru < Rh. [16, 40] For all metals, the activation energy is the same, $E_a = 12$ kcal mol^{-1}. [40] Aromatics are generally hydrogenated at moderate pressure and temperature, *e.g.* 50 bar and 100–150 °C. Industrially, less than 100 bar is preferred because of equipment costs.

Aromatic hydrogenation is largely insensitive to substituents, except for steric effects on reaction rates. This includes even phenols and other groups with electronic effects on the benzene ring. Aromatic hydrogenation is promoted by a protic solvent.

Adams PtO_2 has usually been used in the laboratory, because Pt/Al_2O_3 and Pt/C are not very active. Such preparations often feature a large, even stoichiometric amount of catalyst. This makes it difficult to predict whether the same metal would work in support form, because not only yield, but also poisoning and selectivity can change. Benzene and other aromatics are hydrogenated in 2–26 h at 2–3 atm and 25–30 °C, and in 12–30 min at 215 atm. [25] Acids speed up the reaction, *e.g.* HCl or HBr double the speed. [32] Another method is to use the acidic solvent AcOH. This effect is probably caused by alkaline residues on the catalyst.

Rhodium can be used as a massive catalysts as RhO_2 or Rh black at 3–4 atm and room temperature. [25] Rhodium is four times as active as Pt when dispersed as 5% on Al_2O_3 and in acetic acid solvent. [104] Supported 5% Rh/Al_2O_3 has been used at 2–3 atm and 25–80 °C. [54, 25] Rh/C (10%) also hydrogenates alkylbenzenes with water as a solvent at 5 atm and 80 °C. [113] The Nishimura catalyst, a 3:1 mixture of PtO_2 and RhO_2, is more active than either and avoids hydrogenolysis. Nishimura also ring-hydrogenated benzyl alcohol. [36] However, like Adams platinum, Nishimura RhPt is an unsupported catalyst.

Ruthenium supported as Ru/C or Ru/Al_2O_3 hydrogenates aromatics at high pressure, *e.g.* 175 atm and 140 °C. [54]

Raney nickel generally requires high pressures and high temperatures (170–180 °C), but the more active grade W-6 is already capable of aromatic hydrogenation at ordinary conditions. The difference between grade W-6 and others is that a continuous neutralization is conducted under hydrogen. [54] The selectivity of nickel is improved by using a silane to reduce the nickel, so that it is even possible to reduce benzylic alcohols. [114]

Palladium is less active, but it is still used industrially, for example for terephthalate ring hydrogenation at 172 bar and 160 °C [115] or at 138 bar and 250 °C in $\sim$90% yield. [116] The potential for side reactions is larger; *e.g.* benzylic alcohols are certainly hydrogenolyzed. The catalyst may be activated and reactivated by steaming, treating with NaOH and heating in nitrogen-air mixture at 350 °C. [116]

Inactive catalysts for aromatic hydrogenation include copper chromite, which rather hydrogenolyzes furans than hydrogenates aromatics. [41] Other metals with low activity are also incapable of aromatic hydrogenation: SnO_2, TiO_2, V_2O_5, Cr_2O_3, WO_3, Fe_2O_3, Fe, SnS, V_2S_3, FeS, CoS, NiS, MoO_3, MoS_3, and WS_3. [56]

2.6.3.1 Hydrogenation of aromatic esters

Generally aromatic esters have been hydrogenated on Pt black in EtOH/H_2O or Adams PtO_2 in AcOH or HCl-acidified alcohol [32] at ordinary or very mild conditions, or with Ni at 92 atm and 225 °C (ethyl benzoate). At high pressure and 200–250 °C, nickel may cause decarboxylation, *e.g.* *p*-hydroxybenzoate gave cyclohexanol. [56] Brown hydrogenated ethyl benzoate with Adams PtO_2 at 3 atm and 70 °C in 4 h. [32]

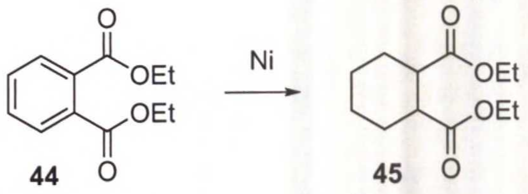
Of supported catalysts, 5% Ru/C could be used for ring hydrogenation of aromatic esters at 175 atm and 140 °C. Furthermore, the ester group was reduced at more drastic conditions of 520–700 atm and 150–175 °C (see section Esters below on 47). [54] Also, 5% Rh/C ring-hydrogenated benzoic acid at 150 bar and 130 °C; water promoted the reaction. [117]

2.6.3.2 Hydrogenation of benzenepolycarboxylic esters and acids

There are early examples of phthalate hydrogenations where mostly platinum has been used. For example, Komppa and Rohrmann used colloidal platinum to ring-hydrogenate diethyl terephthalate, with a large amount of catalyst, at 3 atm and 50–60 °C. [118] Similarly, phthalic acid has been hydrogenated on Rh/Al_2O_3 in ordinary conditions. [56]

The production of 1,4-cyclohexanedimethanol has received attention. The conventional method is that dimethyl terephthalate is hydrogenated with a supported palladium catalyst at 160–180 °C and 300–480 bar. [80]

Adkins successfully hydrogenated diethyl phthalate into diethyl hexahydrophthalate over nickel at 200 °C in a 93% yield (Scheme 16). See also section 2.6.4.1, p. 49 for the ester. [23] The same reaction was also in Amend's patent, where Ni/SiO_2 was used at 138 bar and 160 °C. [119] The same for the dimethyl diester has been accomplished preparatively by *e.g.* McCusick with Raney nickel at 175 °C (no pressure given). [120] The more selective form, nickel reduced from nickel chloride with triethyl silane, hydrogenated the ring in dimethyl terephthalate at 50 atm and 135 °C. [114]



Scheme 16. Ring hydrogenation of a phthalate with nickel.

Halcour's patent (1981) concerns a catalyst where Ru is supported on a lithium-aluminum spinel. In the examples dimethyl phthalate was hydrogenated on $Ru/LiAlO_n$ at 100 bar and 140 °C and dimethyl isophthalate at 100 bar and 150 °C. [76] Spinels are more resistant to acids, and because water and acids are byproducts in aromatic ester hydrogenation, acid and water resistance is needed.

Itoh (SK NJC, 2001) patented a process where 0.5 % Ru/Al_2O_3 reduces the ring of a diester at 40 bar and 140 °C. At over 200 °C, side reactions are said to dominate. [121] Similarly, Brunner (BASF, 2005) has a patent where 0.8% Ru/Al_2O_3 hydrogenates the methyl esters of *e.g.* isophthalate and trimellitate, in THF at 200 bar and 80 °C. The isophthalate gives a 95% yield but the trimellitate gives only a 33% yield. [122]

Leon (ExxonMobil, 2004) patented a method of catalyst preparation where the metal forms an amine complex, which is then thermolyzed, improving the activity. Di-isononyl phthalate was hydrogenated with 0.5% Ru/SiO_2, using 5 w-% of this preparation with respect to substrate. Both catalysts were prepared from ruthenium nitrosyl nitrate, but triethanolamine was added to the impregnation solution for Leon's inventive catalyst. Within 7.5 h at 58 bar and 120 °C, the conversion was 93.7% for regular catalyst (1.22% lights) and 99.6% (0.44% lights) for Leon's catalyst. Also at 207 bar and 80 °C, in 3 h the conversion was 37.9% for regular catalyst and 73.5% for Leon's catalyst, approximately twice the conversion. Also, at 207 bar and 120 °C Leon's catalyst gave a conversion of 99.9% with 0.35% lights in 3 h; this was not compared to the regular catalyst. In this case, the preparation method improved activity by 32%. [87]

Schlosberg (ExxonMobil) has applied for a World Patent that claims hydrogenation of all phthalates on Ru, such as Ru/SiO_2, particularly mesoporous silica. The examples concern branched esters of phthalates. The pressure is 58 bar and the temperature 120 °C, conversion 97–99% and 0.35–0.90% lights are produced. [123]

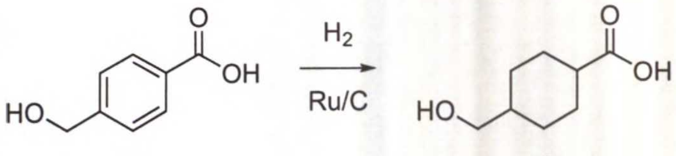
Another recent application is by Grass (Oxeno). It was found that Ru/TiO_2 is the best; it has the most micropores. The support must also be acid-resistant. Of these, α-Al_2O_3 catalyst is 20 times slower and ZrO_2 catalyst 2 times slower. Phthalic acid was hydrogenated with 0.8% Ru in H_2O at 100 bar in 100 °C, without catalyst deactivation, and DINP at 50 bar and 120 °C in 2.5 h. [124]

Phthalic acid salts have also been hydrogenated. In Ferstandig's 1958 patent, sodium isophthalate was hydrogenated on Ru black at 60–90 bar and 110 °C. [125]

2.6.3.3 Hydrogenation of benzylic alcohols

Benzylic alcohols are readily hydrogenolyzed and this may occur even on Adams PtO_2, when a low pressure (1–2 bar) and acidic solvent (AcOH) is used. [126]

In Satoh's patent, 5% Ru/C hydrogenated *p*-hydroxymethyl benzoic acid **46** with 87% selectivity to *p*-hydroxymethyl cyclohexane carboxylic acid **47**, at 49 bar and 100 °C (Scheme 17). [127, 128] The patent itself is chiefly about the oxidation of xylenes.



46 **47**

Scheme 17. Hydrogenation of a benzylic alcohol.

Adams observed that nickel catalyzes mainly hydrogenolysis to toluene for benzyl alcohol at 25–100 atm and 125–175 °C. [39] However, nickel reduced using triethylsilane was selective: at 60–70 bar and 130 °C, benzyl alcohol attained a 71% conversion in 4 h with 95% selectivity to hexahydrobenzyl alcohol. [114]

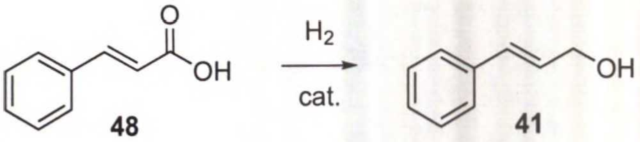
With RhPt, Nishimura reduced benzyl alcohol [37] and ethyl benzoate. [129] The procedure was similar to Adams platinum.

2.6.4 Hydrogenation of esters

Esters are typically hydrogenated with copper chromite in industrial practice, and $RuSn/Al_2O_3$ is possibly replacing it. Other catalysts are Ru/C at a very high pressure, rhenium (Re), and the combination RuRe. [130] Conditions are severe: 40–375 atm and 100–300 °C. [41] Hydrogenation of esters is an equilibrium reaction and is strongly favored by high hydrogen pressures. Hydrodeoxygenation increases when temperature is raised instead. The finding of the right temperature requires careful optimization.

2.6.4.1 Hydrogenation of esters with copper chromite

Copper chromite is usually promoted with barium oxide and requires high pressures and temperatures. At 220 atm and 120 °C, copper chromite hydrogenates fatty acid ethyl esters in 98% yield. [19] The reaction is used for production of fatty alcohols for *e.g.* detergents. The selectivity of copper chromite is illustrated by hydrogenation of cinnamic acid **48** into cinnamyl alcohol **41** at 220 atm and 120 °C (Scheme 18). [19] The aromatic and the conjugated olefin functions are not hydrogenated.



Scheme 18. Cinnamic acid selective hydrogenation.

Malonic and phenylethanoic acid esters deactivate copper chromite by causing reduction of the catalyst. [19] Copper chromite also hydrogenates lactones, *e.g.* pentanolactone into pentanediol in 83% yield at 200 atm, 250 °C. [41] Also, with or without barium, copper chromite hydrogenates a diester (diethyl adipate) at 138–207 bar and 255 °C. [131]

Copper chromite has to be used in a large amount; with a small amount, there is even no reaction. Ideally the temperature is low (as low as 125–150 °C, if possible) and the pressure must be high. The absolute activity of the catalyst is still low, and reactions are slow. For example, hydrogenation of an adipate diester took 12 h at high pressure (354 bar) and temperature (150 °C) with catalyst in excess (150 m-%). [132]

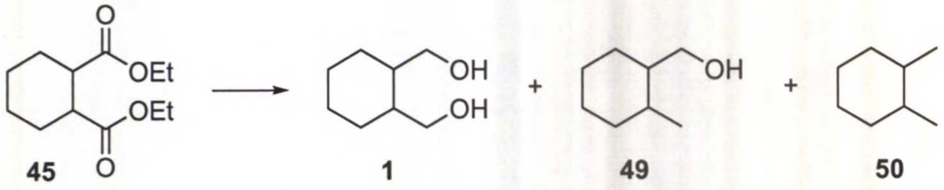
Lurgi has developed a process for hydrogenation of fatty acids via an ester. In this process, fatty alcohol from the process is esterified with the fatty acid, in an uncatalysed esterification driven by removal of water, and this "wax ester" is then hydrogenated with copper chromite. [133]

Side reactions may occur also on copper chromite. Aromatic alcohols may also hydrodeoxygenate on copper chromite, the reaction being sensitive to temperature. At 280 °C and 375 atm, aromatic alcohols are hydrogenolyzed (85%). [41] In the absence of hydrogen, aromatic carboxylates are decarboxylated, *e.g.* a quinoline in 83% yield at 230–250 °C. Overreduction, *i.e.* hydrodeoxygenation can also occur. [41]

Copper chromite can be reactivated by washing with acetone (volume $\frac{1}{4}$ of catalyst) and drying at 130–140 °C in air for 3 h. An oxidation reaction occurs, which may heat the material to incandescence. [134]

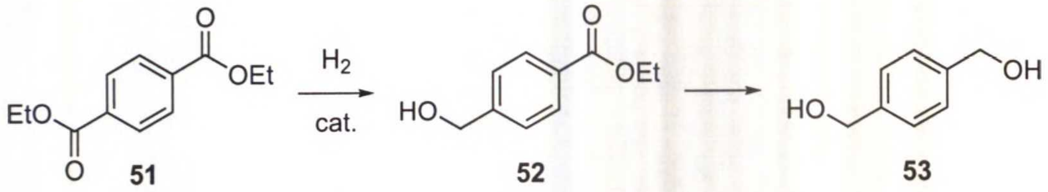
The alternative zinc chromite will also function as a Lewis acid, *e.g.* by catalysing aldol condensation of acetone. [18] Other similar catalysts are manganese chromite and copper-zinc oxide, the latter being inferior to copper chromite. [18]

Adkins *et al.* (1933) tried copper chromite at 100-170 atm and 250 °C for diethyl phthalate **44** and hexahydrophthalate **45**. The former **44** mostly hydrogenolysed and gave a maximum yield of 9% of the aromatic diol. The latter **45** gave a yield of 0–40% of the alicyclic diol **1** (Scheme 19). The main product was the monoalcohol **49**, with dimethylcyclohexane **50** as a minor side product. The temperature, 250 °C, appears to be too high, and the catalyst to substrate ratio was only 1:8. Thus, copper chromite may be a viable catalyst. [23]



Scheme 19. Products of diethyl hexahydrophthalate hydrogenation.

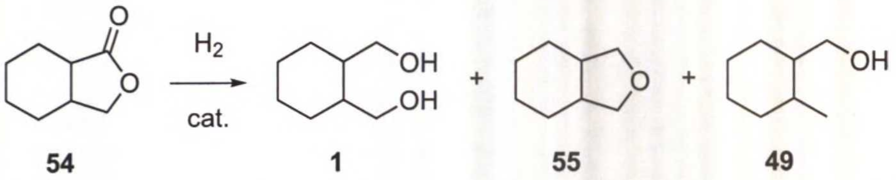
In Wanatabe's patent (Nippon Mining Co Ltd., 1972), barium-promoted copper chromite hydrogenated diethyl terephthalate **51** into *p*-xylelene glycol **53** in EtOH at 110 bar and 150 °C (Scheme 20). 70% of the result was diol **53**, and the rest consisted of the intermediate hydroxymethyl carboxylate **52**. With a 5.6:1 substrate-to-catalyst ratio, 67% conversion was be attained in 45 min. Wanatabe claims that a pressure of at least 60 bar is necessary. [135]



Scheme 20. Terephthalate ester hydrogenation.

In Itoh's patent (SK NJC Co Ltd., 2001), dimethyl terephthalate is reduced with Ru/Al_2O_3 and the ester with copper chromite at 200 bar and 230 °C. The solvent is the product, and the solution is dilute to control the exothermic reaction. [121]

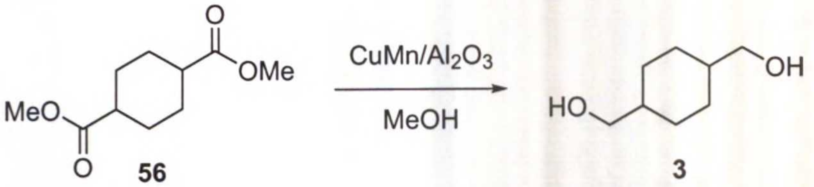
Bousquet's patent (du Pont, 1936) is about hydrogenation of the lactone hexahydrophthalide **54** (neat) into the diol **1**, using barium-promoted copper chromite. Without solvent, at 180–250 bar and 250 °C, a 51% yield of the diol **1** was produced with a 12:1 substrate-to-catalyst ratio in 7 h (Scheme 21). Side products were the cyclic ether octahydroisobenzofuran **55** and the hydrogenolysed methylcyclohexyl carbinol **49**. The ether **55** is produced by the facile dehydration of the diol, a reaction that is readily catalyzed by acids. [109] The hydrogenolysis product **49** probably forms by hydrogenolysis of the ether **55**. The direct hydrogenolysis of the lactone **54** would give a methylcyclohexyl carboxylic acid. The severe conditions probably explain the moderate yield of about 47%. Bousquet claims that 25 atm and 240 °C are the minimum. [136]



Scheme 21. Hydrogenation of the lactone **54** to diol **1** with side products ether **55** and hydrogenolyzed monoalcohol **49**.

2.6.4.2 Hydrogenation of esters with copper-manganese

Appleton's U.S. patent (Eastman, 1995) describes a gas-phase process where an aluminum-containing copper-manganese catalyst accomplishes hydrogenation of the methyl ester **56** at 40 bar and 200 °C (Scheme 22). The reaction mixture is maintained above its dew point. The catalyst contains only a trace of chromium (0.26%). The feed contains acidic material, particularly the corresponding monoester-acid. It is demonstrated that a copper chromite catalyst deactivates rapidly compared to this catalyst. [137]



Scheme 22. Gas-phase hydrogenation of the diester **56** into diol **3**.

Scarlett's U.S. patent (Eastman, 1993) describes in detail a process for the same gas-phase ester hydrogenation (Scheme 22) with CuMn at 62 bar and 220 °C. First, it is recognized that esterification, etherification and polymerization occur. It is necessary to reactivate the reactor, because the polymers produced by side reactions are not removed from copper. Secondly, pore distribution affects selectivity, which is illustrated in the examples. The catalyst is $CuMn/Al_2O_3$, with a 50 m^2/g surface area. Two near-identical preparations were made, both with ~50% micropores, but macropores and mesopores in different proportions: the good catalyst A with mostly macropores (80% of other than microporous surface area), and the mediocre catalyst B with fewer macropores (30%) and mostly mesopores. The feed was of 99,42% purity (sum of *cis* and *trans* isomers) and presumably from aromatic hydrogenation, with 0.17% monoester acid. The feed was diluted to 70% with methanol, and the gas to substrate ratio was high, 676–726. For the good, macroporous catalyst A, the selectivity was generally 99%. For the mediocre, mesoporous catalyst B, it was 97% in identical conditions. It improved to 98% by decreasing the hydrogen ratio to 382. All side reactions, hydrodeoxygenation (to **68**, Scheme 24), etherification (to **67**, Scheme 24) and miscellaneous, were faster with catalyst B. [75]

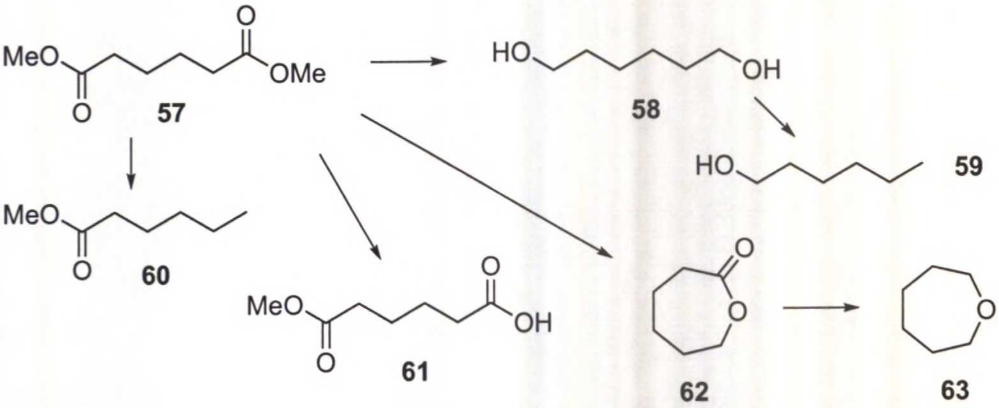
2.6.4.3 Other catalysts for hydrogenation of the ester function

Ruthenium as *e.g.* 10% Ru/C [54] or RuO_2 [25] works for ester hydrogenation at very high pressures. Water promotes ester hydrogenation on ruthenium and can be used as a solvent. For example, 10% Ru/C was used for dimethyl adipate hydrogenation at 520–700 atm and 150–175 °C with water as a solvent. [54] However, with monometallic catalysts at a less extreme pressure, the problem is that acids are produced instead of alcohols, *e.g.* dimethyl adipate gave monomethyl adipate over ruthenium (Scheme 23). [138]

Re_2O_7 (and also other rhenium compounds) hydrogenate esters. [25] For example, Re_2O_7 hydrogenated ethyl benzoate into benzyl alcohol in cyclohexane at 290 atm and 250 °C. The conversion was 89% in 48 h with 2 m-% rhenium. [26] That is, the activity is moderate but definite.

Raney nickel also hydrogenates esters at high pressures. [25]

Santos attempted hydrogenation of dimethyl adipate **57** with Ru, Pd, Rh and Pt on Al_2O_3 at 50 bar and 255 °C (Scheme 23). Clearly this pressure was insufficient for monometallic catalysts, which gave no 1,6-hexanediol **58**; instead undesidered hydrogenolysis reactions occurred. Ru/Al_2O_3 gave the acid **61** in 70% selectivity. Other catalysts (Pd, Rh, Pt) initially gave **61** but then hydrogenolysis occurred. [138]



Scheme 23. Reactions observed by Santos [138] in dimethyl adipate **57** hydrogenation. **59**, **60**, **61**, **63** are hydrogenolysis products.

2.6.4.4 Hydrogenation of esters with ruthenium-tin

Ruthenium-tin (RuSn) hydrogenates both esters and acids. In high temperatures and pressures, the product alcohol and the starting material form an intermediate ester. With RuSn, Pouilloux *et al.* found that the hydrogenation of "wax ester" is operationally the rate-determining step. Pouilloux *et al.* used RuSn/Al_2O_3 prereduced with $NaBH_4$ and hydrogenated methyl oleate into oleyl alcohol at 80 bar and 270 °C. [139]

The production of 1,4-cyclohexanedimethanol **3** from dimethyl terephthalate **64** is the subject of various patents and investigations. For example, Qiu's (Rugao Hengxiang Chemical, 2006) Chinese patent claims a trimetallic RuSnMn/Al_2O_3 (ruthenium-tin-manganese) catalyst for direct hydrogenation of **64** to **3** at 97–98% selectivity and conversion. The Ru loading was 5%, but tin and manganese loading was very small, 0.03–0.06%. The reaction was conducted in two phases: first, at 55–60 bar and 150 °C for 1 h, then 80 bar for 250–260 °C. [140] Presumably, the first conditions were for the ring and the second for the esters.

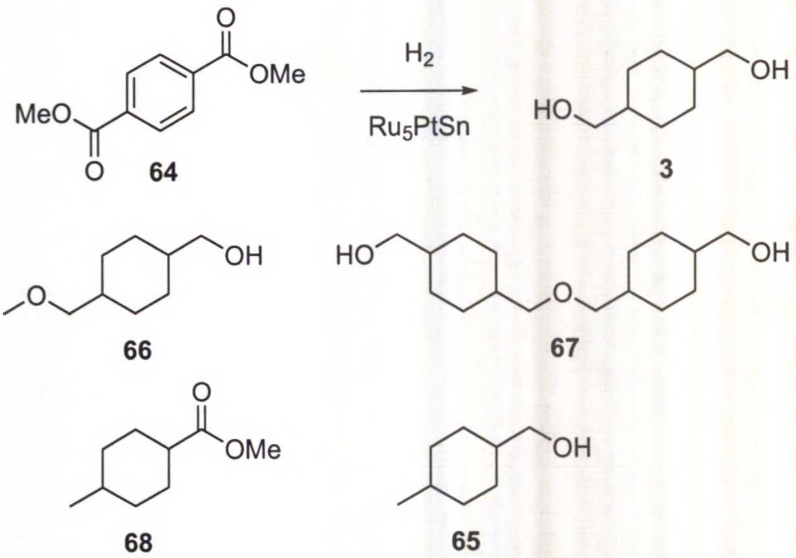
2.6.4.5 Hydrogenation of esters with ruthenium-based nanoparticles

Hydrogenation of dimethyl terephthalate (**64** ⟶ **3**, Scheme 24) has been used as a test reaction for nanoparticles. Raja *et al.* found that Ru_5Pt and $Ru_{10}Pt_2$ are exceptionally active and more selective than Ru_6Sn, Pd_6Ru_6 or Cu_4Ru_{12} for this reaction (all on SiO_2). The tests were at 20 bar and 100 °C, with EtOH as a solvent. Initial turnover frequency (TOF) was 155 h^{-1} for Ru_5Pt and 714 h^{-1} for $Ru_{10}Pt_2$ (in 4 h).

However, in the experiments, a small amount of catalyst (50:1 mass ratio) was used, and the yield was swamped by etherification of the products into dimers (see Scheme 24). $Ru_{10}Pt_2$ was more active and selective. In 24 h, Ru_5Pt gave a 37% conversion to a 61:39 mixture of ring-hydrogenated and diol dimer product. $Ru_{10}Pt_2$ gave 67% conversion to a 51:49 mixture. The conditions are remarkably mild for ester hydrogenation, although the results themselves are difficult to apply. [79]

Another catalyst for the same is Ru_5PtSn/SiO_2, described by Hungria *et al.* [80] The catalyst loading was extremely small, 0.31–0.53%,[1] and furthermore the mass ratio of this preparation to substrate was 1:50, so per metal, the ratio is 1:9400–16300. These reactions (Scheme 24) were more successful. In 24 h, at 20 bar and 100 °C, TOF was 242 h^{-1} and the conversion of 65% was attained to the mixture 63% diol **3**, 36% ring-hydrogenated product and only 1.5% dimers, with no hydrogenolysis. This result is impressive given the catalyst loading.

Even a slight increase in temperature from 100 °C to 120 °C and 140 °C immediately decreased selectivity. At 20 bar and 120 °C, the TOF was 290 h^{-1} and the conversion was 77%, but the product contained 8.9% hydrogenolysis products (**68**, **65**) and 16.4% dimers (**66**, **67**). A very similar product mixture was formed at 140 °C, except that the reaction time was shortened to one third at 8 h. It was found that RuPt and RuSn nanoparticles were inferior. Characteristically, Ru$_6$Sn caused hydrogenolysis and Ru$_5$Pt caused dimerization, and not *vice versa*. [80]



Scheme 24. Dimethyl terephthalate (**64**) hydrogenation over Ru$_5$PtSn nanoparticles with side products (**66**, **67**, **68**, **65**).

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[1] Source claims 0.0015–0.0025 mmol per 400 mg. For M(Ru$_5$PtSn) = 819.14 mg/mmol, it is 1.23–2.13 mg per 400 mg.

2.6.4.6 Hydrogenation of phthalates with zirconia

Zirconia (ZrO_2) is an inactive catalyst and generally gives aldehydes from esters, but Yokoyama found an anomaly: at 1 atm and 350–380 °C, dimethyl phthalate gives no aldehyde, but phthalide (55%) and a decarboxylated product (33.9 %) at 50.5% yield. [141] Dimethyl isophthalate and dimethyl terephthalate, where the carboxylates are not adjacent, gave aldehydes. Carboxylates bind strongly to zirconia, particularly dimethyl phthalate, which chelates with its two carboxylates. [142] The aldehyde is not as strongly bound, explaining the selectivity. Addition of Cr, In or Zn increased aldehyde selectivity.

2.6.5 Hydrogenation of carboxylic acids

Carboxylic acids are difficult to hydrogenate, and monometallic catalysts require extremely high pressures. In industrial practice, the problem of carboxylic acid hydrogenation is circumvented by conversion to esters followed by hydrogenation with copper chromite. There has recently been interest to develop a direct process. [70] Carboxylic acids can be hydrogenated on RuSn, as in RuSn/Al_2O_3, and Re or PtRe. The catalyst and support have to be resistant to acids and the produced water. Copper chromite is not acid-resistant and cannot be used; acids dissolve the copper and deactivate the catalyst. Similarly, γ-Al_2O_3 cannot be used as a support, because it is sensitive to water and acids. Spinel-structured supports have been developed for acid resistance.

Copper chromite is ineffective for acids: the reaction takes days, slows down with time, and has a low yield. It produces an intermediate wax ester. Ni and Pt hydrogenated the acid directly, but also caused hydrogenolysis. [143]

2.6.5.1 Hydrogenation of carboxylic acids with monometallic catalysts

RuO_2 and Ru/C (10%) hydrogenate carboxylic acids at a very high pressure of 520–700 bar and about 150 °C. Adipic acid was hydrogenated to give 48% 1,6-hexanediol after distillation. Pt/C and Pd/C were ineffective under the same conditions. [33] Other sources give the pressures and temperatures of 354–690 atm, 130–225 °C [35] and 600–800 atm, 250 °C. [144] However, at such conditions, esterification of the alcohol product with the acid produces an ester that retards the reaction and which Ru does not hydrogenate. [35]

Re_2O_7 hydrogenates monocarboxylic acids at 150–170 °C and dicarboxylic acids at 200-250 °C at 135–1270 atm. [26] Water reduces the formation of esters. Copper chromite is slightly better for ester hydrogenation, but rhenium is better for acids. Aromatics remain unreduced in the presence of carboxylic acids. Phenylacetic acid gave the alcohol and ester in 160 atm and 149 °C; however, benzoic acid hydrogenolyzed into toluene at 190 atm and 250 °C. Rhenium also hydrogenates aromatic esters: ethyl benzoate gave benzyl alcohol at 290 atm and 250 °C (11 h).

2.6.5.2 Hydrogenation of carboxylic acids with ruthenium-tin

Ruthenium-tin as $RuSn/Al_2O_3$ hydrogenates carboxylic acids, *e.g.* at 98 bar and 260 °C. [67, 68] Toba hydrogenated terephthalic, isophthalic and phthalic acid using $RuSn/Al_2O_3$ at 65 bar and 240 °C. [145] Generally saturated diacids gave good yields, but phthalic acids did not. Phthalic acid gave phthalide (lactone) in 80.4% yield. The reactions on isophthalic and terephthalic acids were unselective, mostly overhydrogenating. Acids are more reactive than esters on this catalyst. [145]

A trimetallic modification PtRuSn/C is more active than RuSn/C and was used for direct hydrogenation of terephthalic acid to 1,4-cyclohexanedimethanol at 85 bar and 230 °C (Scheme 25). The diacid was hydrogenated for 3 h in a 29% water solution with 1.6 m-% Ru substrate.[2] With 6% Ru-5% Sn/C, the conversion of 79.0% (rate 0.33 h^{-1}) gave a yield of 26% cyclohexane-1,4-dimethanol **3**, 35% monohydrogenated acid **47**, 17% dimeric esters such as **72**, 0.4% hydrogenolysis product **71** and 0.1% decarboxylation product **70**. The remaining 10% is not identified in the article. In contrast, with additional 2% Pt, the conversion of 98.4% (rate 1.11 h^{-1}) consisted of 82% cyclohexane-1,4-dimethanol **3**, 0.9% monohydrogenated acid **47**, 2% dimeric esters such as **72**, 0.7% hydrogenolysis product **71**, 0.6% decarboxylation product **70** and 13% not identified. In other words, the rate increased by a factor of 3.4, and less dimeric esters were produced. Although the amount of hydrogeno-

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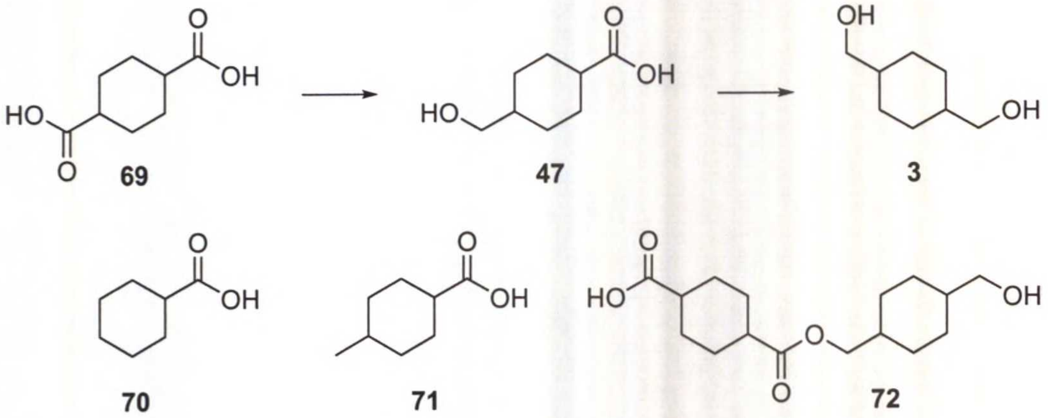
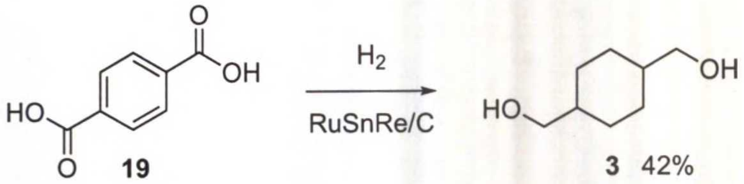
[2] Source claims 87 mmol cyclohexanedicarboxylic acid = 14.6 g, 4 g catalyst with 6% Ru, and 35 g water.

lysis and decarboxylation was higher, this is not to be overinterpreted, because the reaction was brought nearer to completion, where competetion between the main reaction and side reactions is greater. Also, it was said that at 100% conversion, the yield of cyclohexane-1,4-dimethanol was 93%, owing to formation of dimeric esters. Other loadings of platinum (1% 3.5%, 5%) were also tested and found to give a slower reaction, with significantly more decarboxylation (2.3% at 3.5% Pt) with increasing platinum loading. The catalyst PtSn/C had no activity at all in these conditions. [70]

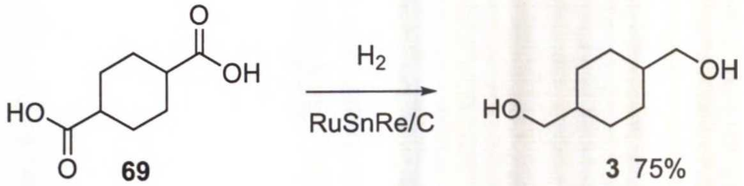


Scheme 25. Products observed in hydrogenation of terephthalic acid with RuSn and RuPtSn.

Konishi and Ueno patented (US, EP, JP, WO) catalysts based on RuSn/C for carboxylic acid and anhydride hydrogenation. The combinations tested were RuSn, RuSnRe, RuSnPt, RuSnMo, RuSnPd, RuSnAg and RuSnNi. Particularly RuSnRe was found to be active. The catalyst in the example was 5% Ru, 3.5% Sn and 5.6% Re on activated carbon. The carbon was activated with zinc chloride ($ZnCl_2$). [146] Direct hydrogenation of aromatics was attempted: terephthalic acid **19** was hydrogenated into cyclohexane-1,4-dimethanol **3** at 150 bar and 250 °C in H_2O, in 42% selectivity (at 97% conversion) with a 1:100 ruthenium-to-substrate mass ratio in 5 h (Scheme 26, Example 14 in patent). The other products were not identified in the patent, but they were probably products of hydrogenolysis, which is promoted by the aromatic ring. The ring-hydrogenated acid, cyclohexane-1,4-dicarboxylic acid **69**, was hydrogenated with 75% selectivity with a 1:140 ratio in the same conditions in 3.5 h (Scheme 27). [146]



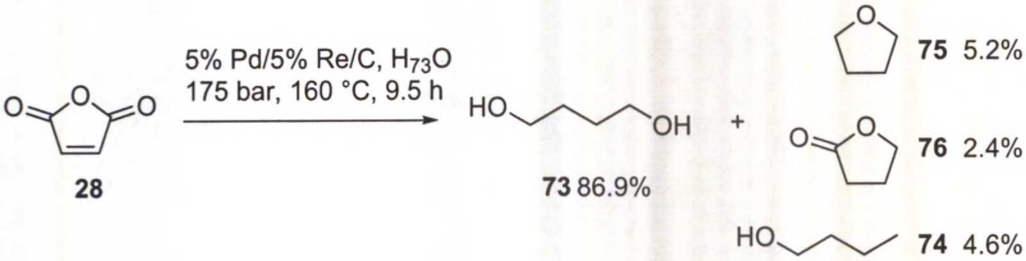
Scheme 26. Direct hydrogenation of terephthalic acid. [146]



Scheme 27. Hydrogenation of hexahydroterephthalic acid. [146]

2.6.5.3 Hydrogenation of carboxylic acids with rhenium catalysts

The hydrogenation of maleic acid (a butenedioic acid) into 1,4-butanediol has been studied for commercial applications. The challenge is that ring-closing reactions produce γ-butyrolactone and tetrahydrofuran. For example, in Pedersen's 1997 patent, a PdRe/C catalyst was used for hydrogenation of maleic acid **28** at 172 bar and 160 °C (Scheme 28). The carbon was specifically oxidized, *e.g.* with nitric acid. The main product (87%) is 1,4-butanediol **73** and side products are tetrahydrofuran **75**, γ-butyrolactone **76** and n-butanol **74**. In the process, the main reaction is to hydrogenate both acid anhydride and alkene functional groups. Pedersen claims 80–90% yield. [147]



Scheme 28. Catalytic hydrogenation of maleic anhydride with PdRe/C.

However, processes concerning C_4 compounds such as tetrahydrofuran are not directly applicable to the targets, because the in conditions described, C_4 compounds are often in the gaseous state. Heavier compounds may be liquids, which is significant because diffusion is slower and may lead to lower selectivity. On the contrary, the heavier analogue, adipic acid (C_6), has also been hydrogenated to 1,6-hexanediol with the same PdRe catalyst. [25]

Fischer (BASF, 2007) patented the PtRe catalyst and demonstrated that the ring-closing reaction of 1,4-butanediol can be run preparatively at low pressure. For example, at 20 bar and 235 °C, the same reaction as in Scheme 28 produced 37% tetrahydrofuran **75** and 43% γ-butyrolactone **76**, with only 1% diol **73**. [148]

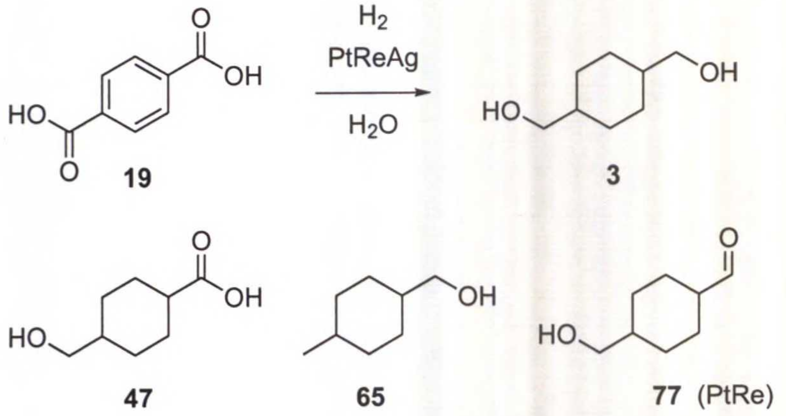
2.6.5.4 Hydrogenation of carboxylic acids with platinum-rhenium

Fischer's (BASF, 2001) patent claims the combination of Pd, Ru or Pt with Re and an additional metal, with PtRe as the best. In the examples, the combination PtReAg is used. The compounds PtO_2, Re_2O_7 and $Ag(OAc)_2$ in the mass ratio 1:2:1 were reduced in H_2O at 60 bar and 270 °C. The reaction works with metal oxides and salts as is, or deposited on a support. The resulting catalyst preparation contains a mixture of elements and intermetallic compounds. Terephthalic acid **19** was hydrogenated into 1,4-cyclohexanedimethanol **3** in 100 bar and 150 °C with a yield of 83%, in 2 h with 0.1 g PtO_2 and 0.2 g Re_2O_7 per 1 g of terephthalic acid (Scheme 29). The other products were the intermediate acid **47** and the hydrogenolysis product **65**. The former (**47**) represents partial conversion. With PtRe (no Ag), the yield was 71% and additionally an aldehyde intermediate **77** was found in the resulting mixture. [149]

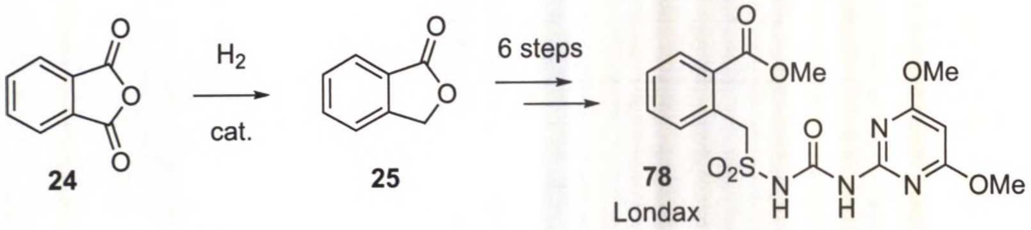
2.6.6 Hydrogenation of acid anhydrides

Acid anhydrides are readily reduced to the aldehyde oxidation level and into esters by most common catalysts. The water formed in the reaction hydrolyses the anhydride. [150]

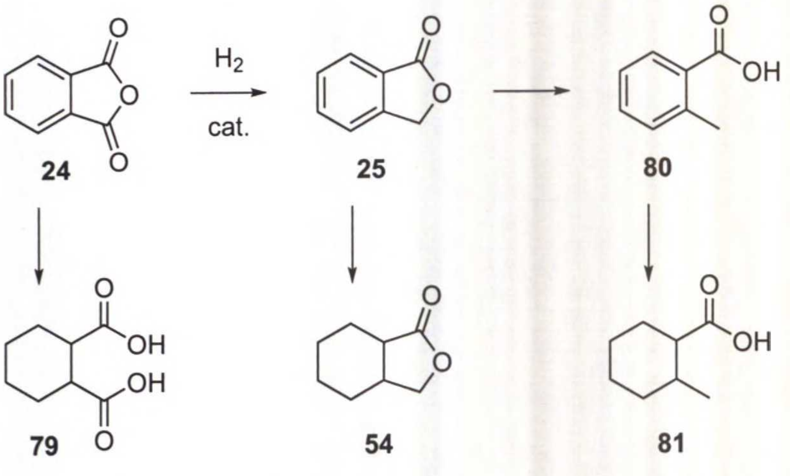
Cyclic anhydrides, such as phthalic and hexahydrophthalic anhydrides are a special case, because their re-dehydration is an equilibrium reaction favored by high



Scheme 29. Direct hydrogenation of terephthalic acid with PtReAg.



Scheme 30. The first step in production of Londax, a rice herbicide.



Scheme 31. Reactions in hydrogenation of phthalic anhydride. Adapted from Austin *et al.* 1937. [152]

temperatures due to steric reasons. An example of a commercial use of the hydrogenation of phthalic anhydride is that the product lactone, phthalide, has been produced from phthalic anhydride for uses such as an precursor to the rice herbicide Londax (Scheme 30). [151]

Willstätter and Jaquet (1918) hydrogenated phthalic anhydride **24** with platinum and acetic acid at ordinary conditions. Rather extensive hydrogenolysis occurred: the ring-hydrogenated product, hexahydrophthalide **54**, was formed in equal amounts to hydrogenolysis product (acid **81**) by mass, and additionally the anhydride was hydrolyzed and the ring-hydrogenated acid **79** accordingly produced (Scheme 31). [150] The reason for the result is that the acidic solvent and the benzylic position of the product alcohol promoted hydrogenolysis. It was found that oxygen activation of the platinum is necessary. Anhydrides inhibit the catalyst from aromatic hydrogenation, particularly phthalic anhydride. Even isophthalic acid often contains phthalic acid as an impurity that is a catalyst poison. [150]

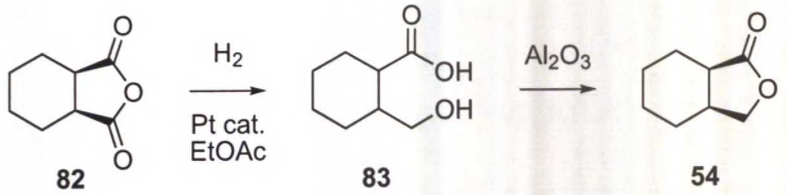
Austin *et al.* (1937) hydrogenated phthalic anhydride **24** to phthalide **25** with Raney nickel, nickel on silica and copper chromite. The main side reactions were hydrolysis and ring saturation to **79**, and hydrogenolysis to **80**, which was ring-hydrogenated to **81** (Scheme 31). Nickel was found to hydrogenate the rings also, to give hexahydrophthalide **54** and acids **79** and **81**. Hydrogenation with plain copper chromite and benzene as a solvent gave a 83% yield of phthalide **25** at 270 °C and 204–241 bar. Without a solvent, the yield was 56%. Barium-promoted copper chromite (Cu–Ba–Cr) was inferior, with 10% yield. Nickel was also a good catalyst for anhydride hydrogenation at 47–133 atm and 150 °C. On nickel, temperature had an effect on selectivity: at 140 °C, the reaction was slow; at 150 °C, 10% was lost to hydrogenolysis, and at 160 °C, 20%. [152] The use of copper chromite may, however, risk catalyst degradation, because of the co-presence of acid anhydrides and water producing a copper-chelating acid.

Adkins also investigated the hydrogenation of anhydrides with nickel and copper chromite and also confirmed the effect that the aromatic ring labilizes the carbinol towards hydrogenolysis. At 100–170 atm and 150 °C on nickel, phthalic anhydride **24** was converted unselectively to phthalide **25**, *o*-toluic acid **80** and hexahydrotoluic acid **81**. See section 2.6.4.1, p. 49 for esters. [23]

Manogue's (du Pont, 1990) U.S. patent describes the production of phthalide **25**, with the aim of avoiding ring saturation. Manogue claimed that existing methods involved solvents and catalysts that are either expensive or difficult to handle, or both. The U.S. patent claims anhydride hydrogenation with: any group VIII metal, any group VIII (platinum group) metal added with Re or Fe, specifically PdFe, PtReFe, on any support; and also the combinations RuRe, RuAg, and RuCu. In the description, recommended pressures are 34–53 bar and temperatures are 150–250 °C. In the patent examples, there are PdRe, in various proporties, promoted with varied amounts of $FeCl_3$, supported on carbon, SiO_2, and TiO_2, in addition to RuCu, RuAg, RhRe, and plain Ru/C. The selectivities are about 71–93% in various yields. RhRe/C, PtRe/C and $RuCu/La_2O_3$ are markedly slower, giving 7–8% conversion in same reaction time and identical conditions, as is RuRe/C, which gives 23% conversion with 82–86% selectivity. In the examples, the temperatures are either 150 °C or 200 °C; 250 °C gives a markedly lower selectivity (44–46%). Plain Ru/C gave no phthalide; the formed products were not identified. [151]

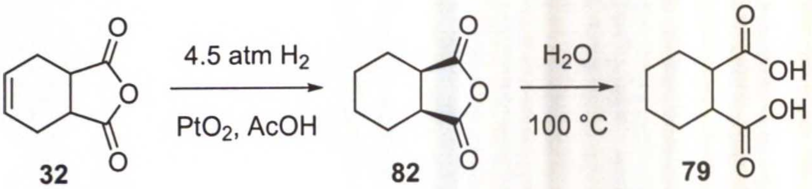
The World Patent of Henkelmann *et al.* (BASF, 2008) claims that the best catalysts for hydrogenation of phthalic anhydride (**24**) into phthalide (**25**) were $PdO \cdot PrO_2/Al_2O_3$, $PdO \cdot AgO \cdot MnO_2/Al_2O_3$, $NiO \cdot ZrO_2/SiO_2$, $RuSn/Al_2O_3$ (Scheme 31). The conditions were 260 bar and 200 °C. [8] PrO_2 is praseodymium oxide, a rare earth metal oxide.

McCrindle also hydrogenated cyclic anhydrides with platinum, in ethyl acetate. *Cis*-hexahydrophthalic anhydride **82** gave the hydroxyacid **83**, which was dehydrated to *cis*-hexahydrophthalide **54** on acidic Al_2O_3 (Scheme 32). As before, a large quantity of PtO_2 was used. In acetic acid, hydrogenolysis of the alcohol occurred instead to give 2-methyl acid **80**, even if the alcohol was not benzylic. McCrindle also found by IR that a hemiacylal is produced, and for some anhydrides, can be even isolated. [22]



Scheme 32. McCrindle's reaction sequence for hexahydrophthalide **54**.

The reactivity of cyclic anhydrides is not overwhelmingly high. Jenkins and Costello hydrogenated the Diels-Alder product, *cis*-Δ^4-tetrahydrophthalic anhydride **32** into hexahydrophthalic anhydride **82** directly with (excess) Adams platinum in AcOH at 4.5 atm and room temperature (Scheme 33). That is, the alkene bond reacted in presence of the anhydride. Furthermore, the produced anhydride was recrystallized from water at 0 °C. The hydrolysis was conducted in boiling water, from which the diacid crystallized on cooling. [5]



Scheme 33. Alkene hydrogenated in presence of an anhydride.

An interesting alternative for the production and further hydrogenation of lactones in general is the bimetallic catalyst NiRe, or the trimetallic catalyst NiMoRe. Nickel is usually not suitable for anhydrides, because it is deactivated by acids and in extreme cases may be dissolved. The addition of rhenium prevents this. The catalyst can produce γ-butyrolactone and tetrahydrofuran from succinic anhydride. The amount of added rhenium is rather small: 0.018–0.03 parts of Re per Ni was added to the 40% Ni on diatomaceous earth (calcium carbonate). [153] The role of molybdenum in this catalyst is to increase selectivity to tetrahydrofuran in a certain range of loadings. With no molybdenum, the lactone was the main product; selectivities were 74% for lactone, 20% for tetrahydrofuran and 6% for sundry hydrogenolysis products. With 0.1 parts molybdenum per nickel, nearly identical results were obtained as without molybdenum. However, in the optimal range for tetrahydrofuran production, between 0 and 0.1 Mo/Ni, the selectivities were 48% for lactone, 37% for tetrahydrofuran and 15% for hydrogenolysis. Hydrogenolysis and dehydration both increased. [153]

2.6.7 Hydrodeoxygenation of the product

Hydrogenolysis of the product alcohols removes oxygen (in a hydrodeoxygenation) and is an undesirable side reaction. The rate of hydrogenolysis increases in the order Ru < Rh < Pt < Pd; for palladium, it is faster than aromatic hydrogenation. [30] The reaction is promoted by Brønsted acids and protic solvents. It is also energetically favorable compared to hydrogenation: aldehydes have free energies lower than alkenes by 40 kcal mol^{-1}, thus it is easy to produce fully saturated products. [16] Hydrogenolysis produces water, which can be a problem. With benzyl alcohols, the solvent must be water-soluble, to prevent clumping of the catalyst wetted by hydrogenolysis-produced water. [30]

Hydrogenolysis occurs more readily in benzylic positions to produce methylaromatic compounds. This reaction is known for nickel, [16, 154] and even for Cu/Al_2O_3 in 150 atm at a high temperature, 300 °C. [17] Alcohols are the most sensitive: at 50 atm and 100 °C, hydrogenation of benzyl alcohol on Ru/C in H_2O produces 75% of cyclohexanemethanol and 25% of methylcyclohexane. [30]

Selective hydrogenation of two ester groups in a molecule is more difficult than one for several reasons. The first is pure probability. Let the probability of hydrodeoxygenation be p with one ester group, so that $1-p$ is the selectivity. Then, for a diester, the probability of both esters surviving is $(1-p)(1-p)$ — hydrodeoxygenation of either ester group represents a loss of yield — which gives a selectivity of $1-2p+p^2$. If p is small, the selectivity is about $1-2p$. Thus, a 90% monocarboxylate selectivity gives 81% dicarboxylate selectivity, other things being equal. The second problem is that the half-hydrogenated forms, hydroxymethyl carboxylates, can polymerize into polyesters.

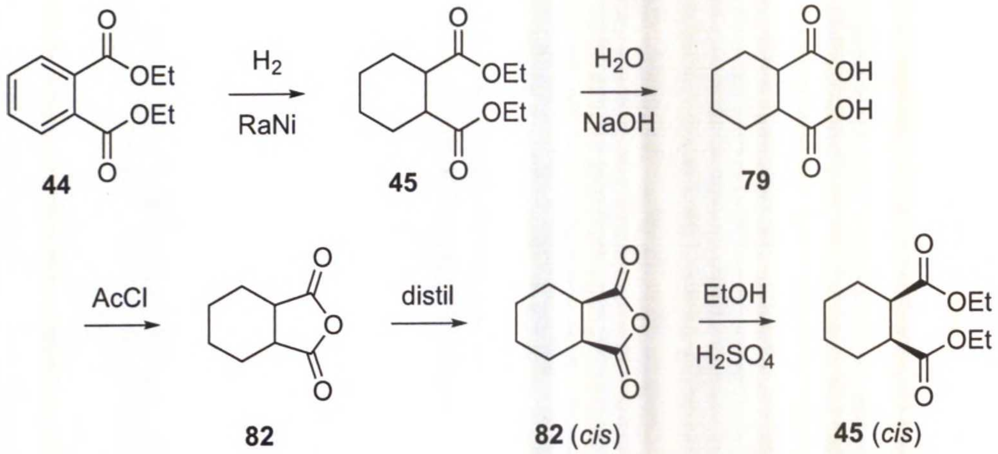
Increasing the dispersion of the catalyst decreases hydrogenolysis activity, suggesting that the hydrogenolysis site is a different, larger site than a hydrogenation site. [60] Hydrogenolysis can be reduced by poisoning the catalyst. The same principle operates as with poisoning: because the site has multiple atoms, addition of a poison reduces activity exponentially. Suppose we add 50 mol-% poison. Then, 1-atom sites deactivate to 50% of former activity, 2-atom sites to $(50\%)^2 = 25\%$, 4-atom sites to $(50\%)^4 = 6.25\%$, etc. Thus, the poison does not need chemical specificity towards hydrogenolysis sites in particular, in order to reduce hydrogenolysis more than hydrogenation. Examples of this phenomenon are *e.g.* PtSn, RuCu and RuAg. [60]

There is another phenomenon that can decrease hydrogenolysis, examplified with NiCu and RuCu. Copper is known to gather to the surface, because the cohesion in bulk copper is weaker than Ni-Cu or Ru-Cu adhesion. The result is that alkane hydrogenolysis is greatly reduced. For example, with nickel, adding a few percent copper, alkane hydrogenolysis activity is greatly reduced. At 5%, copper is the main metal at the surface. In the range 10–80% alkane hydrogenolysis activity is one fourth of that of nickel. Hydrogen adsorbs only weakly to copper, but both weakly and strongly (no desorption in vacuum) to nickel. [60] This explains the change of selectivity. The same phenomenon occurs with RuCu, although the metals do not form an alloy; *e.g.* 1.5% Cu reduces hydrogen adsorption by 60%, decreasing alkane hydrogenolysis by three orders of magnitude. 1.5% is a monolayer of Cu in this case (seen by XRD and ESCA-XPS). [60]

2.7 *Cis* and *trans* isomers of cyclohexanedimethanols

Hydrogenations of di-, or polysubstituted benzenes generally give a mixture of diastereomers, even though the *cis* isomer, produced by addition of hydrogen on the same side, is preferred. In the case of cyclohexanedicarboxylates and derived dimethanols, methods have been developed to produce only one isomer. The different diastereomers are significant because their properties are different and curiously, for **1**, the mixture of the solid isomers is a liquid. [109] Another example is that *cis*-cyclohexane-1,2-dimethanol is more readily dehydrated to the cyclic ether hexahydrophthalan **55** than its *trans* isomer. The *trans* form can be used as a monomer for PolyTHF-type polyether polymers, but the *cis* form cannot. [155]

Price and Schwarcz produced both isomers of the diester **45** from diethyl phthalate **44** via the anhydride **82** (Scheme 34). Raney nickel at 100 atm and 175 °C hydrogenated the ring (**44** → **45**), and after fractional distillation, the obtained diester **45** was hydrolyzed into the diacid **79**, a mixture of 75% *cis* to 25% *trans*. The mixture of acids was converted into anhydrides **82** with acetyl chloride, and distilled to separate the isomers. Re-esterification with EtOH and sulfuric acid gave the *cis*-diester **45**. In contrast, the *trans* form was obtained in 95% yield by refluxing the mixture of esters in 1% KOH/EtOH. [156] The alkali catalyses epimerization via an enolate intermediate that can be reprotonated to either isomer. The *trans* isomer is favored, because the substituents are both equatorial. [156]



Scheme 34. Price's route for pure diethyl *cis*-hexahydrophthalate.

Haggis and Owen investigated the *cis,trans*-isomerism of each of the positional isomers of cyclohexane dimethanol: 1,2-dimethanol **1**, [109] 1,3-dimethanol **2**, [157] and 1,4-dimethanol **3**. [130] The diols were produced from the corresponding dimethyl phthalates.

Dimethyl phthalate **86** was ring-hydrogenated in MeOH at 100 atm and 50–60 °C with Raney nickel. The *cis* isomer of the diethyl ester **45** was produced by the same method as above (Scheme 34). The *trans* isomer of **85** was produced directly by isomerization using sodium methoxide in methanol, rather than via the diacid as above. [109]

The 1,3-diester *cis,trans*-mixture was produced from diethyl isophthalate by hydrogenation with Raney nickel in ethanol at 100 atm and 100 °C. This was hydrolyzed to the acid. The *cis*-acid was precipitated as a calcium salt using $CaCl_2$. The yield was 50%. The *trans*-acid was obtained in low yield by isomerizing the mixture with HCl at 180 °C, precipitating the *cis*-acid, extracting the remaining mixture into ether, precipitating the *cis*-acid again and recrystallizing the *trans*-acid.

The diesters were reduced to dimethanols with $LiAlH_4$. Diethyl ether was used as the solvent. The reaction was quenched with "dilute" sulfuric acid, and the aqueous phase was continuously extracted with diethyl ether. [109] Another example of this is by Bartlett, who used hydrochloric acid. [158] The product is water-soluble, so that quenching with excess acidified water leads to this procedure.

The empirical *Auwers-Skita rules* are also mentioned: that *cis*-disubstituted cyclohexanes have higher boiling points, refractive index and density, and that *trans* isomers have higher melting points, lower solubilities and higher stabilities. It is found that this is true for cyclohexane-1,2-dimethanol **1** and cyclohexane-1,4-dimethanol **3**, but the reverse is true for cyclohexane-1,3-dimethanol **2**. [159] The reason for this can be rationalized geometrically by considering the equatorial or axial position of the substituents. In the 1,2-, and 1,4-configurations, the chair form of the *cis* isomer must have one axial and one equatorial substituent, while the *trans* isomer must have its substituents either both axial or both equatorial. The reverse is true for substituents in a 1,3-configuration.

If either isomer of the cyclohexane-1,2-, and -1,3-dimethanols are acceptable for a technical application, the *trans* isomer would be preferentially produced, because it dehydrates less readily. [155] This would require an isomerization of the precursor diester to *trans* form only. The catalyst would be sodium alkoxide for esters, such as sodium methoxide for methyl esters, [109] and sodium hydroxide for acids. [156] Another method patented in 1970 is the removal of *cis*-cyclohexane-1,2-dimethanol from an isomer mixture by preferential dehydration of the *cis* isomer. [155]

2.8 Reaction conditions for hydrogenations

It is preferable to use the lowest temperature possible to suppress side reactions. Generally, hydrogenation is always favored under 200 °C, and dehydrogenation and hydrogenolysis accelerate at higher temperatures. For example, Ipatieff hydrogenolyzed and cracked phthalic anhydride to toluene and *o*-xylene at 300 °C. [17]

With an excess of active catalyst, hydrogenations may occur at ordinary conditions within a reasonable time; the limitation is kinetic, not thermodynamic. For a faster rate, the optimum temperature is in the range 100–200 °C, [56] exact limits depending on the reaction. Aromatics have been hydrogenated in the 120–160 °C range. Hydrogenation of carboxylates over copper chromite or ruthenium-tin requires temperatures in the 200–250 °C range, *e.g.* 220–230 °C. Dehydration of alcohols, however, accelerates with higher temperatures.

2.9 Solvents for hydrogenations

Hydrogenations are generally surprisingly insensitive to solvent effects or pH, excluding solvents that actively poison the catalyst. Many kinds of solvents have been tried, *e.g.* alcohols like methanol and ethanol, alkanes like hexane and heptane, aromatics like benzene, ethers like tetrahydrofuran, 1,4-dioxane and diethyl ether, and acids like acetic acid. For most reactions, a neutral environment is preferred, because the reaction rate is largely insensitive to the pH, but an extreme pH may cause undesirable side reactions. Aprotic solvents may be used for alkenes and aromatics and protic solvents for hydrogenolysis reactions. [30] Acidity increases selectivity towards aromatic hydrogenation, for example rhodium hydrogenated the ketone function preferentially in MeOH and the benzene ring in AcOH. [30]

Furthermore, industrially it may be more cost-effective to use the product as a solvent. However, polymerization side reactions are accelerated. A solvent is recommended, because hydrogenation is an exothermic reaction. Without solvent, hotspots may form inside the reaction, initiating thermal runaway.

To promote rate itself, hydrogen adsorption should be large. In an early publication, the solvents ether, benzene and acetone were found to promote hydrogen adsorption; in water and pure ethanol, hydrogen adsorption was reduced; and alcohols gave an intermediate result. [91] Another concern is that proticity increases the rates of aromatic and carbonyl hydrogenation, but also readily promotes undesirable hydrogenolysis reactions. Thus, there is a balance. [30]

The solvent should not be reducible itself. This excludes aromatics like benzene, toluene and xylene, and carbonyl compounds like esters, ketones and carboxylic acids. Sulfur and nitrogen compounds would poison the catalyst. Organochlorides would be unacceptably toxic.

The solvent should also dissolve the relevant compounds. Nonpolar solvents like alkanes or polar solvents like water would not dissolve the starting materials and products. However, water can often be used as a solvent with carboxylic acids. Solubility is also often increased by temperature. The solvent should be polar and protic. Acids, however, promote undesired hydrogenolysis. Platinum virtually requires an acid, [35] but it is also selective. Another solubility concern is water formed in hydrogenolysis of acids an alcohols. The solvent must be water-soluble for *e.g.* benzyl alcohols for this reason. [30] This excludes alkanes.

Various sources recommend alcohol solvents, such as methanol and ethanol, and indeed, the above discussion demonstrates the motivation for this. The alcohol should have a relatively low boiling point for easy separation. Although methanol is inexpensive, it has a high vapor pressure, which cancels out some of the hydrogen pressure from the total pressure. Thus, a higher alcohol such as ethanol is better. In fact, Takagi found that for benzylic alcohol, ethanol is a slightly better solvent than methanol. [160]

2.9.1 Solvents for aromatic hydrogenation

Austin used ethanol with nickel for phthalide ring hydrogenation. [152]

Takagi investigated the effect of solvent on aromatic hydrogenation of benzyl alcohol and benzoic acid on Pt/Al_2O_3 and Ru/Al_2O_3 at 60 bar and 120 °C. Takagi also observed that cyclohexyl carbaldehyde is produced, probably by allylic rearrangement of the intermediate cyclohexene. With Pt/Al_2O_3, alcohols inhibited the catalyst. [160]

On Ru/Al_2O_3, a correlation between solvent properties and reactivity was found. Conducted neat, isomerization into an aldehyde and hydrogenolysis was greater than with alcohols. Methanol, ethanol and acetic acid had little or no effect on the reaction, giving 80% selectivity, and hexane or heptane were similar, although insignificantly slower. In contrast, acetone, tetrahydrofuran, 1,4-dioxane and diethyl ether inhibited the hydrogenation. The crucial difference is that promoters are net electron acceptors, which is quantified by the difference δ between their donor numbers (Lewis basicity) and acceptor numbers (Lewis acidity): $\delta = \mathrm{DN} - \mathrm{AN}$. All promoting solvents have negative δ values, while the inhibiting solvents have positive δ. [160] Furthermore, in alcohol solution, addition of a carboxylic acid of low relative permittivity, such as acetic acid, butyric acid or lauric acid, increased the rate, but promoted hydrogenolysis. Formic acid was a strong inhibitor due to its high relative permittivity. Additionally, it was found that isopropanol strongly suppressed hydrogenolysis and thus gave cyclohexyl carbaldehyde with a good selectivity. However, isopropanol gave a lower reaction rate, thus the conversion was only about ∼40% when hydrogenations with methanol, ethanol and no solvent reached ∼80% conversion. [160]

2.9.2 Solvents for phthalic anhydride hydrogenation

Willstätter used the corresponding acetic acid when hydrogenating phthalic anhydride with platinum. Rather extensive hydrogenolysis occurred, as indicated above, possibly because of the acidity of the solvent and the activation of the benzylic position. [150]

Austin found that the optimal solvent for the anhydride function depends critically on the catalyst. The conditions were 150–170 °C and 47–133 atm. Copper chromite gave best results with benzene, and did not work with ethanol or neat, resulting in hydrogenolysis. Barium-promoted copper chromite gave a worse result. Raney nickel was best with ethanol. The reason that alcoholysis does not prevent the reaction is because the 5-ring remains closed. Esters and alcohols could be used with nickel on silica. [152]

For production of phthalide from phthalic anhydride, the use of the product as a solvent has been patented by Massonne *et al.* (BASF, 2000). The catalyst was Raney nickel. [7]

3 Materials and methods

3.1 Summary of materials

3.1.1 Starting materials

Starting materials were obtained from SigmaAldrich and used as is, including dry tetrahydrofuran. Ethanol was Altia's Etax AA.

Dimethyl phthalate **86** is a liquid, mp 2 °C, bp. 282 °C. Dimethyl isophthalate **21** is a solid, mp. 64 °C. Phthalide **25** (*phthalolactone, 1-isobenzofuranone*) is a solid, mp. 71 °C, bp. 290 °C. Trimethyl trimellitate **70** is a solid, mp. 38–40 °C, bp. 194 °C at 12 mmHg.

The solubilities of phthalide **25** and dimethyl isophthalate **21** in ethanol were poor, and it was necessary to keep the concentrated solutions heated during handling. It was found that phthalide crystallizes out at 43 °C from a solution containing 1.79 g phthalide per gram of EtOH, *i.e.* 64% phthalide. Dilution of the mixture to 1.04 g/g EtOH (51%) reduced this temperature only slightly, or to 39 °C. The temperature of 43 °C is still an improvement over the melting point of phthalide at 71 °C. The same behavior was observed in dimethyl isophthalate.

3.1.2 Products

Hexahydrophthalide (*hexahydrophthalolactone, or 1-octahydroisobenzofuranone*), is an oil, bp. 70 °C at 15 mmHg. [109]

Dimethyl hexahydrophthalate is an oil, bp. 91–93 °C at 1.3 mmHg [120] or 110–112 °C at 5 mmHg. [6] It has been prepared from dimethyl phthalate using Raney nickel at 175 °C [120] or with nickel prepared from nickel carbonate and ammonia 200 °C. [23] Also, it has been prepared with the Diels-Alder route, where butadiene and maleic anhydride react to give tetrahydrophthalic anhydride, which is esterified with methanol and the alkene hydrogenated to give dimethyl hexahydrophthalate. [6] Disproportionation of dimethyl tetrahydrophthalate on Pd/C also gives dimethyl hexahydrophthalate (68.2%) and dimethyl phthalate (30.6%). [161, p. 973, Table III]

Cyclohexane-1,2-dimethanol isomers are solids, but the mixture is a syrupy liquid, [109] bp. 102–103 °C at 1 mmHg. [158] It has been prepared mainly using $LiAlH_4$, with few exceptions. The $LiAlH_4$ has been quenched with acid. [109] [158] The diol has been prepared to produce the dehydrated cyclic ether for PolyTHF monomer use. [162]

Cyclohexane-1,3-dimethanol has been prepared with $LiAlH_4$ from the diethyl ester (10% HCl quench). [163] Like cyclohexane-1,2-dimethanol, this diol can be dehydrated to a cyclic ether. [162]

Hexahydrophthalic acid was first prepared by Baeyer in 1871. The starting material was mellitic acid (benzenehexahydrocarboxylic acid), which was pyrolyzed, and the tetrahydrophthalic acid obtained was reduced by dissolving sodium. [164]

3.2 General procedures for hydrogenations

The tests carried out in this work were batch hydrogenations run in an 300 ml Parr Model 4566 minireactor at a maximum of 100 bar. The reactor was filled half-full (*ca.* 150 ml). The catalyst was placed in a spinning basket and two side baskets. The spinning rate was 400 rpm. The reactor was equipped with a heating mantle and an internal temperature controller.

The systems were leak-tested to 100 bar. The choices for hydrogen feed were from a flow meter and directly from the pressure-regulating valve of the bottle. The flow meter was rated to 100 bar and furthermore a pressure drop over the meter was required. Thus, the flow meter could not be used at the full 100 bar.

The apparatus is depicted in Figure 8. The pressure vessel had a gas inlet line with sintered metal bubbler. The gas inlet line was connected hydrogen and nitrogen lines with flow meters. The hydrogen flow meter had a bypass that allowed direct admittance of gas from the bottle. The flow meter could be insulated from backflow and excess pressure with the two valves before and after the meter. In contrast, the nitrogen inlet line had only a flow meter.

The reactor had two outlet lines. The sampling line extended to the bottom of the vessel and had a sintered metal endpiece. The other, vapor outlet/manual feed line, was only connected to an opening of the top. The vapor outlet line had a water-cooled condenser and two consecutive spring-operated constant-pressure valves, and a bypass line directly to the dump line. The dump was a large metal drum vented to the ventilation. The manual feed line was used to pressurize the vessel with nitrogen, and feed the reactant with nitrogen pressure. The nitrogen feed and the feed vessel were manually connected each time they were needed.

The reactions were conducted to the following procedure. The catalyst was packed into the baskets, where no special precautions were taken to exclude air. The apparatus was assembled and leak tests were conducted with nitrogen and then hydrogen at 100 bar. The catalysts were then activated overnight in a hydrogen flow of 6–10 l/h and 200-210 °C. The system was then cooled to below the boiling point of the solvent, and the reactor flushed with nitrogen.

A pressure vessel was evacuated into a vacuum and the pre-mixed reaction solution was sucked in. The vessel was connected to the reactor feed line and the manual-feed nitrogen line, and pressurized to 3–14 bar. This pressure propelled the feed into the reactor. Then, the reactor was flushed 2–3 times with hydrogen, to remove the nitrogen. The system was pressurized near the target pressure — to keep the volatiles liquid during heating — and heated to target temperature, with hydrogen flow on if indicated. At this temperature, the pressure was rechecked and adjusted manually if necessary.

Two methods of adding hydrogen were used. In the "flow" method, hydrogen was led through the flow meter, and outflow gases were led to the pressure relief valve,

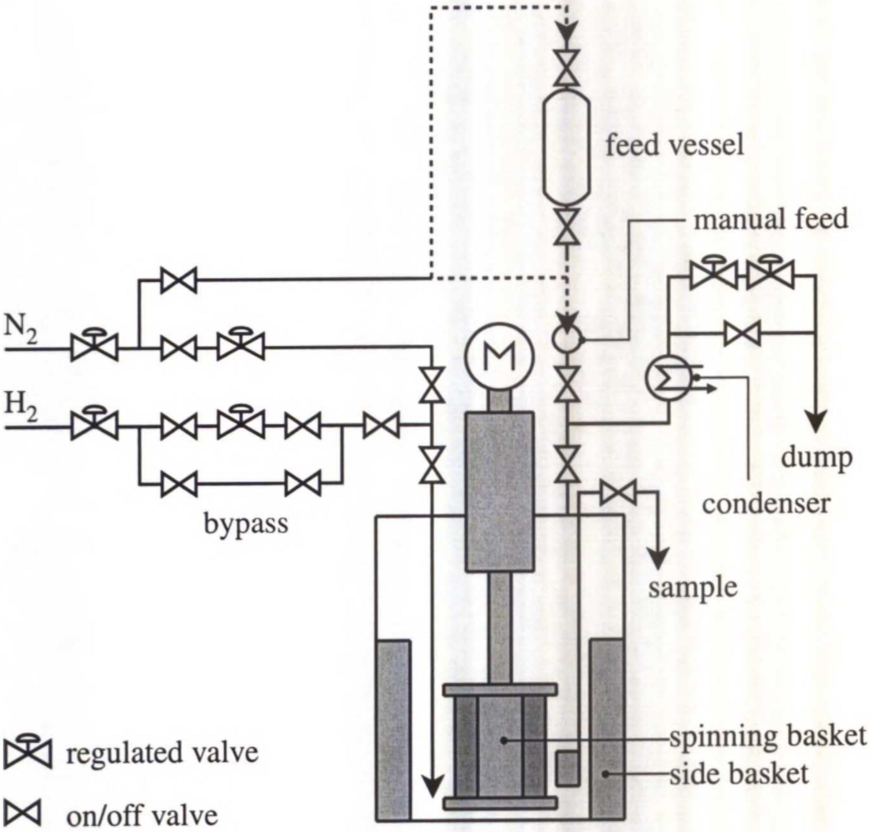


Figure 8. The Parr reactor assembly employed. Broken lines: manually connected lines.

which was adjusted to the desired pressure. In the "bomb" method, hydrogen was led directly from the bottle via the bypass line. The pressure relief valve was still used for safety, but it was set to a higher pressure than the operating pressure.

The reaction was terminated by removing the heating mantle and replacing it with an empty kettle, and then pouring water on the reactor and into the kettle, rapidly cooling the reactor. The reactor was then left pressurized to cool completely. After cooling, the pressure was carefully released, and hydrogen replaced with nitrogen. The reactor was disassembled, the solution decanted and the catalyst removed. The catalyst was washed twice with solvent. The solutions were filtered with a Büchner funnel until clear, and solvents evaporated in a rotavapor, to give crude product.

The crude product was evaporated at 70 °C in 5 mbar and then distilled under reduced pressure at 5 mbar. Generally temperatures near 100 °C were sufficient. The cold trap was cooled with dry ice.

3.2.1 Analysis

The reaction was monitored by taking samples (0.1–1 ml), from a sampling line with a sintered metal cap, into closed vials. The sampling line was flushed by taking a smaller dummy sample before each sample. The weight of the liquid withdrawn was measured.

Gas chromatography was analyzed with area percent only, without calibration. No internal standard was used, and peaks were identified by retention time and relative order. The gas chromatograph used was an Agilent 6850 with a flame ionization detector. The column was a DB-5 column (J&W 100-2000), length 30 m, internal diameter 0.32 mm, 1.00 μm film. The rate of heating was 10 °C/min from 40 °C to 325 °C. The method produced solvent peaks at under 3 min and main products in the 10–25 min range, with cyclohexanes between these ranges (~6–8 min). The peaks of solvents (acetone, ethanol) were not integrated.

Diluted samples for GC were prepared by taking ~30 mg of sample and adding acetone such that the total concentration was 25–30 mg/ml. Furthermore, in special cases, water content was measured with an automated Karl Fischer titrator.

GC with silylation was conducted in an analogous way using a different machine reserved for the purpose. ~50 mg of sample was diluted in 1 ml of pyridine and 0.5 ml of BSTFA (**84**, Figure 9) was added. The reagent derivatizes alcohols into trimethylsilyl ethers, changing the elution time.

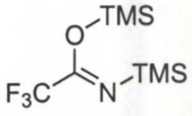


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Figure 9. Bis(trimethylsilyl)trifluoroacetamide. TMS = trimethylsilyl.

GC-MS analysis with interpretation of results was ordered from Neste Oil, Oil Refining division, Research and Technology unit. Peaks larger than 1% were identified. NMR was measured with a Bruker Avance 400 (^{1}H 399.98 MHz, ^{13}C 100.59 MHz) spectrometer, with samples dissolved in $CDCl_3$, and standardized to the $CDCl_3$ residual peak.

3.3 Catalysts

The catalysts used were 1% Pt/Al_2O_3, 2% Ru/C, RuSn/C and RuPtSn/C. Platinum, 1% on 3 mm alumina pellets, was purchased from SigmaAldrich and used as such. Ruthenium, 2% on granular (5 mm) coconut carbon was obtained from Engelhard. The Ru/C was wetted such that 40% of its weight was water; thus, as supplied, it had 1.22% by weight of Ru. RuSn/C and RuPtSn/C were prepared from existing Ru/C.

RuSn was prepared by impregnation with $SnCl_2$. Using a rotavapor for rotating the vessel, 60.01 g (wet weight) 2% Ru on granular carbon catalyst was kept overnight in a solution of 1.07 g $SnCl_2 \cdot 2\,H_2O$ in 51.64 g EtOH. Solvents were then evaporated to leave 52.47 g catalyst, nominally 1.54% Sn. The ethanol dissolves water from the wetted catalyst, but does not evaporate completely, which causes the partial mass loss.

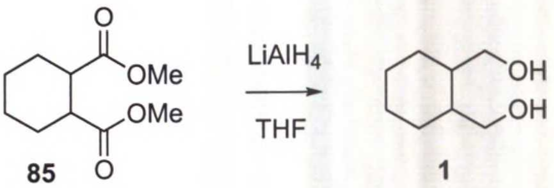
RuPtSn was prepared by precipitation of H_2PtCl_6 with formaldehyde and then impregnation with tin(II) chloride dihydrate under nitrogen. 80.02 g (wet weight, 40% water) of 2% Ru/C catalyst was partially dried under vacuum. The catalyst was immersed in a solution of 0.8735 g hexachloroplatinic acid in 140.73 g water and mixed for 1 h. Then, a small amount (<3 ml) of 20% NaOH was added to adjust the pH to 12. Within the period of an hour, 13.62 g of formaldehyde (37%) in water was slowly added while simultaneously adding 20% NaOH small amounts (<3 ml) at a time to maintain the pH at 12. The solution was then filtered off with a Büchner funnel, and the catalyst was washed with water, such that the washwater had a pH of 7–8. Then, 37 g of EtOH was added to dissolve the water. The vessel was then attached to a rotavapor and solvents were evaporated (10 mbar in 70 °C). The catalyst was mixed with 0.4934 g $SnCl_2 \cdot 2\,H_2O$ and 60.25 g EtOH. Air was purged and replaced with nitrogen by depressurizing to 200 mbar and admitting nitrogen, and repeating this three times. The vessel was left to rotate overnight, without specific heating, although there was 64 °C of residual heat from the previous procedure. The solvents were evaporated to leave 68.44 g of catalyst. Its water or ethanol content was not measured, but self-heating on exposure to the atmosphere was observed. The metal contents per dry weight, nominally based on added amounts, are 2% Ru, 0.69% Pt and 0.38% Sn.

3.4 Lithium aluminum hydride reductions

$LiAlH_4$ was handled in a glove bag. The apparatus was assembled according to the teachings of Vogel. [165] There was a continuous flow of nitrogen for blanketing the reaction. A difference to Vogel's procedure was that for preventing backflow of moisture, the drying tube was replaced by a dry ice cold trap to additionally capture solvent carried by the blanket nitrogen. The reaction was stirred with a stirring rod. The temperature was maintained below the boiling point of THF.

4 Results

4.1 Cyclohexane-1,2-dimethanol



Cyclohexane-1,2-dimethanol was produced with $LiAlH_4$ for testing purposes. First, the reaction was tested with a small amount (14 g) and then at full scale (90 g). In the first case, quenching with H_2O and $Na_2SO_4 \cdot 10\,H_2O$ was tried unsuccessfully, but in the second case, quenching with H_2O, 20% NaOH and H_2O was used. The large-scale reduction (section 4.1.2, p. 78) with $LiAlH_4$ was successful at 84% yield, with 98.9% GC purity. It was apparent also here that $LiAlH_4$ reductions are quantitative, but some yield may be lost into the filter cake.

The quench with, sequentially, water, NaOH solution, and water was found to be a good procedure. Sodium sulfate decahydrate and water produced a gel that was impossible to filter using a sintered glass funnel, which immediately blocked. Also, $MeOH/CH_2Cl_2$ was found to do the same. Aluminum dissolves in methanol as a methoxide, which could explain the crystals in the filtrate and the clogging.

4.1.1 Small scale

To a solution of lithium aluminum hydride (purity 95%, 3.36 g, 84.1 mmol, 123.5 mol-%) in THF (130 g) was added a solution of dimethyl cyclohexane-1,2-carboxylate (purity 97.5%, 13.99 g, 68.1 mmol, 100 mol-%) in THF (27.46 g) within 35 min. After cooling, the reaction was quenched with water (2.87 g, 159.3 mmol, 233.9 mol-%) in THF (2.80 g) and sodium sulfate decahydrate (5.02 g, 15.6 mmol, 22.9 mol-%). Then, dry Na_2SO_4 (1.86 g) was added. Filtration was attempted, but the mixture clogged the sintered glass funnel. 20% NaOH (3 g) was added, then the solution was readily filtered. Solvents were evaporated, the crude product rediluted with CH_2Cl_2 (35 g) and dried again with Na_2SO_4 (0.92 g). After filtering and evaporation of solvent, 4.71 g (47% yield, 98.9% GC purity) cyclohexane-1,2-dimethanol was obtained as a yellow syrupy liquid. Extraction of the filter cake was attempted with 10% MeOH-CH_2Cl_2, but the filter was again clogged by the solution. White crystals could be seen in the filtrate.

4.1.2 Large scale

To a solution of lithium aluminum hydride (purity 95%, 20 g, 500.6 mmol, 113.6 mol-%) in THF (850 g) was added a solution of dimethyl cyclohexane-1,2-carboxylate (purity 97.5%, 90.04 g, 440.7 mmol, 100 mol-%) in THF (162.71 g) within 1 h. Near the end, a water bath was used. After cooling, the reaction was quenched with sequentially: water (21.0 g, 1166 mmol, 264.5 mol-%), 20% NaOH in water (21.04 g, 105.2 mmol NaOH, 23.9 mol-%), and water (20.98 g, 1165 mmol, 264.3 mol-%). The quench caused flocculation of the mixture, which was left to stand overnight. The mixture was filtered through a pad of Celite and solvents were evaporated to give 38.03 g (59%) crude product (clear, yellow syrup). 700 ml of solvent was recovered from the rotavapor and 100 ml from the cold trap. The filter cake was extracted with recycled solvent; first, in three parts, giving 16.81 g more crude product (total 54.84 g, 85%) and then in two parts, giving 6.36 g more crude product (total 61.2 g, 94%). The combined crudes were redissolved in dry THF (53 g), dried with Na_2SO_4 (3 g) and solvents were evaporated to give 53.95 g cyclohexane-1,2-dimethanol (84% yield, 98.9% GC purity) as a yellow syrup.

The product was compared with authentic material, ordered from SigmaAldrich, with GC and ^1H NMR. Additionally, ^{13}C NMR was run and compared to values from literature. According to GC, the product was 98.9% pure and contained 91.6% *cis* isomer. In ^1H NMR, the product had a significantly broader hydroxyl proton peak than the authentic material, and it was at 4.36 rather than at 4.31. Disregarding this and some minor impurity peaks, the ^{1}H NMR spectra were similar. The coupling constants were within ±0.1 ppm of each other. However, the ^{13}C NMR spectrum showed the signatures of both *cis* and *trans* isomers, as found in the literature. [166, p. 9462]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.36 (2H bs, OH); δ 3.66–3.62 (2H dd, J_1 7.98 Hz, J_2 -11.02 Hz, 1); δ 3.48–3.44 (2H dd, J_1 4.24 Hz, J_2 -11.08 Hz, 1); δ 1.87–1.80 (2H m, 2); δ 1.49–1.44 (2H m, 3); δ 1.42–1.29 (2H m, 4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 67.44 (*trans*, 1); δ 63.86 (*cis*, 1); δ 44.57 (*trans*, 2); δ 39.92 (*cis*, 2); δ 29.75 (*trans*, 3); δ 27.16 (*cis*, 3); δ 26.06 (*trans*, 4); δ 24.03 (*cis*, 4).

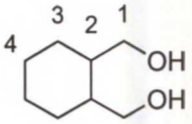


Figure 10. Identification of positions in cyclohexane-1,2-dimethanol.

4.2 Hydrogenations

A summary of hydrogenation experiments run are shown in Scheme 35 and Table 1. There are two points to be taken into account. First, only the intended product is counted towards the yield in the summary. Second, it was evident that the procedure to recover the reaction solution was imperfect, resulting in somewhat lower yield than the GC purity of the final sample would suggest.

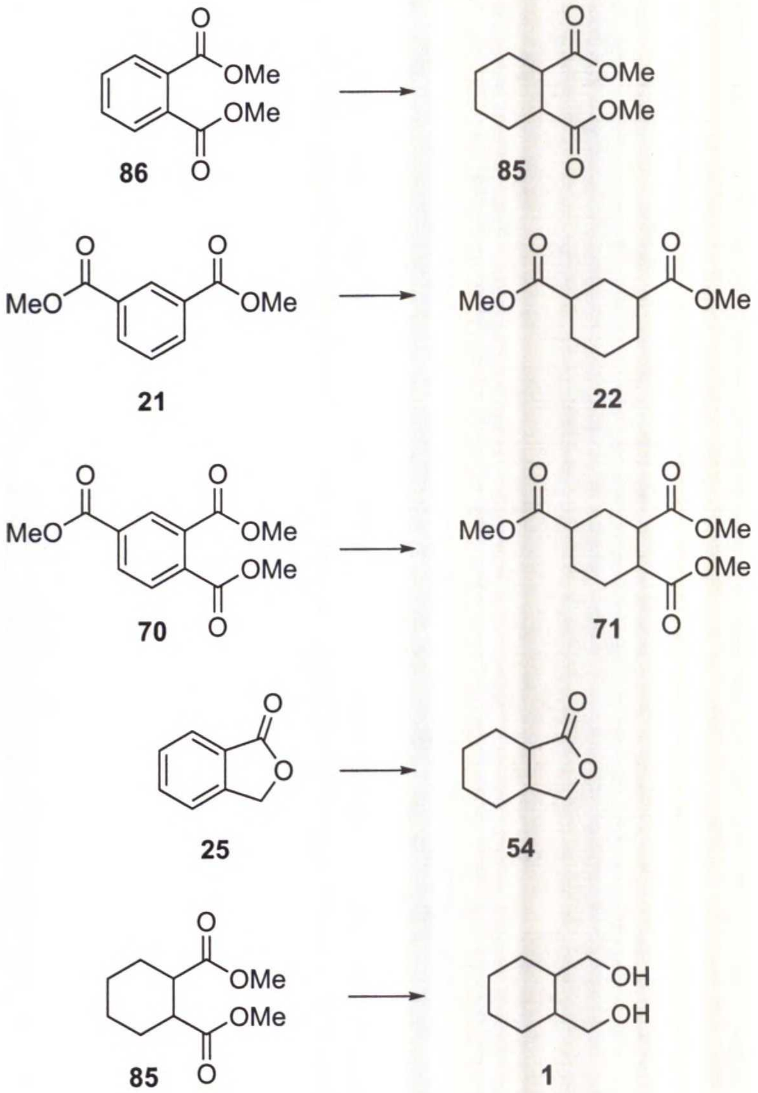
4.2.1 Ring hydrogenations with Ru/C

Pt/Al_2O_3 was unsuccessfully tried for ring hydrogenation (reactions 1, 2, 3, and 4 in Table 1). The reactions did not succeed at elevated temperatures and pressures. A common pattern was that reactions suddenly stopped at low conversion. After the reaction it was also noticed that the solutions were cloudy. This was evidently the result of the alumina dissolving in the solvent. The probable reason for this is water from hydrogenolysis. Evidently the catalyst was readily deactivated by plugging.

Table 1. Summary of hydrogenations. Incidental products were not counted towards the yield, only intended targets.

Run	Substrate	Catalyst	Solvent	P (bar)	T (C)	Time (h)	Cat. m-%	Yield (crude)	Target
1	phthalate **86**	Pt/Al_2O_3	neat	17–21	20	12.5	0.13	no reaction	hexahydrophthalate **85**
2	phthalate **86**	Pt/Al_2O_3	neat	18–58	118	13.5	0.12	stops at 5%	hexahydrophthalate **85**
3	phthalate **86**	Pt/Al_2O_3	neat	54–68	106	20	0.16	stops at 3.65%	hexahydrophthalate **85**
4	phthalate **86**	Pt/Al_2O_3	neat	83–105	120	3.5	0.46	stops	hexahydrophthalate **85**
5	phthalate **86**	Ru/C	neat	79–100	120	71[1]	0.25	48% (55%)	hexahydrophthalate **85**
6	phthalate **86**	Ru/C	AcOH-EtOH	95–100	120	22	0.51	74% (83%)	hexahydrophthalate **85**
7	phthalate **86**	Ru/C	AcOH	95–100	120	30	0.28	79% (84%)	hexahydrophthalate **85**
8	phthalate **86**	Ru/C	EtOH	80–100	120–140	28	0.27	76% (80%)	hexahydrophthalate **85**
9	isophthalate **21**	Ru/C	EtOH	80–95	120	21.5	1.00	66% (74%)[3]	hexahydroisophthalate **22**
10	isophthalate **21**	Ru/C	EtOH	86–92	140	45	0.30	— (39%)	hexahydroisophthalate **22**
11	trimellitate **70**	Ru/C	EtOH	88–97	120	95[1]	0.37	stops (29%)[4]	hexahydrotrimellitate **71**
12	phthalide **25**	Ru/C	EtOH	82–87	140	45	0.30	— (46%)	hexahydrophthalide **54**
13	hexahydrophthalate **85**	$CuCrBaO_x$	EtOH	95–98	150–200	50	39.1	— (6%)[5]	dimethanol **1**
14	hexahydrophthalate **85**	RuSn	EtOH	84–94	240	31	0.72[2]	— (0.23%)[6]	dimethanol **1**
15	hexahydrophthalate **85**	RuPtSn	EtOH	88–90	175–230	95	0.92[2]	—[7]	dimethanol **1**

[1] left to run over weekend
[2] catalyst m-% based on ruthenium
[3] including ethyl esters from transesterification
[4] stops at 39% conversion, purification failed
[5] crude contained 6% diol and 8% hexahydrophthalide
[6] mainly hexahydrophthalide and hexahydrophthalan
[7] product recovery failed; 66% conversion, 9% phthalide

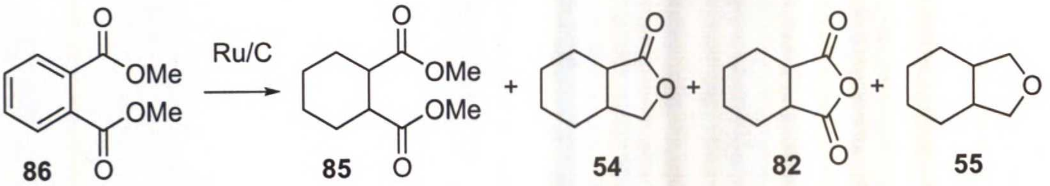


Scheme 35. Summary of intended reactions.

Ru/C, on the other hand, was found to be a reliable catalyst in most cases (reactions 5, 6, 7, 8, 9 and 10). The exceptions are that trimellitate stopped at 39% conversion (reaction 11) and that in phthalide hydrogenation, selectivity was mediocre (reaction 12): only 57% of the reaction mixture was hexahydrophthalide with 5.7% phthalide remaining, the rest (37%) being lost to side reactions. The solvents EtOH and AcOH did not have major effects on reaction rate, but the *cis*-selectivity was found to be 90% with and 80% without AcOH.

Monitoring the reaction with pressure drop was attempted. Calculations showed that the correlation between conversion, as definitely measured by GC, and pressure drop was not stable enough to be usable for reaction monitoring. In reaction 5, it was seen that if the system was closed, the pressure decreased linearly in the 75–100 bar range.

4.2.1.1 Ring hydrogenation of dimethyl phthalate with Ru/C



In reaction 5, dimethyl phthalate (146.48 g) was hydrogenated neat with Ru/C (30.1897 g, or 0.25% Ru per substrate) at 95 bar and 120 °C with hydrogen pressure directly from the bottle. Samples were taken only to 5 h and 32 min, and the reaction was left running over the weekend. In the end, the reaction mixture contained 96.5% dimethyl hexahydrophthalate **85** (of which 78.7% *cis* and 21.3% *trans*) 1.6% hexahydrophthalide **54**, 0.3% hexahydrophthalic anhydride **82** and 0.6% unreacted dimethyl phthalate **86**. The compounds were identified by GC-MS.

The reaction mixture, a clear, slightly viscous liquid with the fruity smell of ester, was decanted (113.06 g) and filtered (109.85 g), without washing the catalyst. Karl Fischer titration indicated a water content of 1%. Thus, drying was attempted. 10 g of K_2CO_3 was mixed in, but this formed a paste that was difficult to filter. It was filtered twice using a Büchner funnel, still leaving it cloudy and losing 20% of the mass to leave 83.56 g (55%) crude, with 0.27% water content. The crude product was distilled at 106.5–107.0 °C and 5 mbar. Four fractions were collected, the first (1.18 g, 91% **85** by GC area) was discarded and the remaining were combined to give 73.77 g (48%, 97.5% GC purity) dimethyl hexahydrophthalate. In addition, 0.3 g of fruity-smelling liquid was collected from the cold trap. It was probably hexahydrophthalan **55**, because the same was also mentioned in the literature. [109, p. 393]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.622 and δ 3.617 (6H 2×s, OMe); δ 2.79–2.77 (1.52H t, 2); δ 2.57–2.55 (0.47H m, 2); δ 2.00–1.91 (2H m, 3); δ 1.75–1.68 (2H m, 3); δ 1.49–1.43 (2H m, 4); δ 1.39–1.26 (2H m, 4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.52 (1, *cis*); δ 174.19 (1, *trans*); δ 51.78

(OMe); δ 51.65 (OMe); δ 44.80 (2, *trans*); δ 42.64 (2, *cis*); δ 28.93 (3); δ 26.24 (3); δ 25.20 (4); δ 23.76 (4).

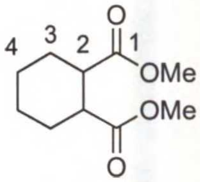


Figure 11. Identification of positions in dimethyl hexahydrophthalate.

The distillation did not change the *cis,trans*-distribution appreciably: the discarded fraction had 71% *cis* and the collected fractions 76, 77 and 79% *cis* product. The *cis,trans*-ratio was measured in the final product. With GC, it was observed that of the hexahydrophthalate, 77.9% was *cis* and 22.1% *trans*. With ^{1}H NMR, the integrals over the peaks 2.79–2.77 and 2.57–2.55 indicated 76.5% *cis* and 23.5% *trans*. A possible reason for this minor discrepancy is that the leg of the *trans* peak is partially under the *cis* peak in the GC data.

4.2.1.2 Ring hydrogenations of dimethyl phthalate in solvents with Ru/C

In reactions 6, 7 and 8 different solvents were used. To compare the kinetics of the runs, see Figure 12. The amount of catalyst was different in each case. Thus, the actual time coordinate has been normalized by multiplying the molar percentage of catalyst with the time, normalizing it to 1 mol-% catalyst metal per substrate.

The linear 0th degree equation was empirically applied to the initial rate:

$$\frac{dN_A}{dt} = km_{cat} \tag{6}$$

where N_A is amount of starting material, k is the reaction rate constant and m_{cat} is the mass of ruthenium. Integrating with $N_A = N_{A0} \ldots N_A$ and $t = 0 \ldots t$ gives:

$$N_A - N_{A0} = km_{cat}t \tag{7}$$

where N_{A0} is the initial amount of starting material. Replacing the amount of matter with conversion X from $N_A = (1 - X)N_{A0}$ gives the linear equation:

$$X = \frac{km_{cat}}{N_{A0}} t \tag{8}$$

The data are fitted to this linear equation, and the reaction rate constant k is calculated from the obtained gradient f.

$$k = \frac{fN_{A0}}{m_{cat}} \tag{9}$$

The rate constants (Table 2) were calculated by fitting a linear curve with the least-squares method into the linear region, thus ignoring X>80% except for AcOH run 7, which was entirely linear.

Table 2. Reaction rate constants for conversions in the linear region.

Run	Rate constant (mol h^{-1} $g_{cat}{}^{-1}$)	Standard error (mol h^{-1} $g_{cat}{}^{-1}$)
5	0.1264	0.0172
6	0.1665	0.0011
7	0.0581	0.0007
8	0.1658	0.0265

In reaction 6, dimethyl phthalate (73.22 g) was hydrogenated in a solvent mixture of 53.79 g EtOH and 26.88 g AcOH with Ru/C (30.6 g, or 0.51 m-% Ru) at 95–100 bar and 120 °C, with 6 l/h hydrogen flow overnight. The reaction was run for 22 h, and the catalyst was filtered off. The crude product (66.19 g, 87.7%) contained 94.5% dimethyl hexahydrophthalate, of which 90% *cis* and 10% *trans*, and 1.5% starting material, 3.73% lights and 0.3% of an unidentified impurity with retention time near that of dimethyl phthalate (hencefort *heavy impurity*). Also, it was found that water was formed, measuring 1.73% at 2 h and 4.85% at 22 h. Apparently at these conditions, uncatalysed esterification of the EtOH and AcOH occurs. Solvents were evaporated to give 66.19 g (83%) crude, which was distilled. Four fractions were collected, the first (0.50 g, 50% GC purity) discarded, and the rest collected to give 57.00 g (74%, 97.5% GC purity) product.

In reaction 7, dimethyl phthalate (136.10 g) was hydrogenated in acetic acid (21.20 g) with Ru/C (31.28 g, 0.28 m-% Ru) at 95–100 bar and 120 °C. During the first

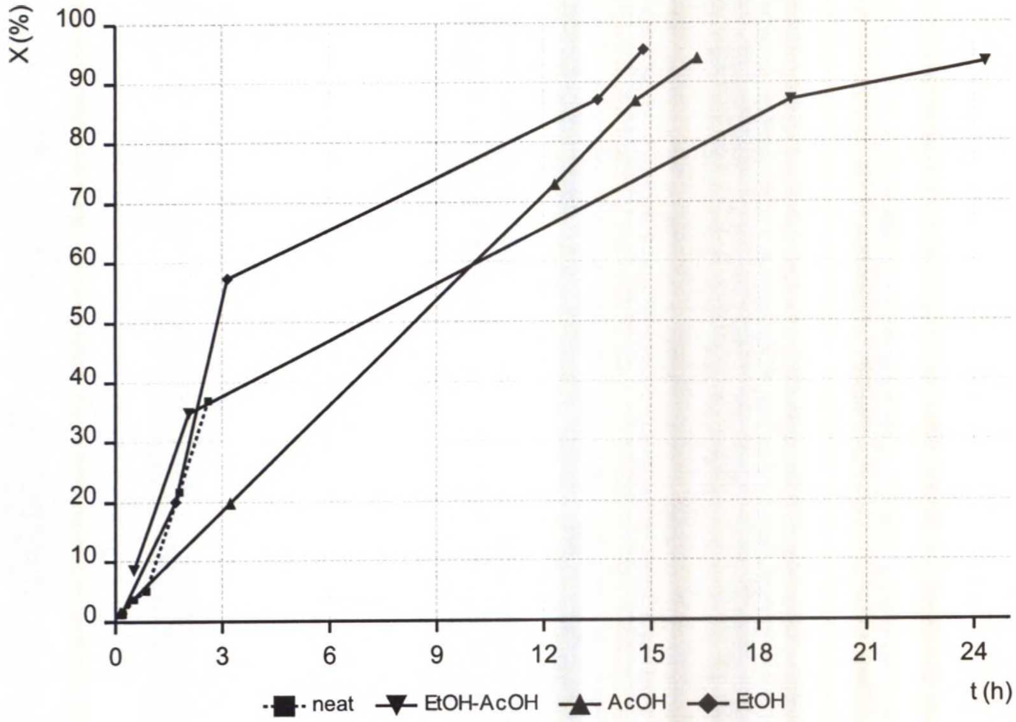


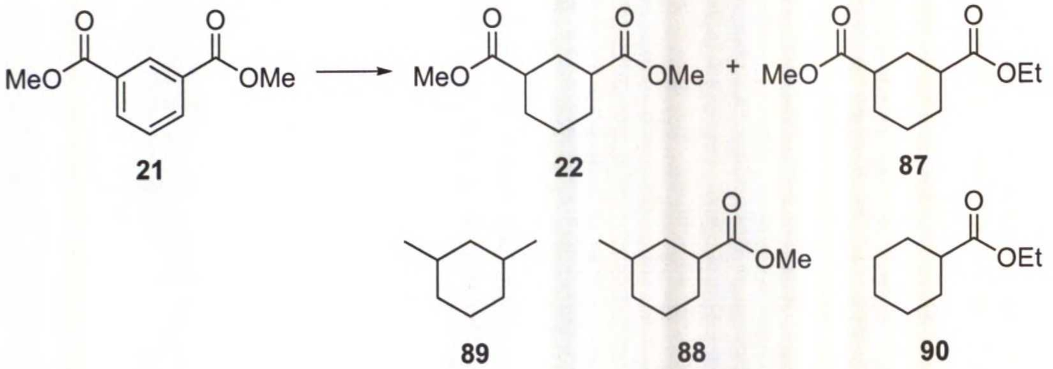
Figure 12. Comparison of solvents, normalized to 1 mol-% catalyst by adjusting the time coordinate.

6 h, stabilization of the pressure with hydrogen flow (6–12 l/h) was attempted, but this manual attempt at pressure control was not successful. The reaction was left to run overnight at 99 bar, pressurized directly from the bottle. The reaction was run for 30 h. First, the catalyst was washed with 2×30 g AcOH and filtered with a Büchner funnel, and solvents were evaporated from the washings to give 14.06 g crude product from the catalyst. The decanted reaction mixture was filtered separately, combined with the previous and solvents evaporated to give 122.54 g (84%) crude, which contained 96.64% dimethyl hexahydrophthalate, of which 91% *cis* and 9% *trans*, and 0.69% starting material, 2.63% lights and 0.04% of heavy impurity, and 1.87% water. The crude product was distilled, with all distillate collected, to give 113.51 g (79%, 97.4% GC purity) product.

In reaction 8, dimethyl phthalate (144.45 g) was hydrogenated in ethanol (16.65 g) with Ru/C (31.787 g, 0.27 m-% Ru) at 80–100 bar and 120–140 °C. The reaction was first heated to 120 °C; at 3 h, the conversion was 21%. After 4 h and 45 min, the temperature was increased to 140 °C. The reaction was then run for 26 h and cooled down, but analysis showed incomplete conversion with 10% starting material and

89% product. The reaction was then reheated and run at 95 bar for another 19 h. The catalyst was washed with 2×30 g EtOH, the washings and decanted reaction mixture combined and filtered with a Büchner funnel, and solvents were evaporated to give 122.57 g (80%) green, slightly cloudy crude, which contained 97.1% dimethyl hexahydrophthalate, of which 81% *cis* and 19% *trans*, and 0.4% starting material, 2.33% lights (identified: 1.6% hexahydrophthalide) and 0.1% of heavy impurities. The crude product was distilled, with all distillate collected, to give 117.00 g (77%, 97.3% GC purity) product.

4.2.1.3 Ring hydrogenation of dimethyl isophthalate with Ru/C



Dimethyl isophthalate **21** was hydrogenated at 120 °C and 140 °C with 1.0 and 0.3 m-% catalyst, respectively. The former (120 °C) gave a better result of 96% ring-hydrogenated diesters in the crude, whereas in the latter case (140 °C) there was only 59% products. Transesterification with the solvent occurred.

In reaction 9, dimethyl isophthalate **21** (37.48 g) was hydrogenated in ethanol (122.42 g) with Ru/C (30.712 g, 1.0 m-% Ru) at 80–95 bar and 120 °C for 21.5 h, with no hydrogen flow overnight. After this, the reaction was cooled and then reheated back to 120 °C, and kept at 88–96 bar pressure and in a 6 l/h hydrogen flow for 8 h, because a product peak was misidentified as starting material. At this point, the actual amount of remaining starting material was 0.5%. Further heating did not change the composition. The reaction mixture was decanted, the catalyst was washed with 2×30 g EtOAc, the combined organics filtered and solvents evaporated to give 29.87 g (77%) crude product as an grayish oil. It was distilled to give 26.12 g (66%) clear, mobile liquid. The products were identified by

GC-MS. The distillate contained at least 84.58% dimethyl hexahydroisophthalate **22** of which 40% *trans* and 60% *cis*. There were also two analogues of areas per cent 2.43% and 3.67% (total 6.10%) that were also identified as "dimethyl hexahydroisophthalate or heavier" on the GC-MS report from Neste. There was also 7.18% methyl ethyl hexahydroisophthalate **87** (identified by GC-MS), and 1.81% lights, of which 0.77% methylcyclohexanecarboxylate **88**. The crude product contained 81.96% product **22** (same 40% *trans*/60% *cis*), 2.43% and 4.34% analogues (total 6.77%), 7.32% methyl ethyl hexahydroisophthalate **87**, 2.15% methylcyclohexanecarboxylate **88** and 1.20% other lights.

The goal was to hydrogenate the ring, thus the analogues (13.3%) are counted towards the yield, too, because the ester function will be hydrogenated anyway. Thus, the GC purities of ring-hydrogenated product are 96.1% for crude product and 97.9% for distillate. The molecular weights are 200.23 g/mol for the dimethyl ester **22** and 214.26 g/mol for **89**. Using GC area-% to approximate m-%, this gives the average molecular weights weighed by m-% 201.30 g/mol and 201.26 g/mol for crude product and distillate, respectively. Calculating the yield with these assumptions gives crude yield 74% and yield 66%.

The rate constant, calculated from the disappearance of starting material, which was 0% at 0 h, 18.48% at 0.36 h and 74.44% at 4.58 h gives the rate constant 0.0847 ± 0.0351 mol h^{-1} $g_{cat}{}^{-1}$. Additionally at 22.58 h the reaction was 99.53% complete (0.47% starting material remaining), which is not in the linear region, as expected from Langmuir-Hinshelwood kinetics.

^1H NMR and ^{13}C NMR was run on the distilled product. In ^1H NMR peaks at 7–8 ppm were absent, indicating the absence of aromatics, but otherwise the spectrum was difficult to analyze, because the distillate was a mixture, and the integrals over the peaks are not integers. The attempt to analyze the spectrum is nevertheless presented, using the assumption that the apparent number of protons is 16.4, a figure approximated from the GC result (85% $C_8H_{16}O_4$ and 13% $C_9H_{18}O_4$). Names of the ring positions are shown in Figure 13. In ^{13}C NMR, major peaks are identified, and the unknown, minor peaks (intensity about 5% of the major peaks) are listed separately.

^1H NMR ($CDCl_3$, 400 MHz): δ 4.10–4.05 (0.1H m, OEt); δ 3.63 (2.2H s, OMe); δ 3.62 (3.2H s, OMe); δ 3.61 (0.2H s, OMe); δ 2.66–2.60 (0.8H m, 2); δ 2.32–2.24

(1.2H m, 3); δ 2.21–2.18 (0.3H m, 3?); δ 2.17–2.15 (0.3H m, 3?); δ 1.93–1.90 (2.1H m, 4); δ 1.87–1.82 (0.7H m, 4); δ 1.74–1.62 (1.7H m, 4); δ 1.52–1.46 (1.4H m, 5); δ 1.37–1.27 (1.9H m, 5); δ 1.22–1.18 (0.3H m, OEt?);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.66 (1); δ 175.54 (1); δ 51.69 (OMe); δ 51.63 (OMe); δ 42.53 (2); δ 39.02 (2); δ 31.06 (3); δ 29.35 (3); δ 28.34 (4); δ 27.87 (4); δ 24.84 (5); δ 22.06 (5). Unknown minor peaks: δ 60.5 (OEt?); δ 68.3; δ 42.68; δ 31.98; δ 29.1; δ 28.73; δ 25.03; δ 14.24 (Et?).

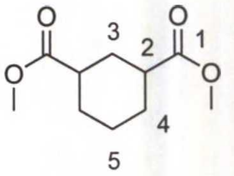
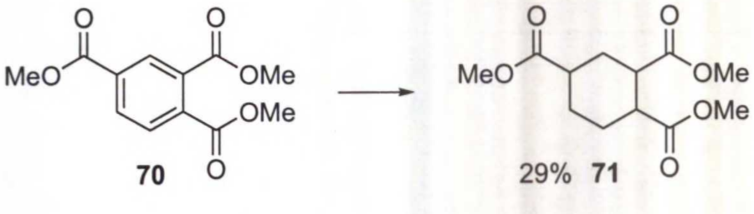


Figure 13. Identification of ring positions in dimethyl isophthalate

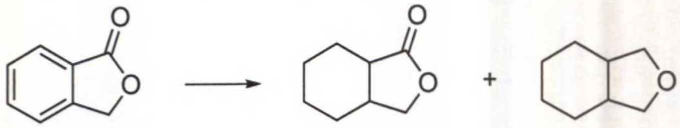
In reaction 10, dimethyl isophthalate (100.59 g) was hydrogenated in ethanol (49.70 g) with Ru/C (24.7650 g, 0.3 m-% Ru) at 86–92 bar and 140 °C for 45 h. After 28.5 h, the reaction still contained 9.2% starting material. The reaction mixture was decanted, the catalyst washed with 2×30 g EtOH, the combined organics filtered and solvents evaporated to give 71.17 g crude. The crude product contained in total 58.68% ring-hydrogenated product, which gives the crude yield of 39%. The complete composition was 22.7% dimethyl hexahydroisophthalate **22** of which 37% *trans* and 63% *cis*, 0.18% and 0.53% analogues (0.72% in total), 35.24% methyl ethyl hexahydroisophthalate **87**, and 21.71% lights, of which 7.94% methylcyclohexanecarboxylate **88**, 6.96% 1,3-dimethylcyclohexane **89**, 4.38% ethyl hexahydrobenzoate **90**, and 19.6% unidentified heavy compounds with retention times longer than that of the dimethyl ester **22**. These may have been diethyl esters, but this was not confirmed.

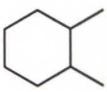
4.2.1.4 Ring hydrogenation of trimethyl trimellitate with Ru/C

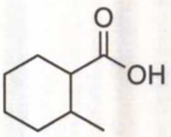


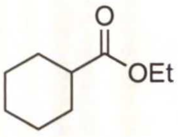
In reaction 11, trimethyl trimellitate (90.42 g) was hydrogenated in ethanol (48.00 g) with Ru/C (27.000 g, 0.37 m-% Ru) at 88–97 bar and 120 °C for 95 h. The reaction was incomplete: at 28 h, 77% starting material remained, and 61% at 95 h. The reaction mixture was decanted, the catalyst washed with 2×30 g EtOAc, the combined organics filtered and solvents evaporated to give 69.42 g (29%, 38.9% GC purity) crude, which was cloudy and brown in color. The crude product contained 46.35% starting material, 33.37% and 5.95% (total 39.32%) products that formed first, thus being most probably trimethyl hexahydrotrimellitate, 5.04% and 3.65% (total 8.69%) unidentified heavier compounds, 3.74% lights and 1.9% other unidentified compounds. Vacuum distillation was attempted unsuccessfully at 5 mbar, but evaporation was too slow even without a column. The distillate contained 48% trimethyl trimellitate and 36% trimethyl hexahydrotrimellitate, and the undistilled portion contained 41% and 43% of the same, respectively.

4.2.1.5 Ring hydrogenation of phthalide with Ru/C


25 **54** **55**


50


81


90

In reaction 12, phthalide **25** (100.48 g) was hydrogenated in ethanol (56.02 g) with Ru/C (24.77 g, 0.3 m-% Ru) at 82–87 bar and 140 °C for 45 h. In the end, the reaction contained 57.3 GC area-% product **54**, 5.7 GC area-% starting material **25** and 7.24% water. GC areas for other compounds were: 10.3% ethyl hexahydrobenzoate **90** "or heavier" in two peaks (identified in the GC-MS report), 13.3% 2-methylcyclohexanecarboxylic acid **81** in two isomers (GC-MS), 2.4% hexahydrophthalan **55**, and 7.8% 1,2-dimethylcyclohexane **50**. There is the caveat that the large amount of water and compounds with unknown response factors make the reported composition an approximation only. The reaction mixture was decanted, the catalyst washed with 3×20 g EtOH, the combined solutions filtered and solvents evaporated to give 76.58 g liquid. At this point the solution contained 6.9%

water, but the phthalide **25** had disappeared, and now the mixture was 65% hexahydrophthalide **54**. The liquid was mixed with 71.5 g hexane, dried with $NaSO_4$, filtered through sintered glass and solvents were evaporated to give 74.06 g crude product (46%, 65.3% GC purity), which contained 65.3% hexahydrophthalide **54**, 16.9% ethyl hexahydrobenzoate **90** "or heavier" in two peaks (GC-MS), 10.9% 2-methylcyclohexanecarboxylic acid **81** in two isomers (GC-MS), 4.19% hexahydrophthalan **55**, and 0.19% 1,2-dimethylcyclohexane **50** (identified by GC-MS). The distillation of the crude product was attempted, but the distillates (69.86 g in total in four fractions) were not pure. The largest fraction, number 3, collected (55.39 g) was 73.5% hexahydrophthalide. The purest fraction was the last, with 87.56% hexahydrophthalide, and it was used to measure NMR spectra.

^1H NMR ($CDCl_3$, 400 MHz): δ 4.17–4.14 (1H m, 8); δ 3.92–3.89 (1H m, 8); δ 2.62–2.58 (1H m, 7); δ 2.46–2.40 (1H m, 2); δ 1.80–1.75 (1H m, 3); δ 1.62–1.53 (4H m+m, 3, 4, 5, 6); δ 1.21–1.13 (3H m, 4, 5, 6). The ^1H NMR result corresponds to literature data. [167, p. 29]

^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.62 (1); δ 71.81 (8); δ 39.50 (2); δ 35.42 (7); δ 27.21 (6); δ 23.46 (3); δ 22.94 (4/5); δ 22.55 (4/5).

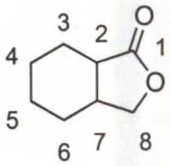


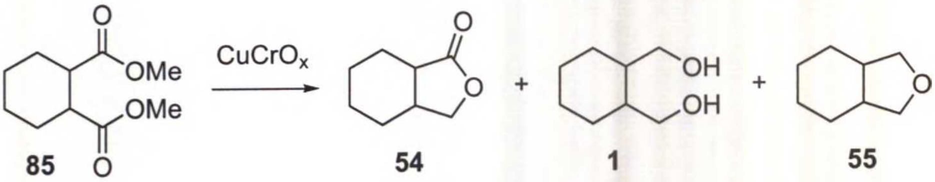
Figure 14. Identification of the positions in hexahydrophthalide.

Althought the GC-MS report identified the carboxylic acid **81**, this was brought into question by the following experiment. Fraction 3 (55.39 g) was added with 44.30 g hexane and 4.20 g dry K_2CO_3 and left to stand for half an hour. It was then filtered, solvents were evaporated and 55.43 g material was left. There was no change in GC profile despite the use of a basic salt; free acid should at least adsorb on the polar, basic K_2CO_3.

4.2.2 Hydrogenations of the ester function

Copper chromite, RuSn/C and RuPtSn/C were tried for dimethyl hexahydrophthalate hydrogenation with ethanol as a solvent. Generally very little or no diol was produced; instead, the reactions did produce the half-hydrogenated hexahydrophthalide **54**. Additionally a large amount of sundries was usually created, and the impurity profile as seen by GC was dissimilar between experiments.

4.2.2.1 Hydrogenation of dimethyl hexahydrophthalate with copper chromite



In reaction 13, dimethyl hexahydrophthalate (52.03 g, 81.4% *cis*) was hydrogenated in ethanol (81.67 g) with barium-promoted copper chromite (51.8 g, 39.1 m-% total, Süd-Chemie G-22/2, Cu 38.0%, Cr 24.5%, Ba 5.2%, SiO_2 10.0%) at 95–98 bar and 150 °C, then 200 °C. The reactor was heated to 150 °C first and kept for 23 h with 10 l/h hydrogen flow. After this, there was 95.8% starting material **85**, 2.2% hexahydrophthalide **54**, 1.6% compounds heavier than **85** and 0.5% lights. Then, the reactor was heated to 200 °C and kept for 27 h. The final sample contained 74.4% starting material **85** (82.1% *cis*), 8.1% hexahydrophthalide **54** (single peak), 6.0% cyclohexane-1,2-dimethanol **1** (35.1% *cis*), 1.5% hexahydrophthalan **55** (single peak), 1.5% lights and 8.6% compounds heavier than **85** (most in two peaks). The heavy compounds were probably methyl ethyl esters, although a positive identification was not made. The reaction mixture was decanted, the catalyst washed with 2×16 g EtOH, the combined solutions filtered through Celite and solvents evaporated (200 mbar and 80 °C) to give 23.19 g clear green liquid.

It was found that the product *cis*-**1** and the starting material *cis*-**85** did not resolve in regular GC, so GC with silylation was run on a different machine. It was found that the silylated *trans*-**1** gave the response 12.6% by area and 3.9% when unsilylated. This gives the rough approximation that the silyl ether ($C_{14}H_{32}Si_2O_2$) has a response 3.24 times that of the diol itself ($C_8H_{16}O_2$). Response factors are assumed to be the same for the *cis,trans*-isomers. In the last sample, 6.8% was the area-% of the silylated *cis* diol, which gives the approximation 2.1% when unsilylated. Since the compounds had unknown response factors, absolute responses were not converted to masses per cent, rendering these figures rather inaccurate.

4.2.2.2 Hydrogenation dimethyl hexahydrophthalate with ruthenium-tin on carbon

In reaction 14, dimethyl hexahydrophthalate (36.75 g, 91% *cis*) was hydrogenated in ethanol (91.85 g) with 2% ruthenium-1.54% tin on carbon (21.205 g, 0.72 m-% Ru, at 84–94 bar and 240 °C for 31 h. The heating took 45 min, but it was confirmed by GC that no reaction took place during this time. After 5 h, there was 55.38% starting material **85**, of which 89.6% *cis*, 0.91% hexahydrophthalide **54**, 42.68% compounds heavier than **85** and 1.03% lights. The breakdown of the unidentified heavy compounds is 3.38%, 22.65%, 1.46%, 15.18% in order of elution. They were probably ethyl esters. At the end at 31 h, all starting material and heavier compounds had disappeared. The reaction solution contained 4.77% hexahydrophthalide **54**, 38.51% hexahydrophthalan **55** (single peak), 0.23% *trans*-cyclohexane-1,2-dimethanol **1** specifically, and other compounds not positively identified: 17.88% of a compound eluted near hexahydrophthalan **55** that could be its other isomer, and 38.84% other compounds not identified, of which 10.96% eluted before hexahydrophthalan, 24.43% between hexahydrophthalan and hexahydrophthalide, and 3.46% after hexahydrophthalide.

The reaction mixture was decanted, the catalyst washed with 2×17 g EtOH, the combined solutions filtered through Celite and solvents evaporated (70 mbar and 70 °C). The obtained slightly pink solution was added with hexane (21.28 g) dried with Na_2SO_4, filtered through sintered glass and solvents evaporated to give 12.74 g crude. The main components of the crude product were 41.78% hexahydrophthalan **55** (single peak), 17.93% the probable other isomer of hexahydrophthalan **55**, 6.45% hexahydrophthalide **54**, and 33.84% sundries not identified.

4.2.2.3 Hydrogenation dimethyl hexahydrophthalate with ruthenium-platinum-tin on carbon

In reaction 15, dimethyl hexahydrophthalate (49.92 g, 78.6% *cis*) was hydrogenated in wet ethanol (98.59 g EtOH, 1.49 g H_2O) with 2% ruthenium-0.69% platinum-0.38% tin on carbon (22.611 g, 0.92 m-% Ru), at 88–90 bar and 175 °C for 5 h, then at 200 °C for 20 h, and then at 230 °C for 70 h. After 3.5 h (175 °C), there was little reaction to be observed: 96.93% starting material **85**, 1.52% hexahydrophthalide **54**, and 1.55% lights (one peak, probably methylcyclohexane). After 19 h (200 °C), there was 82.05% starting material **85**, 3.18% hexahydrophthalide **54**, 0.62% lights, and 14.16% unidentified heavier compounds. After 7 h (230 °C). there was 68.94% starting material **85**, 4.64% hexahydrophthalide **54**, 0.60% lights, and 25.82% unidentified heavier compounds. After 65 h or 94 h reaction time in total, there was a remarkably small change in conversion: 66.00% starting material **85**, 9.01% hexahydrophthalide **54**, no lights, and 24.99% unidentified heavier compounds. There was a large number of heavy peaks, some of which shifted when silylated, some of which did not. They could be ethyl esters or compounds with one alcohol group only, but none were positively identified. The *cis,trans*-ratio of the starting material did not change much during the reaction (78.6% to 76.7%). The reaction mixture was not recovered because of an accident, but it was noted that in the last sample, white flakes appeared, and the catalyst was somewhat slimy. This would suggest polymerization.

5 Discussion

5.1 Summary of experimental results

The experiments revealed several things. The loss of material on work-up was considerable, giving smaller yields than suggested by analysis of samples taken during the reaction. The yield is of interest for preparing small amounts in the laboratory. However, the composition of the reaction mixture is more informative with respect to selectivity and scale-up of the reaction. Thus, the latter is discussed below.

It was found that Adams platinum dioxide procedures, where platinum is in excess and activated by oxygen, are not transferable to supported platinum. The 1% platinum on alumina catalyst quickly deactivated. Moreover, alumina was wetted and leached into the solution. The minute amounts of water formed by hydrogenolysis led to this result.

Ruthenium on carbon was found to be a selective and effective catalyst for ring hydrogenation of dimethyl phthalate (Table 3). The effect of solvents (neat, EtOH, AcOH, EtOH-AcOH) on the reaction rate was minor. However, the runs featuring AcOH, an acid, gave 90% *cis* product, and neutral runs gave 80% *cis* product (see Table 3). Water was produced in the reaction, but in the 1–2% range only. A minor side reaction with dimethyl phthalate was that a small amount of hexahydrophthalide was observed.

Dimethyl isophthalate was also hydrogenated by ruthenium on carbon in good yields at 80–95 bar and 120 °C with 1 m-% Ru, such that 85% of the product was dimethyl hexahydroisophthalate. It was confirmed that no aromatics remained after the reaction. Apparently transesterification of the product in ethanol produced

Table 3. Results of dimethyl phthalate hydrogenation.

Run	Solvent	P (bar)	T (C)	Time (h)	% **85** at end	*cis*-%
5	neat	79–100	120	weekend	96.5	79
6	AcOH-EtOH	95–100	120	22	94.5	90
7	AcOH	95–100	120	30	96.6	91
8	EtOH	80–100	120–140	28	97.1	81

ethyl esters. Thus, the proportion of cyclohexyl diesters in the crude product was 96%. The composition of the unknown reaction products should be confirmed, or the reaction run in methanol. At 140 °C and with 0.3 m-% Ru, the proportion of products was only 59%, with 21% lights and 20% unidentified heavy compounds. This illustrates the sensitivity of hydrogenolysis to temperature.

Trimethyl trimellitate hydrogenation was unsuccessful: the reaction stopped to a similar conversion, 39%, as noted in the literature (see section 2.6.3.2, p. 45 and reference [122]).

Hydrogenation of phthalide into hexahydrophthalide was insufficiently selective: the hexahydrophthalide content was 57% in the final mixture. The rest was lost to hydrogenolysis and decarboxylation.

Ester hydrogenations failed to produce significant amounts of diol, and confirmed the fact that dimethyl hexahydrophthalate gives hexahydrophthalide by spontaneous lactonization. That is, the catalyst should be able to hydrogenate hexahydrophthalide into cyclohexane-1,2-dimethanol. This reaction is known to have a low selectivity (consider Bousquet's patent [136] below, section 5.2, p. 96). Another problem observed was that dehydration into hexahydrophthalan was observed, most severely with RuSn/C. This is likely a result of the Lewis acidity of Sn^{2+}. Also, it was found that in ethanol, transesterification occurs between methyl esters and the solvent, making analysis of results more difficult.

Ester hydrogenation results were different for each catalyst. With copper chromite, as much as 74% starting material remained after 50 h, suggesting that the temperatures used, 150–200 °C, were too low. The main product was 8.1% hexahydrophthalide **54**, but also the second step to diol occurred, and 2.1% cyclohexane-1,2-

dimethanol **1** and 1.5% hexahydrophthalan **55**, in total 3.6%, was found. Only a minor amount of lights (1.5%) was produced, but there were ethyl esters (8.6%).

With RuSn/C, all starting material and heavy compounds had disappeared at 31 h. The main product was 38.5% hexahydrophthalan (one isomer) and 17.9% of an unidentified compound that was possibly the other isomer of the same. There was also 4.8% hexahydrophthalide **54** and 0.23% *trans*-cyclohexane-1,2-dimethanol, and 38.8% unknown lights. The run proved the effectiveness of RuSn/C for diester hydrogenation, as there were 56.6% dihydrogenated products, but alas, it was also effective for dehydration of the product. Only *trans*-diol was found free, confirming the earlier observation that the *cis*-diol is more readily dehydrated. [155]

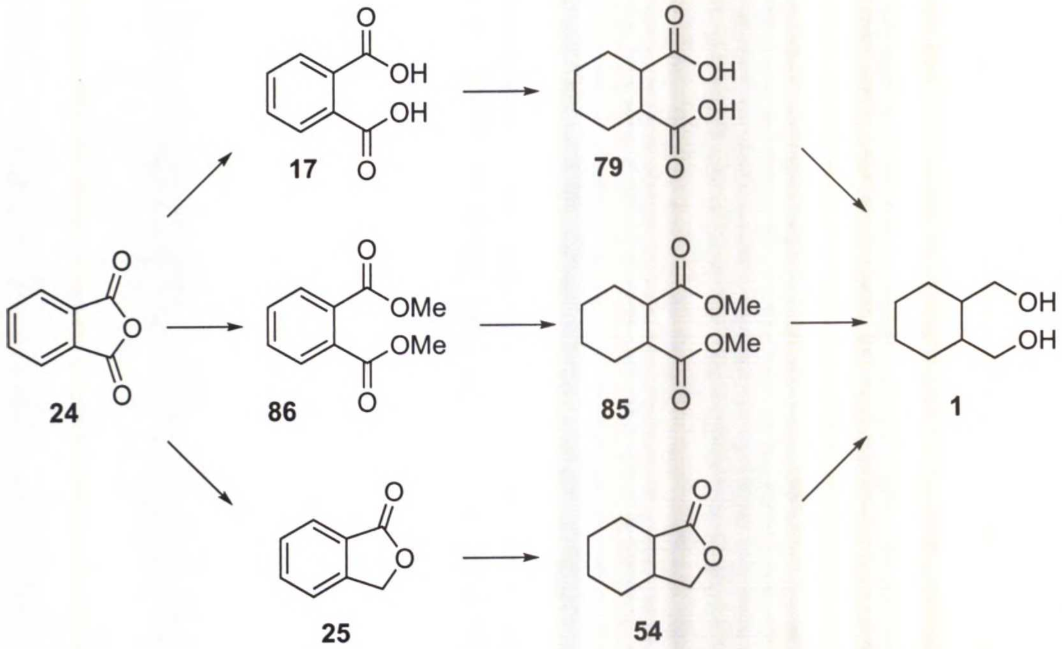
With RuPtSn/C, there was still 66.0% starting material after 95 h, and the reaction proceeded slowly after 7 h. The main product was 9.0% hexahydrophthalide **54**, and secondarily 25.0% numerous heavy compounds not identified were found.

5.2 Routes

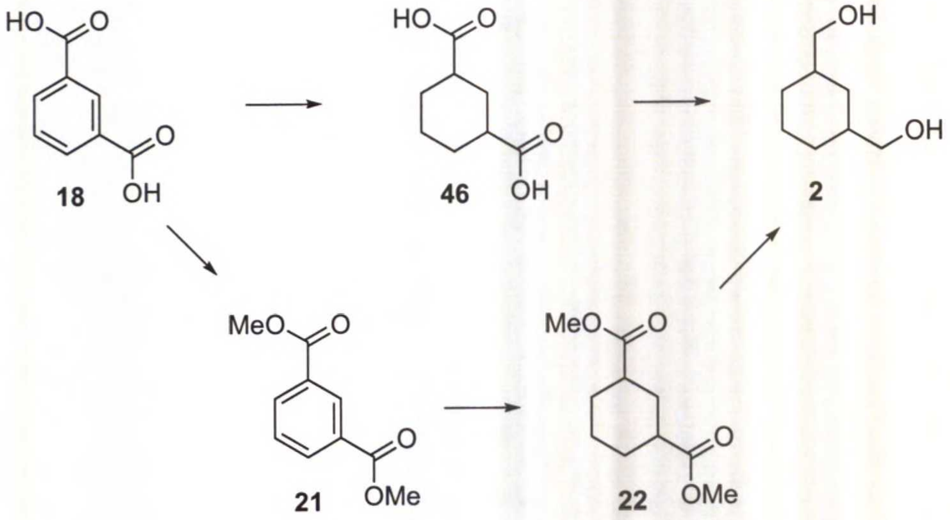
The production of cyclohexanediols in two steps can be approached in several ways. All of them were not experimentally evaluated. The considered routes are presented in Scheme 36.

The order of hydrogenation in each case would be ring first, then the carboxylates. This is because of the observations that the aromatic ring activates a benzylic alcohol towards hydrodeoxygenation. Adkins actually tried to hydrogenate both diethyl phthalate and diethyl hexahydrophthalate with copper chromite under identical conditions (100–170 bar, 250 °C) and found that the former would hydrodeoxygenate completely and even the latter would give a very poor yield (70–94% hydrodeoxygenation). [23] Another reaction with copper chromite was mentioned in Bousquet's patent, where hexahydrophthalide gave the selectivity of 47–51% to cyclohexane-1,2-dimethanol. [136]

The first route is that phthalic anhydride **24** would be hydrolyzed to give phthalic acid **17**, which would be ring-hydrogenated to **79** and then reduced to the diol. This route would require an extremely active and selective catalyst for the reduction of



Scheme 36. Routes to the diol **1**: via phthalic acid **17**, dimethyl phthalate **86** and phthalide **25**.



Scheme 37. Routes to diol **2**: via hexahydroisophthalic acid **46** and dimethyl hexahydroisophthalate**22**.

the diacid **79** to the diol **1**. For example, RuSn and PtRuSn, and Re-based catalysts are known acid reduction catalysts.

The experimental results suggest that with acid, the result would be hexahydrophthalide, which is an ester. Thus, the catalyst should be able to hydrogenate both esters and acids, something that RuSn does. However, the experiment where phthalide was hydrogenated suggested, although did not prove, that hexahydrophthalide may break down on ruthenium and ruin the yield. Also, Bousquet's result (see reference [136]) that about 50% selectivity is attained with copper chromite suggests, considering that copper chromite is a very selective and rather inactive catalyst, suggests that it is difficult to hydrogenate hexahydrophthalide selectively. Finding of suitable catalyst for this transformation was not attempted within the timeframe of this work.

The second route begins with esterification of the anhydride **24** with methanol to give a dimethyl ester. Copper chromite and RuSn or PtRuSn are able to hydrogenate esters. Again, the problem would be that hexahydrophthalide would be produced, and its reduction would be difficult.

The third route avoids the ring-opening. Direct reduction of the anhydride **24** into phthalide **25** and subsequent ring hydrogenation would give hexahydrophthalide **54**. This is a lactone that would be hydrogenated similarly to an ester. The production of phthalide is a known process and a large variety of catalysts hydrogenate anhydrides. The question is whether phthalide can be ring-hydrogenated with high selectivity, without hydrogenolysis of the benzylic alcohol position. Experimental results in this work suggest that this is likely difficult. Ruthenium is a selective ring-hydrogenation catalyst that is specifically recommended for sensitive compounds. When only about 57% selectivity is attained using Ru, the only other metal that could be considered is rhodium.

Cyclohexane-1,2-dimethanol is known to readily dehydrate into a cyclic ether by acid catalysis, *e.g.* H_2SO_4 in cold acetone or refluxing HCl in MeOH. [109] This is a known complication of 1,4-diols and particularly cyclic 1,2-dimethanols. The experiments showed that the production of hexahydrophthalan does indeed occur as the preferred reaction on RuSn/C, which contains the Lewis acid Sn^{2+}. As tin functions as a Lewis acid for carbonyl activation in the catalyst, it would be difficult to mitigate the problem in any obvious manner. Should hexahydrophthalan be produced, its hydrolysis would be probably difficult, because it could polymerize into a PolyTHF-type polymer, when activated by the same Lewis acid that is necessary for its hydrolysis.

The case of isophthalate is similar but simpler, because the acid does not form a lactone (see Scheme 37). The ring hydrogenation was found to be 94% selective at 120 °C, but not 140 °C. Transesterification made it difficult to evaluate the results, however.

5.3 Conclusions

Ring hydrogenations of dimethyl phthalate and dimethyl isophthalate ruthenium on carbon were about 95% selective and successful with 0.25–1.00 m-% catalyst at 80–100 bar and 120 °C. It was confirmed that solvents — ethanol, acetic acid or none — have only a minor effect on the reaction rate. It was observed that with AcOH, the *cis*-selectivity was slightly higher, 90% instead of 80%. Platinum on alumina was found to deactivate very quickly and alumina dissolved in the reaction mixture. It was found that RuSn is an effective catalyst, and may be a considerable alternative to copper chromite. This work did not yet produce a method to produce cyclohexane-1,2-dimethanol with catalytic hydrogenation, although the substance was successfully produced using lithium aluminum hydride. It was found that main products are the lactone hexahydrophthalide and the cyclic ether hexahydrophthalan.

5.4 Future studies

Cyclohexane-1,3-dimethanol was not produced within the timeframe of this work. Rhodium catalysts could be tried for ring hydrogenation, although it is known that the supported versions may not be as effective as rhodium oxide. Rhenium-based catalysts could be tried for ester and acid hydrogenation. The acid route, particularly cyclohexane-1,3-dimethanol from hexahydroisophthalic acid was not evaluated. Previous studies on ester hydrogenation with copper chromite or RuSn often featured hydrogen pressures starting from 200 bar, but the equipment available for this work limited the pressure to 100 bar only. This could improve selectivity towards cyclohexane-1,2-dimethanol, because it would allow lower temperatures, reducing hydrogenolysis, while maintaining equivalent reaction rates. Pure *trans*-hexahydrophthalates, which could be produced by base-catalyzed isomerization of the hydrogenation product, and the corresponding *trans*-cyclohexane-1,2-dimethanol, were not produced.

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