

Synthesis of bio-based terephthalic acid

Master's Thesis

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<p>Terephthalic acid (TPA) is a monomer used widely in the production of poly(ethylene terephthalate) (PET) and other polyesters. The other monomer of PET, ethylene glycol, can already be produced from bioethanol. However, TPA is still produced via the traditional route from petrochemical sources, but the global demand for environmental-friendly options has increased throughout the past years making the synthesis of bio-based TPA an attractive research target. Several companies have formed a collaborative to support the development of 100% bio-based PET and thus bio-based TPA. The challenge is not only to develop an ecologically beneficial but also a cost-effective process.</p> <p>In the literature section of this work, the current methods to produce bio-based TPA have been reviewed. A highly attractive option is to use lignocellulosic biomass - cellulose, hemicellulose and lignin - as the starting material due to its high abundance and low cost. Lignocellulosic biomass can be utilized directly via biotechnical pathways by using either catalytic fast pyrolysis or fermentation and reforming strategies. The other option is to convert it into small platform chemicals, for instance HMF, furfural and acrolein, which are then used in Diels–Alder approaches to get TPA or its precursors. Besides lignocellulose, other viable starting materials, like monoterpenes, have been discussed.</p> <p>The experimental of the thesis is focused on N-heterocyclic carbene (NHC)-catalyzed umpolung reactions in order to make TPA-precursors and other value-added chemicals from benzaldehyde. The research hypothesis was that by forming an electron-rich enaminol, called Breslow intermediate, from benzaldehyde and NHC, we could reverse the reactivity of benzaldehyde from <i>ortho,para</i>-deactivating to <i>ortho,para</i>-activating. Two NHC-precursors were synthesized, isolated and characterized. Several pathways utilizing both two-electron and single-electron transfer were attempted, but unfortunately no success in these reactions was achieved.</p>			
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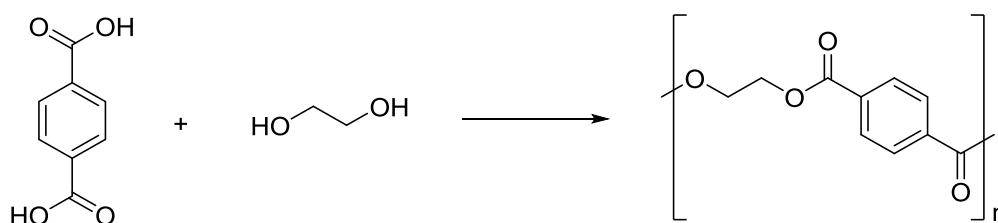
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LIST OF ABBREVIATIONS

BTX	Benzene, toluene, xylenes
<i>cc</i> MA	<i>cis,cis</i> -Muconic acid
CBA	4-Carboxybenzaldehyde
CFP	Catalytic fast pyrolysis
CST	Crude sulfate turpentine
DA	Diels–Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DET	Diethyl terephthalate
DMF	2,5-Dimethylfuran
DMT	Dimethyl terephthalate
FDCA	2,5-Furandicarboxylic acid
HMF	5-Hydroxymethylfurfural
HMFA	5-(Hydroxymethyl)furoic acid
NHC	N-Heterocyclic carbene
<i>p</i> C	<i>p</i> -Cymene
PET	Poly(ethylene terephthalate)
<i>p</i> TA	<i>p</i> -Toluic acid
<i>p</i> TALD	<i>p</i> -Tolualdehyde
<i>p</i> X	<i>p</i> -Xylene
TPA	Terephthalic acid
THF	Tetrahydrofuran
<i>tt</i> MA	<i>trans,trans</i> -Muconic acid
WHSV	Weight hourly space velocity

1. INTRODUCTION

Terephthalic acid (TPA) is widely used in condensation reactions with glycols to produce polyesters. One of the most common polymers is poly(ethylene terephthalate) (PET), formed from the polycondensation of TPA and ethylene glycol (*Scheme 1*). Instead of TPA, its methyl ester, dimethyl terephthalate (DMT), can be directly used for the polymerization. PET has a lot of uses in the packaging industry due to its excellent properties, such as light weight, high strength and having no negative effects on health.¹



Scheme 1. The condensation reaction of TPA and ethylene glycol to form PET.

Originally, both TPA and ethylene glycol were produced from petrochemical sources, but the increasing global demand for environmental-friendly options has resulted in growing research on the possibility of utilizing bio-based feedstocks. Recently, major progress has been the development of the Coca-Cola Company's PlantBottle™ PET, which is fully produced from bioethanol-derived ethylene glycol. However, only 30% of this bio-PET originates from biosources, as TPA is still produced from fossil fuels.² In 2012, approximately 47 million tons of TPA was consumed globally and the amount was estimated to increase to 65 million tons by 2018.³ Hence, the bio-based production of TPA is an attractive research target. In order to support the development of 100% bio-based PET, the Coca-Cola Company, Ford Motor Company, H. J. Heinz Company, Nike Inc. and the Procter & Gamble Company have formed the Plant PET Technology Collaborative.¹ In addition to being ecologically beneficial, the bio-based process should be cost-effective as the majority of customers prefer low price over environmental benefit.²

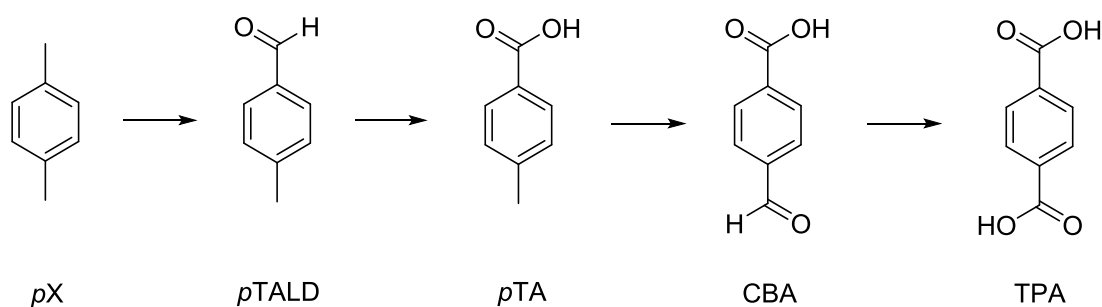
To the author's best knowledge, three reviews have been published considering alternative bio-based routes for the production of TPA.¹⁻³ In this work, the recent progress in the synthesis of bio-based TPA is discussed and compared to the current petro-based process.

To the author's knowledge, most of the methods for producing TPA from preferably inedible bio-sources developed thus far are reviewed in the following section. The yields are given as molar yields unless otherwise stated. Selectivity is used in the meaning of conversion-based yield.

2. SYNTHESIS OF TEREPHTHALIC ACID FROM PETROCHEMICAL SOURCES

TPA is currently produced via fossil-fuel-derived *para*-xylene (*pX*), which is typically obtained in five steps. First, low-octane naphtha cuts are catalytically reformed to yield a stream of benzene, toluene and xylenes (BTX) together with other aromatics. The BTX fraction and ethylbenzene are separated from the stream by solvent extraction, followed by distillation to isolate the xylenes and ethylbenzene. Because this fraction still contains all three isomers of xylene, *ortho*- and *meta*-xylenes are isomerized to *pX*, which is then collected by solvent extraction. The purification of *pX* from the BTX fraction is difficult due to the similar structures of xylene isomers.^{2,3}

The final step is to oxidize *pX* to TPA by the AMOCO process, which was originally developed by the Mid-Century Corporation in 1955.^{4,5} In this process, *pX* is oxidized using molecular oxygen from compressed air as an oxidant in glacial acetic acid. Several manganese and cobalt salts can be used as catalysts, but preferably manganese and cobalt acetates are used. An ionic bromine compound, typically sodium bromide, acts as a promotor. The reaction is carried out at 175–225 °C and 15–30 bar in a continuous tank reactor. The intermediates of the reaction are *p*-tolualdehyde (*pTALD*), *p*-toluic acid (*pTA*) and 4-carboxybenzaldehyde (CBA), shown in *Scheme 2*. The AMOCO process gives up to 98% conversion of *pX* and over 95% yield of TPA. To achieve the high-purity TPA needed for the polymerization, purification processes are performed to reduce CBA and to remove other impurities contained in the crude product. The development of the AMOCO process made it possible to directly use TPA instead of its methyl ester, DMT, in the production of PET.⁶



Scheme 2. The stepwise oxidation of pX to TPA.

3. SYNTHESIS OF BIO-BASED TEREPHTHALIC ACID

3.1 Lignocellulosic biomass as a biosource

Lignocellulosic biomass is the most promising source for bio-based TPA, as it is both the cheapest and the most abundant bioresource available. Its annual production is estimated to be 200 billion tons.¹ Lignocellulose would be the optimal feedstock to use for the production of TPA, since it is inedible unlike starch or sugar plants, which are therefore competitive as food supplies.

3.1.1 Biotechnical pathways

3.1.1.1 Catalytic fast pyrolysis

Pyrolysis is a method in which biomass is decomposed by heating under anaerobic conditions, so that aromatics, including *pX*, can be obtained directly. To maximize the amount of the liquid product (pyrolysis oil), the heating is done rapidly at moderate temperatures. Such fast pyrolysis can be combined with catalysis to adjust the composition of the resulting pyrolysis oil. This method is called catalytic fast pyrolysis (CFP). Among alkanes and olefins, the pyrolysis oil includes several value-added aromatic compounds. However, only *pX* content is discussed here. The conventional, slow pyrolysis is usually used for carbonization to get the solid biochar as the main product.⁷

Huber *et al.*^{8–11} have patented a process for CFP of biomass to produce *pX* among other value-added products. This technology is under development by Anellotech Inc. Multiple sources of biomass were used for the process, including glucose, cellobiose, cellulose, sugarcane, wood and corn stover. CFP was carried out at temperatures of 500–1000 °C for 240 s. Several heterogeneous mixed oxide catalysts (e.g. silica/alumina mixtures, zeolites and WO_x/ZrO_2) were used to catalyze the pyrolysis, but ZSM-5 zeolite was the only one to yield a significant amount of aromatics. While the *pX* yield was not clearly stated, the aromatic carbon yield (moles of carbon in the product divided by moles of carbon in the feedstock, determined by GC-MS) was up to 31%, 26% and 21% when cellulose, wood and corn stover were used as the pyrolysis feedstock, respectively. Additionally, the pore openings of the zeolite catalysts could be reduced by addition of gallium, in order to induce higher selectivity towards *pX* among the xylene fraction.¹¹

Besides the Anellotech process, there have been several other reported studies concerning the production of *pX* by pyrolyzing biomass. Farha *et al.*¹² focused instead on the production of toluene, which can be carbonylated to *pTALD* and then oxidized to TPA. However, they stated that this could never replace the currently commercially used process from *pX* to TPA¹² so their process is not discussed in detail here.

Thring *et al.*¹³ performed pyrolysis of lignin in an acetone solution using a HZSM-5 zeolite catalyst. The reaction was carried out in a continuous down-flow fixed bed microreactor. Different temperatures and weight hourly space velocities (WHSVs) were tested, and the highest amount of liquid product (43 wt%, determined by GC) was achieved at 550 °C with a WHSV of 5 h⁻¹. These conditions also gave the highest yield of xylenes, 33 wt% of the liquid product (determined by GC). However, the composition of the xylenes was not reported. A drawback of the process was using acetone as a solvent, as it is a value-added chemical itself.¹³

Zhou *et al.*¹⁴ studied the effect of boron-impregnation of the ZSM-5 zeolite catalyst. They performed CFP using both cellulose and mixtures of cellulose and low-density polyethylene (LDPE) as a feedstock. The 10:1 (w/w) mixture of the catalyst and the reactant was pyrolyzed at 590 °C for 60 s. B-impregnated catalysts were screened for plain cellulose and the best yield of *pX* was obtained with ZSM-5 and 1 wt% of B. With a one-to-one mixture of cellulose and LDPE, the carbon yield of *pX* increased from 3.7% to 5.7% (determined by

GC). The authors suggested that the enhanced selectivity towards *pX* of B-impregnated zeolites was due to the pore narrowing of ZSM-5 caused by boron deposition.¹⁴

The same group also performed CFP for pine wood and LDPE mixtures using three gallium-impregnated zeolite catalysts (Ga/ZSM-5, Ga–Al–Si and Ga–Si).¹⁵ The pyrolysis temperature was 550 °C for 60 s, with a catalyst-to-reactant ratio of 15:1. It was found that the amount of monoaromatics in the product mixture was enhanced by Ga-containing zeolites. The highest yield of *pX* was achieved with Ga–Si catalyst containing 8.6% Ga₂O₃. As with cellulose, the *pX* yield was significantly increased when a 2:1 mixture of pine wood and LDPE was used, the carbon yield rising from 3.7% to 7.7% (determined by GC).

HZSM-5 zeolites impregnated with different metals, including Zn, Ni, Ga and Ga-Ni mixture, were also studied by Schultz *et al.*⁷ *Eucalyptus urophylla* was pyrolyzed at 600 °C for 18 s. In agreement with the aforementioned studies, the carbon yield of *pX* was highest (2.9%, determined by GC-MS) with a Ga-impregnated catalyst containing 7 wt% Ga. The yield could be increased to 3.8% by raising the catalyst-to-reactant mass ratio from 5 to 10. The same group also studied the effect of iron-modified HZSM-5 zeolites, but the addition of iron only decreased the *pX* yield.¹⁶

3.1.1.2 Fermentation and reforming

Another important biotechnical pathway is the fermentation of biomass. A few processes are fully based on fermentation or reforming to produce either *pX* or TPA (Section 3.1.1.2.1), but it is also possible to combine biotechnical and chemical pathways by obtaining platform chemicals from biomass fermentation and then using them as starting materials in chemical methods (Section 3.1.1.2.2).

3.1.1.2.1 Full processes based on fermentation and reforming of biomass

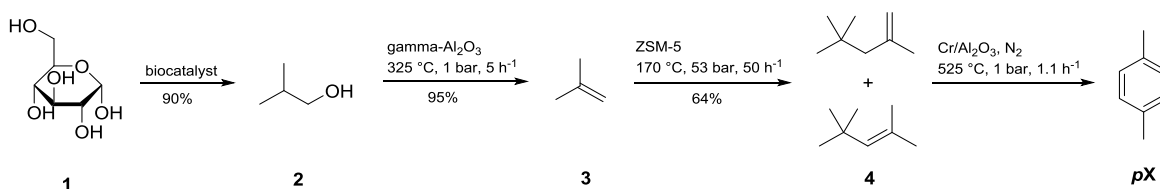
Isobutanol **2** can be produced by fermenting biomass-derived glucose **1** and further converting it to *pX* (Scheme 3), one of the most common intermediates in the synthesis of TPA. This four-step-process has been developed and patented by Gevo Inc.¹⁷

First, carbohydrate-containing biomass such as cellulose, hemicellulose, lignin or starch is pretreated to obtain monosaccharides, normally glucose. Glucose is fermented using a genetically modified biocatalyst (e.g. bacteria, fungi or yeasts) capable of converting sugars selectively to isobutanol via metabolic routes. The biocatalysts are discussed in detail in a separate patent by Gevo Inc.¹⁸ The dehydration of isobutanol to isobutylene **3** is typically carried out in a fixed-bed reactor. The reported yield of isobutylene was e.g. 95% when the reaction was performed on a γ -alumina catalyst at 325 °C at a pressure of 1–5 bar and a WHSV of 5 h⁻¹.¹⁷

The dimerization of isobutylene to diisobutylene **4** can be carried out either separately or in one pot with the dehydration step, if the catalyst is capable of catalyzing both reactions. In a stepwise manner, an example of suitable reaction conditions used zeolite ZSM-5 as a catalyst at 170 °C at a pressure of 53 bar and a WHSV of 50 h⁻¹. The product stream contained 64% diisobutylene. Both the unreacted isobutanol and the unreacted isobutylene could be recycled back into the respective reactors, or they could act as diluents in the following steps.

Finally, the dehydrocyclization of diisobutylene is performed in a reactor loaded with a chromium-doped alumina catalyst at a pressure close to 1 bar and a temperature of 400–600 °C. Gases like H₂ or N₂ can be used as a diluent in the dehydrocyclization feedstock, but H₂ formed in the process can also be captured and used in other processes. Despite the low conversion (20–50%), the reaction provides at least 75% selectivity towards *p*X among the xylene fraction and the unreacted feedstock can be recycled back into the dehydrocyclization reactor.¹⁷ Gevo Inc has also developed a similar procedure in which isobutanol is first converted into 2,5-dimethylhexadiene and subsequently to *p*X.¹⁹

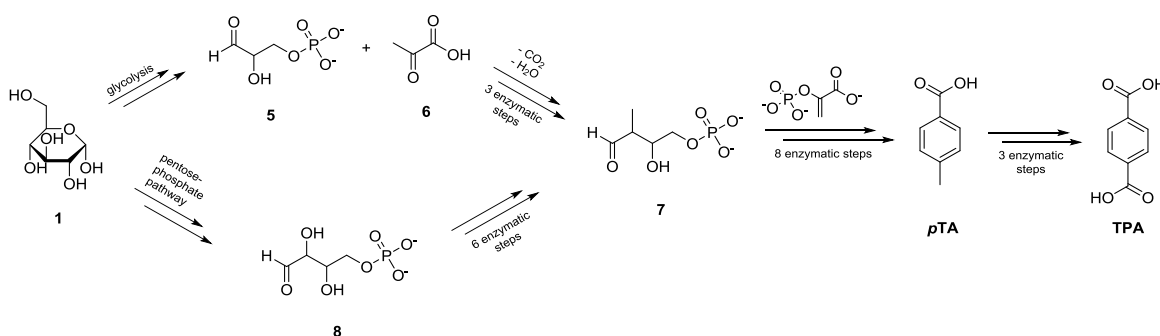
In the patent of Sun *et al.*, *p*X is made from acetic acid that can be derived, for example, by fermenting C₅ and C₆ sugars. Acetic acid is converted to isobutylene at 415 °C with a WHSV of 0.16 h⁻¹ in the presence of a Zn_xZr_yO_z mixed oxide catalyst. In these conditions, the selectivity for isobutylene was 57% (determined by GC). Isobutylene is then treated in a similar fashion to the Gevo process to finally obtain *p*X.



Scheme 3. The Gevo process for the production of *pX* from glucose **1** via fermentation to isobutanol **2**.¹⁷ The yields are exemplary and determined by GC-FID.

Another approach is the fermentation of carbohydrates to *pTA* or TPA by genetically modified microorganisms (Scheme 4). This process was developed by Genomatica Inc. In their first patent²⁰, glyceraldehyde-3-phosphate **5** and pyruvic acid **6** were enzymatically converted to (2-hydroxy-3-methyl-4-oxobutoxy)phosphonate **7**. Glucose was converted to pyruvic acid by glycolysis, **5** being one of the key intermediates in the same pathway. Metabolic engineering was used to develop non-naturally occurring microbial organisms (e.g. bacteria and yeast) capable of producing *pTA* from **7** via a multi-step metabolic pathway. Finally, *pTA* was oxidized to TPA in three enzymatic steps. The culture conditions can be scaled up for commercial production of TPA.²⁰

Glucose can be enzymatically converted to **8** via the pentose phosphate pathway, which is another native metabolic route parallel to glycolysis. Genomatica Inc developed a method of converting **8** to **7** (Scheme 4).²¹ Alternatively, 4,5-dihydroxy-2-oxopentanoate derived from arabinose and xylose could be used as a starting material for **7**, which was then converted to TPA by the same enzymatic pathway that was used in the first patent. The processes for recovering TPA from a culture medium using either monosaccharides or biomass as a feedstock were also discussed in the patent.²¹



Scheme 4. The pathways for enzymatic production of TPA starting from glucose **1**.^{20,21}

Besides the aforementioned methods, DuPont^{22,23} and BASF²⁴ have developed microorganisms capable of converting *p*X to *p*-(hydroxymethyl)benzoic acid or *p*TA, respectively. Both of these compounds can be oxidized to TPA by existing methods.

In order to avoid using microorganisms and other delicate manufacturing systems, Virent Inc has developed a process which utilizes catalytic reforming of biomass for the production of *p*X.²⁵⁻²⁸ The procedure is somewhat similar to the commercial fossil-fuel-based method (Section 2), giving a wide distribution of alkanes and preferentially giving aryls as products.

The Virent process consists of three steps, after which *p*X can be oxidized to TPA by AMOCO process (Section 2). First, the feedstock (e.g. cellulose, hemicellulose or sometimes lignin) is deconstructed to oxygenated hydrocarbons by reacting it with hydrogen on a heterogeneous catalyst, for example Fe, Co, Ni, Ru, Rh or Pd supported on alumina or silica.²⁸ In addition to this, other deconstruction methods, including hydrolysis, organosolv pulping and pyrolysis, can be used. The resulting hydrolysate is treated with methods such as filtration, extraction or ion exchange chromatography to reduce ash components.

The aqueous feedstock of oxygenated hydrocarbons is then further reacted with H₂ over a dehydrogenation catalyst (e.g. group 8 metals either with or without a heterogeneous support). The advantage of this process is that H₂ can be generated *in situ* as it is produced as a side product in the aqueous phase reforming. The deoxygenation yields small oxygenates, such as alcohols, ketones and aldehydes. Finally, a product stream of aromatics and alkanes is obtained from the catalytic condensation reaction of the oxygenated intermediates. The condensation catalysts can be e.g. carbides, nitrides, zirconia, alumina or zeolites. The product composition can be varied by using different catalysts and different oxygenates as the feedstock. In an exemplary reaction, the feed comprising mostly of propylene glycol in the presence of a Ni-modified ZSM-5 catalyst provided 65% of aromatics, while only 31% was obtained from the feed containing mostly *n*-propanol.²⁷ The analysis method of the product composition was not given.

3.1.1.2.2 Production of platform chemicals by fermentation

Genetically modified microorganisms are able to produce starting materials for chemical routes. The sources for three biomass-derived compounds, *cis,cis*-muconic acid, malic acid, and isoprene (Figure 1), are discussed briefly here.

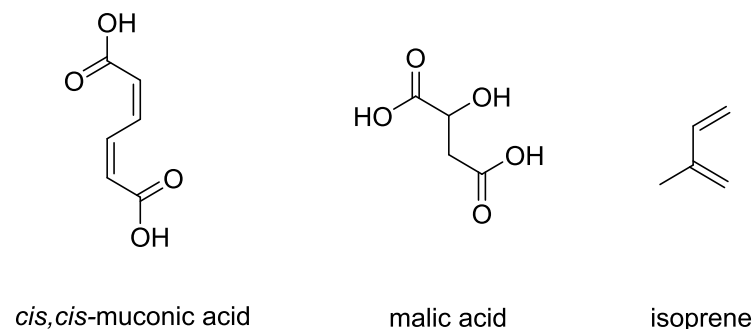
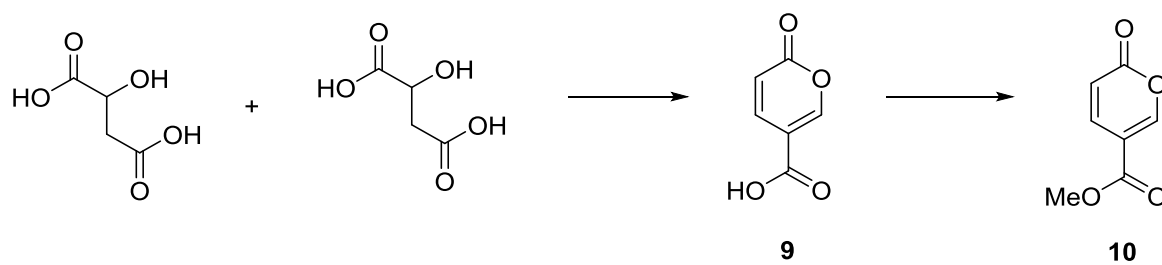


Figure 1. The structures of the compounds obtainable by fermentation of biomass.

Metabolic engineering has been used to develop strains of *Escherichia coli*²⁹, *Saccharomyces cerevisiae*^{30,31} and *Pseudomonas putida*³² able to convert either glucose or lignin-derived aromatics into *cis,cis*-muconic acid (*ccMA*). After isomerization to *trans,trans*-muconic acid (*ttMA*), it can be used in Diels–Alder (DA) cycloaddition with ethylene (Section 3.1.2.2.3).^{33–35}

Malic acid can be produced from glucose by fermentation. Malic acid is a key intermediate of the citric acid cycle which makes it possible to produce it either in native fungal species or in genetically modified species. Since the fungal fermentation is complicated to scale up to the industrial scale, metabolic engineering has been used to create strains of yeasts and bacteria capable of producing high yields of malic acid.³⁶ Two malic acid molecules can undergo acid-catalyzed self-condensation to coumalic acid **9** (Scheme 5). After esterification of coumalic acid to methyl coumalate **10**, the latter can be used as a diene in a DA reaction.^{37,38}



Scheme 5. The synthesis of methyl coumalate **10** from biomass-derived malic acid.

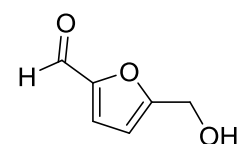
Besides the two carboxylic acids, isoprene (2-methyl-1,3-butadiene) has been used as the diene in several DA approaches to produce *p*TALD or *p*TA, depending on the dienophile.^{39–}
⁴³ Isoprene is typically produced from petrochemical sources, but a bio-based process for its production (BioIsoprene) has also been developed. This metabolically engineered *E. coli*-based system can convert glucose to isoprene via the mevalonic acid pathway.⁴⁴

3.1.2 Chemical pathways

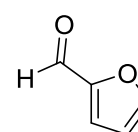
3.1.2.1 Conversion of biomass to platform chemicals

Cellulose and hemicellulose can be converted to monosaccharide units and further to various important platform chemicals, such as 5-hydroxymethylfurfural (HMF), furfural, acrolein and acrylic acid (Figure 2). They are used as starting materials in chemical pathways to produce TPA or its intermediates, such as *p*X, *p*TALD and *p*TA. The common factor for these multi-step syntheses is that one key step is typically a DA cycloaddition (Section 3.1.2.2). The bio-based sources for the aforementioned compounds are discussed briefly here.

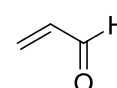
HMF is a platform chemical which can be either hydrogenolyzed to 2,5-dimethylfuran (DMF) or oxidized to 5-(hydroxymethyl)furoic acid (HMFA) or 2,5-furandicarboxylic acid (FDCA) (Figure 3). These compounds have been widely used in cycloadditions with bio-based dienophiles.^{45–52} Almost quantitative yields from the conversion of HMF to FDCA have been obtained with Au/CeO₂ and Au/TiO₂ catalysts in aqueous conditions.⁵³ Good yields for the hydrogenolysis of HMF to DMF by numerous catalysts have also been reported.⁵⁴ Copper catalysts are usually preferred due to their ability to cleave C–O bonds rather than C–C bonds, thus maintaining the aromaticity of the furan ring. For example, a copper-zinc alloy catalyst has provided a 90% yield of DMF with cyclopentyl methyl ether as a solvent.⁵⁵ Different methods for the synthesis of both FDCA and DMF are discussed in the review by Wang *et al.*⁵⁴



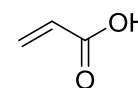
HMF



furfural

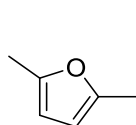


acrolein

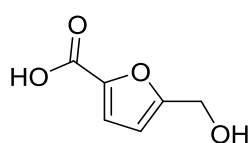


acrylic acid

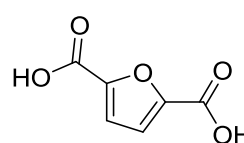
Figure 2. The structures of the platform chemicals.



DMF



HMFA



FDCA

Figure 3. The compounds derived from HMF.

Several catalytic systems have been developed for the dehydration of glucose or fructose to obtain high yields of HMF. Due to both the wider availability and the lower cost, glucose is the preferred feedstock for this purpose. Glucose is the monomeric unit of the most abundant biopolymer, cellulose, which can be decomposed to glucose units for example by dilute acid hydrolysis or enzymatic hydrolysis.⁵⁴

Furfural is another important biosourced feedstock. It has gained less attention than HMF in the production of bio-TPA. Recently, it has been successfully converted first to maleic anhydride and then to TPA via multi-step synthesis (Section 3.1.2.2.3).⁵⁶ Furfural is mainly produced from the dehydration of C₅ sugars such as xylose and arabinose, which are contained in hemicellulose. Using lignocellulose as a feedstock is a desirable option as it contains up to 25 wt% of xylan and 5 wt% of arabinan, depending on the type of the feedstock. Grasses have the highest content of xylan, and thus agricultural residues like corn cobs, oat husks and bagasse are normally utilized in the processes to produce furfural.⁵⁷

To make the DA reactions entirely bio-based, the dienophiles also have to be produced from biomass. The simplest dienophile, ethylene, can be produced by fermenting carbohydrates to make bioethanol and then dehydrating it into ethylene.³⁶ Another bio-based dienophile is acrolein, which can be used directly or after oxidizing it to acrylic acid. Glycerol is an abundantly available starting material for the production of acrolein because it is formed as a side product in the biodiesel production. There is constant research into new catalysts for the dehydration of glycerol to acrolein even though no commercial application has yet been launched.⁵⁸ Because of the toxicity of acrolein, methods for direct oxidehydration of glycerol to acrylic acid have been developed. So far, the selectivities of those methods remain lower than those of the dehydration to acrolein.⁵⁸

3.1.2.2 Cycloadditions of biomass-derived compounds

3.1.2.2.1 Synthesis of *p*-xylene

While *p*X is the most common naphtha-sourced precursor for TPA, it can be synthesized from several different carbohydrate-derived molecules using DA cycloaddition. The most

commonly utilized pathway uses DMF and ethylene as starting materials. DMF can be derived from HMF as was discussed in Section 3.1.2.1.

Brandvold⁴⁵ has patented a catalytic process for converting DMF and ethylene to *pX* (Table 1). The reaction is carried out at elevated temperatures (100–300 °C) and high ethylene pressures (11–101 bar). Activated carbon, acid-washed activated carbon, rare-earth exchanged zeolite Y, zinc chloride, silica and γ -alumina can be used as catalysts, providing at least 30% yield of *pX*. The optimal conditions were not specifically discussed.

Williams *et al.*⁴⁶ have performed the cycloaddition of DMF and ethylene on various zeolitic catalysts (Table 1). They found out that adding Brønsted acid sites to the catalyst had a significant impact on the reaction rate, changing the rate-determining step to be cycloaddition instead of dehydration. The density of the Brønsted acid sites did not have any relation to the catalyst activity, but the cage microstructure of the zeolite H-Y was more active than the channel structure of HZSM-5 and H-BEA. High conversion of DMF (95%) and good selectivity for *pX* (51%) were achieved when the reaction was done on zeolite H-Y (Si/Al = 30) at 300 °C with an ethylene pressure of 63 bar. When *n*-heptane was added as a solvent, the selectivity increased to 75%, the yield of *pX* being then 71%. The main side-product was 2,5-hexadione, formed by hydrolysis of DMF. Economic analysis of this process has been performed by Lin *et al.*⁵⁹

Chang *et al.*⁴⁷ have applied the usage of *n*-heptane as a solvent with other heterogeneous catalysts in similar conditions as in the procedure by Williams *et al.* (Table 1). Besides zeolites, they screened the catalytic activity of γ -Al₂O₃ and niobic acid. H-BEA (Si/Al = 12.5) showed significantly higher activity compared to the catalysts, giving almost quantitative conversion of DMF. When the conversion of DMF increased, the side-product 2,5-hexadione was also converted to *pX*, thus providing the final selectivity of 90% for *pX*.

Wang *et al.*⁴⁸ have performed the cycloaddition of DMF and ethylene with several different Lewis acid and Brønsted acid catalysts, including trifluoroacetic acid, TiO₂, SiO₂/Al₂O₃ and WO_x-ZrO₂ in addition to those previously mentioned. They made similar observations to Williams *et al.* showing that catalysts having Brønsted acid sites had higher selectivity towards *pX*. The catalyst having both the best selectivity and the highest stability was WO_x-ZrO₂. It was suggested that its mesoporous structure caused its higher resistance to the catalyst deactivation. When DMF was fully converted to products at 250 °C and an ethylene

pressure of 20 bar, using hexadecane as a solvent and a $\text{WO}_x\text{-ZrO}_2$ catalyst calcined at 650 °C, the yield of *pX* was 80% (*Table 1*).

In the patent by Micromidas Inc.⁴⁹, several metal salts, both unsupported and supported, with varying counteranions were tested as catalysts for the cycloaddition of DMF and ethylene. They compared the metal catalysts to other types of catalysts previously used in this reaction, including activated carbon, zeolites and heteropolyacids. For the best catalysts (copper(II) triflate, copper(II) chloride and ytterbium(III) triflate), different temperatures, ethylene pressures and aliphatic solvents were screened. Excellent yields were achieved with several reaction conditions. For example, when 0.5 wt% of $\text{Cu}(\text{OTf})_2$ was used to catalyze the cycloaddition in dioxane at 250 °C, a 99% yield of *pX* was obtained after 7 h (*Table 1*, *Scheme 6*). The pressure of ethylene was 35 bar.

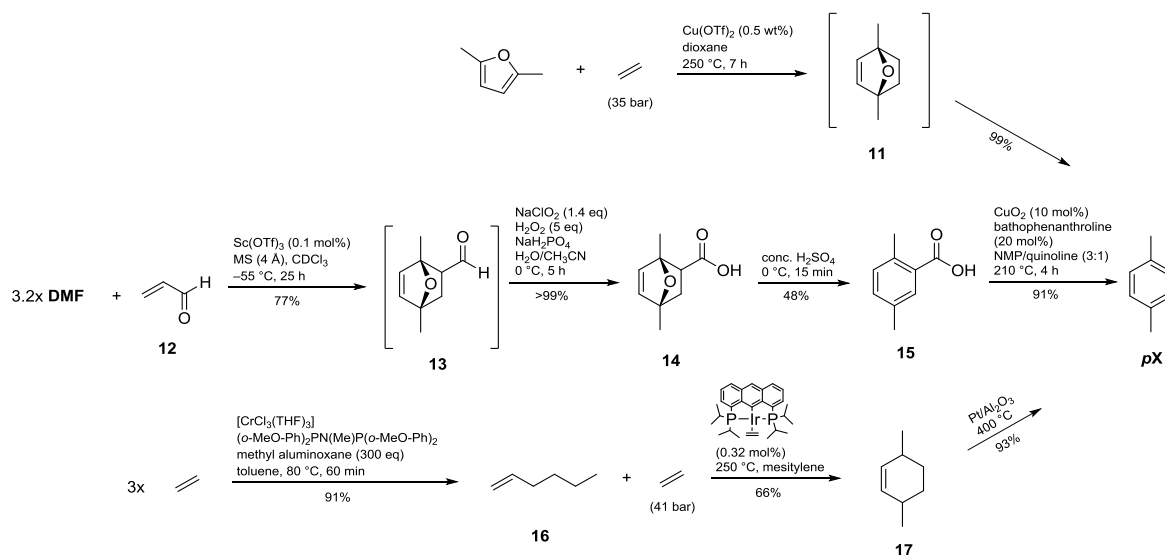
Due to the high temperatures and ethylene pressures used in the aforementioned cycloadditions, other biomass-derived compounds have been considered as a replacement for ethylene. Shiramizu and Toste⁵⁰ have used acrolein **12** in a DA cycloaddition with DMF (*Table 1*, *Scheme 6*). The common Lewis acids and metals from groups 3 and 4 were screened, and scandium(III) triflate was found to be the best catalyst. The optimal amount was 0.1 mol% because of the prolonged reaction time with smaller amounts and the decomposition of acrolein with greater amounts of the catalyst. The yield of the cycloaddition was highly temperature dependent and needed to be carried out at a temperature of at least -55 °C for it to progress in a reasonable time. The cycloadduct **13** turned out to be highly unstable at ambient temperature both in the presence and the absence of the active catalyst so it was directly oxidized to carboxylic acid **14**. The yield of **14** was 77%. The aromatization to **15** was achieved with concentrated H_2SO_4 giving only 48% yield. Other methods, such as base-catalyzed dehydration or direct pyrolysis, could not be used due to the presence of unprotected carboxylic acid and the retro-DA that occurred upon heating. **15** was then converted to *pX* using an existing copper(II) oxide catalyzed decarboxylation procedure.⁶⁰ Because of the low yield of the aromatization step, the yield over the three steps was only 34%.

Lyons *et al.*⁶¹ have used bio-ethylene as the sole feedstock for *pX* production in 4 steps (*Table 1*, *Scheme 6*). First, ethylene was trimerized to hexene **16** using, for example, an existing chromium-catalyzed procedure.⁶² Hexene was then disproportionated to a mixture of hexadienes and hexane. The cycloaddition with ethylene produced mainly 3,6-

dimethylcyclohexene **17**. The disproportionation and cycloaddition could be done in one pot with an iridium pincer catalyst at 250 °C with an ethylene pressure of 41 bar. After 192 h, the yield of **17** was 66%. **17** was then dehydrogenated to *pX* using the optimized conditions of 400 °C on a Pt/Al₂O₃ catalyst. The overall yield starting from ethylene was 56%. The disadvantage of this method was that a mole of hexane was produced together with a mole of hexadienes in the disproportionation step. When disproportionation was directly followed by cycloaddition, ethylene was able to act as a hydrogen acceptor, thus providing higher yields than the stepwise approach.

Table 1. Comparison of the different methods to produce *pX*.

Reference	Starting materials	Number of steps	Catalyst for the cycloaddition	Yield of <i>pX</i> (%), determination method
Brandvold ⁴⁵	DMF + ethylene	1	several options	at least 30, not given
Williams <i>et al.</i> ⁴⁶	DMF + ethylene	1	zeolite H-Y	71, GC-FID
Chang <i>et al.</i> ⁴⁷	DMF + ethylene	1	zeolite H-BEA	90, GC-FID
Wang <i>et al.</i> ⁴⁸	DMF + ethylene	1	WO _x -ZrO ₂	80, GC-FID
Micromidas Inc ⁴⁹	DMF + ethylene	1	Cu(OTf) ₂	99, ¹ H NMR
Shiramizu and Toste ⁵⁰	DMF + acrolein	3	Sc(OTf) ₃	34, ¹ H NMR
Lyons <i>et al.</i> ⁶¹	ethylene	4	Ir-pincer catalyst	56, GC



Scheme 6. Selected synthetic pathways to *pX* from different starting materials via DA cycloaddition.^{49,50,61}

3.1.2.2.2 Oxidation of *p*-xylene to terephthalic acid

The oxidation of *pX* to TPA is typically carried out with the current commercial AMOCO process (Section 2). Some alternative methods have been suggested to replace it, such as applying zirconium as a co-catalyst, carbon dioxide as a co-oxidant or *N*-hydroxyimides or guanidine as a promoter. Preferable oxidation conditions would be mild and eco-friendly. Water has been studied as the solvent media for *pX* oxidations. So far, some excellent yields of TPA have been obtained in supercritical water with a manganese bromide catalyst and hydrogen peroxide as an oxidant. However, this method requires harsh temperature and pressure conditions. Alternative systems for the oxidation of *pX* are discussed in more detail in the review by Tomás *et al.*⁶

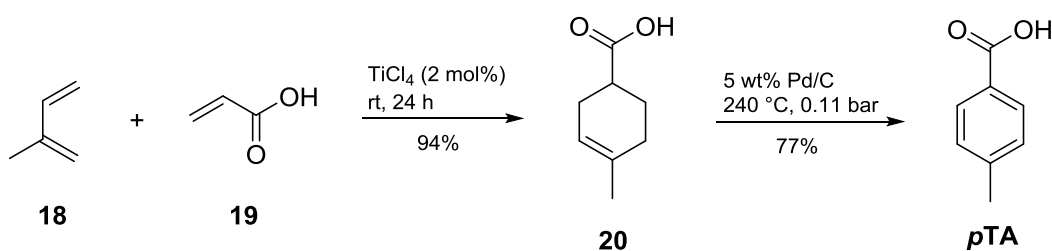
3.1.2.2.3 Synthesis of oxidized intermediates and terephthalic acid

Miller *et al.*³⁹ have synthesized *pTA* from biomass-derived isoprene **18** and acrylic acid **19** (Table 2, Scheme 7). Their catalytic system overcame the problem with a former cycloaddition in which the ratio of *p*- and *m*-cycloadducts in the product was only 3:1.⁶³ The equimolar amounts of starting materials reacted in the presence of a Lewis acid catalyst at room temperature under argon for 24 h. The highest yield of *p*-cycloadduct **20** was obtained

with titanium tetrachloride with the *para/meta* ratio of 23:1. When the reaction temperature was decreased, a 50:1 ratio could even be achieved with a longer reaction time of 100 h. Different counteranions for Ti^{4+} were tested, but only chloride resulted in an excellent yield of **20** (94%). The aromatization of **20** was done by distillation through a Pd/C catalyst dispersed in silica at 240 °C and 0.11 bar, resulting in 77% yield of *p*TA. Aliphatic carboxylic acids formed as side products.

A couple of high-yielding reactions for just the cycloaddition step have been published. Xiao and Malhotra⁴⁰ used ionic liquids to catalyze the cycloaddition of isoprene and acrylic acid at low temperature (0 °C). Using 1-ethyl-pyridinium trifluoroacetate as an equimolar solvent resulted in a 89% yield of the *p*-cycloadduct after 2 h but the selectivity dropped from 98% to 74% when the temperature was increased to 45 °C. The yield was determined by GC and the selectivity by ¹H NMR. The ionic liquid could be recovered for several runs without any decrease in the yield. Polyelectrolytes have also been used as catalysts yielding selectivities of up to 98% of *p*-adduct (determined by NMR) after 30 min at room temperature.⁴¹

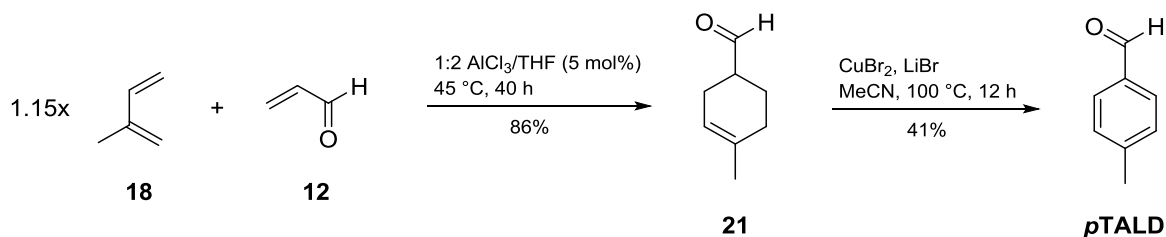
Lately, Frost and Wang⁴² have patented several boron-based catalysts for the DA cycloaddition. All of them provided excellent yields and selectivities towards *p*-cycloadduct **20** either in solvent-free conditions or with a small amount of solvent in which the catalyst was dissolved. In general, the reactions were carried out at room temperature in the presence of 2 mol% of the catalyst. The best yield (97%, isolated) was obtained with Cl₂BOTFA.



Scheme 7. Synthesis of *p*TA from isoprene **18** and acrylic acid **19**.³⁹ Yields determined by NMR.

Wang and Tong⁴³ used acrolein **12** in a cycloaddition with isoprene **18**. They developed a flexible route to synthesize either *p*X or TPA via *p*TALD (Table 2, Scheme 8). The cycloaddition between isoprene and acrolein was catalyzed by a 1:2 mixture of aluminium chloride and tetrahydrofuran (THF) at 45 °C without a solvent. After 40 h, 86% of

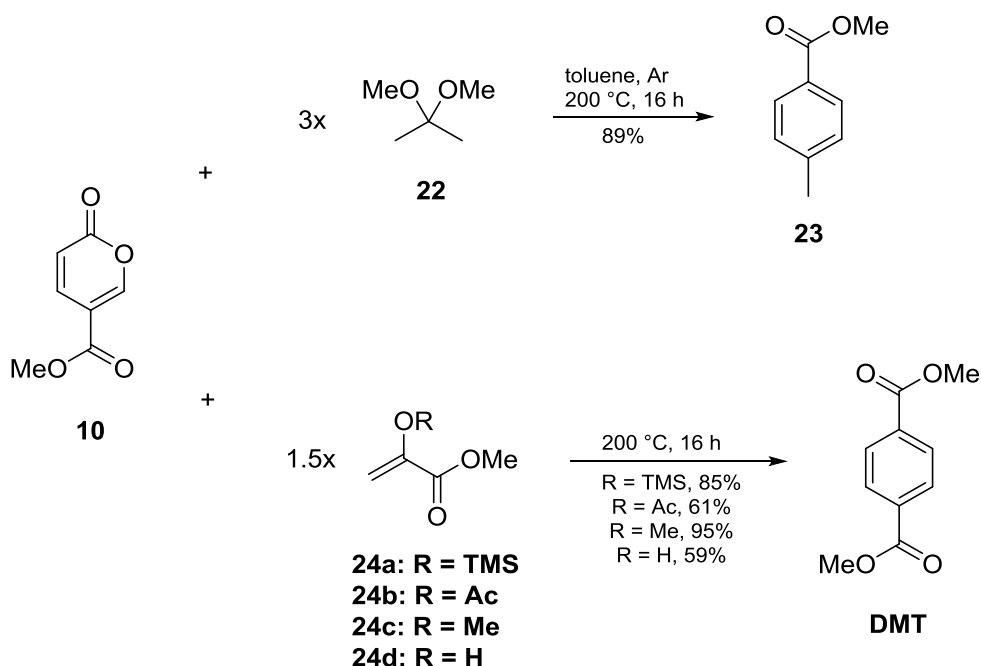
cycloadduct **21** was obtained. The aromatization of **21** was carried out with copper(II) bromide and lithium bromide at 100 °C, resulting in only a 41% yield of *p*TALD. The oxidation to TPA could be done either with potassium permanganate and sodium hydroxide (95% of TPA) or with a modified AMOCO process using *N*-hydroxyphthalimide as a radical chain carrier instead of NaBr (91% of TPA). The overall yield after 3 steps was up to 33%.



Scheme 8. Synthesis of *p*TALD from isoprene **18** and acrolein **12**.⁴³ Isolated yields.

Methyl coumalate **10** was used as a starting material for an inverse electron-demand DA reaction by Lee and Kraus³⁷. After heating at 200 °C for 16 h with 3 equivalents of commercially available 2,2-dimethoxypropane **22**, methyl *p*-toluate **23** was obtained in a 89% yield (Table 2, Scheme 9).

Lee and Kraus³⁸ have developed another inverse electron-demand DA reaction, producing dimethyl terephthalate from methyl coumalate and derivatives of methyl pyruvate **24** (Table 2, Scheme 9). Methyl pyruvate is a convenient option as a starting material since it is easily derived from pyruvic acid, the main product of glycolysis. Protected enol forms of methyl pyruvate were used with methyl coumalate, providing good to excellent yields in the cycloaddition. The optimization of the reaction conditions was based on the previous procedure.³⁷ In this case, no solvent was needed and 1.5 equivalents of dienophile was enough for full conversion of methyl coumalate in 16 h at 200 °C. Alternatively, the reaction could be done at 150 °C with 3 equivalents of dienophile without affecting the yield. The purification of DMT occurred by sublimation simultaneously when the reaction proceeded. The best yield (95%) was achieved with 2-methoxyacrylate **24c** but it had to be produced from methyl pyruvate via 2 steps. However, the ketal intermediate methyl 2,2-dimethoxypropanoate turned out to provide as high a yield as **24c**. Even methyl pyruvate **24d** provided a fair yield (59%). For the latter, the yield could possibly be improved by increasing the reaction time, because methyl coumalate was not fully converted after 16 h.



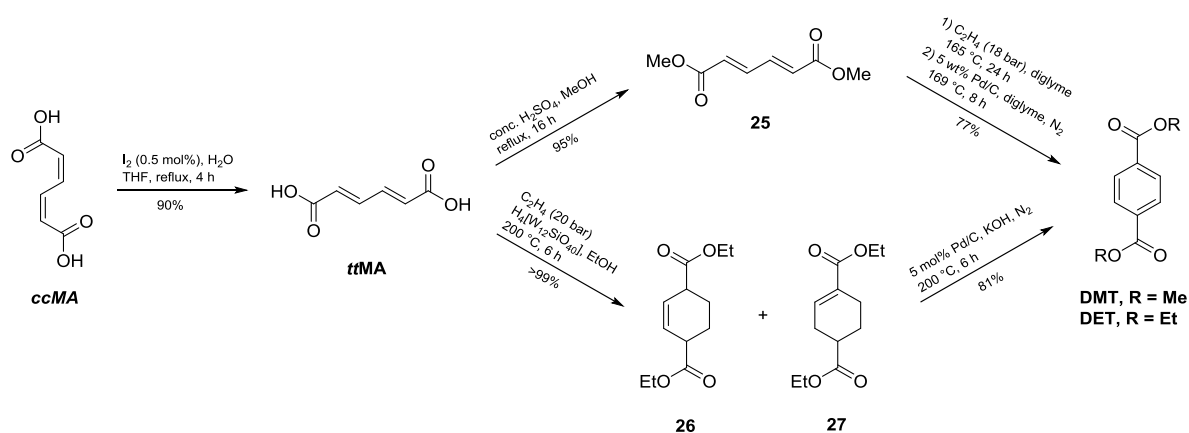
Scheme 9. Syntheses of methyl *p*-toluate **23** and DMT from methyl coumalate **10**.^{37,38} Isolated yields.

*cc*MA has to be isomerized to *tt*MA in order to make it DA active. In the method developed by the Draths Corporation³³, *cc*MA is refluxed for 4 h in THF with a catalytic amount of iodine. The highest yield of *tt*MA (90%) was obtained when 5 wt% of water was added to the reaction. Several possibilities for producing either TPA or DMT are discussed in the patent. The DA reaction can be done with *tt*MA or *trans,trans*-dimethyl muconate **28** and the following aromatization can be carried out in the same solvent or in a separate step. The best yields are achieved when esterification is done prior to the cycloaddition. The esterification of *tt*MA was performed by refluxing in methanol for 16 h in the presence of concentrated H₂SO₄, yielding 95% of **25**. Dimethyl ester **25** was then dissolved in diglyme and heated for 24 h in a Parr reactor pressurized with ethylene. The solution was diluted with diglyme and refluxed for 8 h using 5 wt% Pd/C as a catalyst (Table 2, Scheme 10). A 77% yield of DMT was obtained.

Carraher *et al.*³⁴ performed a mechanistic analysis of the isomerization reaction to discover the optimal conditions for the complete isomerization to the *trans,trans*-form while avoiding the lactonization that may occur as a side reaction. They obtained a 55% yield of *tt*MA when the *cis,cis*-isomer in DMSO was placed in a 75 °C oven for 2 weeks. Isomerization was also achieved by adding lanthanum(III) salts to an aqueous solution of *cc*MA, adjusting the pH

to 4.34 with NaOH and HNO₃. The best yield was also 55% in the latter method, with a rather long reaction time of 10.5 days at 75 °C. The yields were determined by NMR.

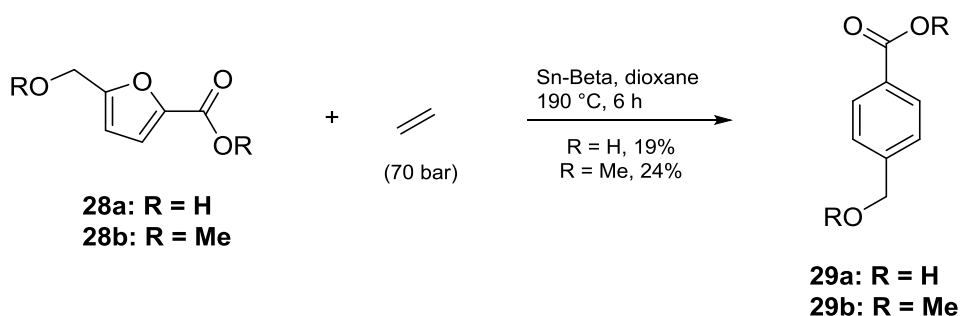
Lu *et al.*³⁵ synthesized diethyl terephthalate (DET) starting from the combined esterification and DA reaction of *tt*MA and ethylene, directly followed by dehydrogenation of the cycloadducts (*Table 2, Scheme 10*). The first step was performed at 200 °C with the ethylene pressure of 20 bar, using ethanol as a solvent and silicotungstic acid as a catalyst. After 6 h, nearly quantitative conversion of *tt*MA to the isomers **26** and **27** of the cycloadduct was obtained. The crude product could be used without purification in the aromatization step which was carried out at 200 °C in a nitrogen atmosphere. Different metals supported on activated carbon were screened as catalysts, and the highest yield was obtained with 5 mol% Pd/C when potassium hydroxide was added to neutralize the silicotungstic acid. The yield of DET was 81% after 6 h.



Scheme 10. Synthetic pathways to dialkyl terephthalates starting from ccMA. Yields determined by isolation³³ and HPLC³⁵.

A few procedures starting from oxidized furanics have been published. In a patent by the BP Corporation⁵¹, either FDCA or its methyl ester was pressurized with ethylene in the presence of a solvent (preferably water with FDCA or toluene with the ester). The temperature was varied from 100 to 250 °C and the ethylene pressure was in the range of 2–140 bar. The reaction time was several hours. The yield of one particular reaction was extremely low, only 0.14% of TPA (determined by HPLC). This was probably due to the strong deactivating effect of the two carboxyl groups of FDCA.⁵²

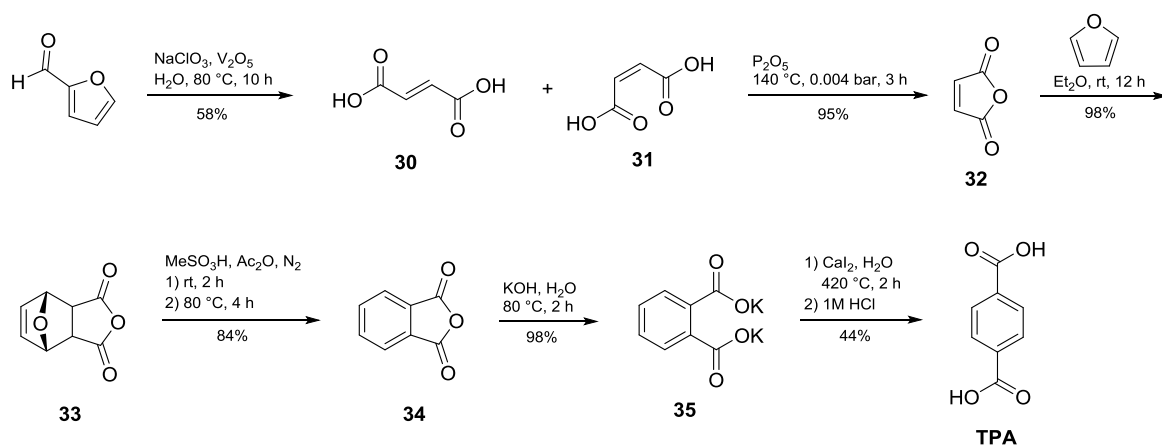
Pacheco and Davis⁵² have screened the reaction conditions for the DA reactions of HMFA and its mono- and dimethylated derivatives (*Scheme 11*). The dehydration occurred simultaneously right after the cycloaddition. FDCA was also tested but no reaction was obtained. The optimal solvent was found to be dioxane and the reaction was performed at 190 °C for 6 h with an ethylene pressure of 70 bar. HMFA **28a** and methyl 5-(methoxymethyl)furan-2-carboxylate **28b** gave similar yields of the corresponding dehydrated cycloadduct **29** (19% and 24%, respectively), but the selectivity was higher with **28b** whereas unprotected HMFA resulted in higher conversion. The catalyst in the reaction was β -zeolite doped with Sn^{4+} metal centers. In the reaction of **28b**, both Sn- β and Zr- β gave almost the same yield but the selectivity was significantly higher with the latter (81% compared to 48%). This was probably caused by **28b** reacting faster on Sn- β but having fewer side reactions on Zr- β . By increasing the reaction time on Zr- β , the yield could be increased while maintaining the selectivity.



Scheme 11. Synthesis of p-(hydroxymethyl)benzoic acid 29a and its methylated derivative 29b from oxidized furanics.⁵² Yields determined by ¹H NMR.

Tachibana *et al.*⁵⁶ have developed a synthetic pathway which utilizes biomass-derived furfural as a starting material (*Table 2, Scheme 12*). Furfural is first oxidized to a mixture of fumaric acid **30** and maleic acid **31**. The vanadium(V) oxide-catalyzed oxidation with sodium chlorate was not the highest yielding process in the literature but the authors chose it due to its practicality.⁵⁶ The yield of acids **30** and **31** was 58% altogether. **30** and **31** are converted to maleic anhydride **32** in nearly quantitative yield using phosphorus pentoxide at reduced pressure. Phosphoric acid is formed in the reaction, causing simultaneous isomerization of fumaric acid to maleic acid. Maleic anhydride is then reacted in the DA cycloaddition with furan, which can be obtained by decarbonylation of furfural. The reaction

is performed at room temperature for 12 h to yield 98% of the cycloadduct **33**. The cycloadduct is then dehydrated by treating it with trifluoromethane sulfonic acid and acetic anhydride, resulting in phthalic anhydride **34** which is hydrolyzed to dipotassium phthalate **35** by KOH. Finally, it is converted to dipotassium terephthalate by the Henkel method⁶⁴, an industrial process which was formerly used for the production of TPA. The overall yield over six steps is only 20%, mostly due to the low yield of the transfer reaction.



Scheme 12. Synthesis of TPA starting from furfural.⁵⁶ Isolated yields.

Table 2. Comparison of the different methods to produce the oxidized intermediates and TPA.

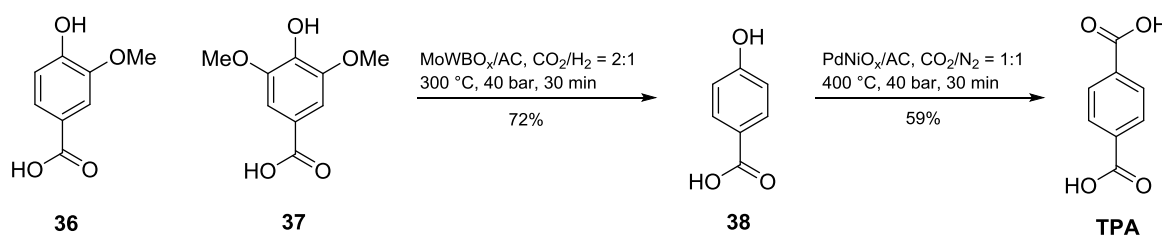
Reference	Starting materials	Number of steps	Catalyst for the cycloaddition	Product and yield (%)
Miller <i>et al.</i> ³⁹	isoprene + acrylic acid	2	TiCl ₄	<i>p</i> TA, 69
Wang and Tong ⁴³	isoprene + acrolein	3	1:2 AlCl ₃ /THF	TPA, 33
Lee and Kraus ³⁷	methyl coumalate + 22	1	heat	methyl <i>p</i> -toluate, 89
Lee and Kraus ³⁸	methyl coumalate + 24c	1	heat	DMT, 95
Draths Corporation ³³	<i>tt</i> MA + ethylene	2	heat	DMT, 73
Lu <i>et al.</i> ³⁵	<i>tt</i> MA + ethylene	2	H ₄ [W ₁₂ SiO ₄₀], heat	DET, 81
Pacheco and Davis ⁵²	HMFA + ethylene	1	Sn- β zeolite, heat	<i>p</i> -(hydroxymethyl) benzoic acid, 19
Tachibana <i>et al.</i> ⁵⁶	furfural + furan	6	-	TPA, 20

3.1.2.3 Lignin as a biosource

Lignin is the third major component that comprises lignocellulosic biomass in addition to cellulose and hemicellulose. It is less often used as a feedstock due to its lack of any particular repeating units. However, out of the three lignin is the only biopolymer that has an aromatic-based structure. There are techniques for conversion of lignin to several value-added chemicals. These may include either *pX*⁶⁵⁻⁶⁷ or a mixture of phenols, which can be converted to BTX fraction and further to TPA via existing processes⁶⁸. The strategies for the fractionation of lignin are discussed in the review by Zakzeski *et al.*⁶⁹

Recently, Bai *et al.*⁷⁰ have proposed a two-step synthesis of TPA from vanillic acid **36** and syringic acid **37** (*Scheme 13*), which can be produced from lignin by deep oxidation depolymerization. First, the phenolic acids are demethoxylated to *p*-hydroxybenzoic acid **38** by using boron-doped group 6 metal oxides as catalysts. They are supported either on β -

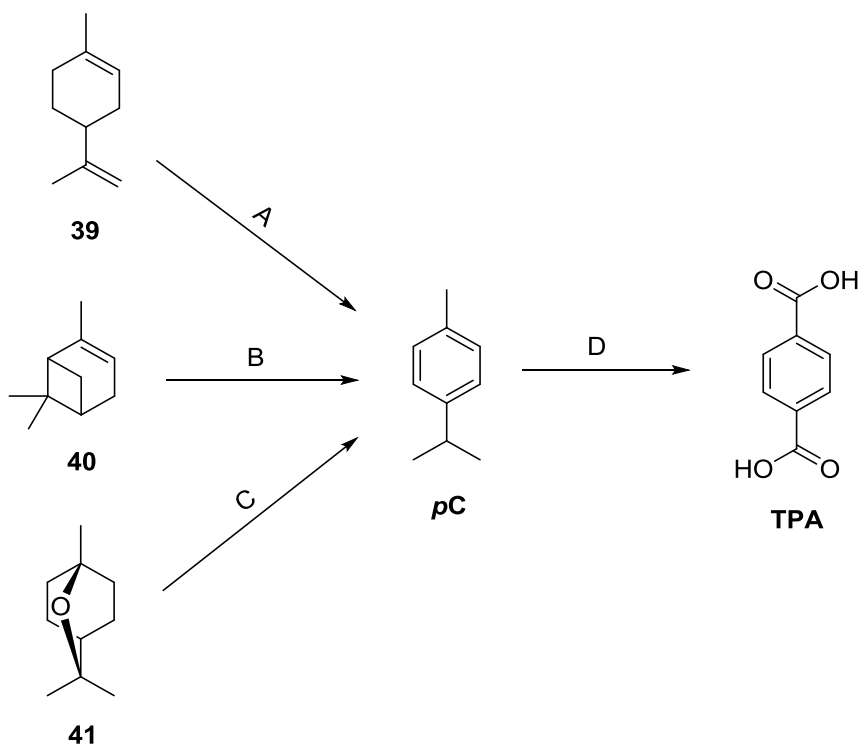
zeolite or activated carbon. The catalyst screening showed that bimetallic MoWBO_x/C provides high selectivity towards **38** and also the best yield (72%) when the reaction is performed under 2:1 mixture of CO₂ and H₂, respectively. It is necessary to add CO₂ gas to the reaction in order to avoid the decarboxylation of the starting materials. The second step is carried out in the same micro fixed-bed reactor as the first one with the CO₂/N₂ ratio of 1:1. Both single-metal-based and bimetallic catalysts containing Pd and/or Ni were tested for the reaction. Bimetallic PdNiO_x supported on activated carbon provides the highest yield of TPA, 59%. The side products are mainly polymers.



*Scheme 13. The synthesis of TPA from lignin-derived vanillic acid **36** or syringic acid **37**.⁷⁰ Yields determined by HPLC.*

3.2 Monoterpenes as a biosource

Monoterpenes are a class of compounds that occur widely in nature. They consist of two linked isoprene units having the formula C₁₀H₁₆. Terpenoids are functionalized terpenes. *p*-Cymene (*p*C) is a common synthetic precursor for TPA. It has been synthesized by dehydrogenation using various different conditions starting from limonene **39**^{71,72,81–85,73–80} (Section 3.2.1), α -pinene **40**^{71,86–90} (Section 3.2.2) or eucalyptol **41**^{91–93} (Section 3.2.3). *p*C is then oxidized to TPA (Section 3.2.5).^{83,84,94–96} The monoterpene pathway is shown in *Scheme 14*. Mixtures containing several different terpenes have also been successfully used as a starting material for the synthesis of *p*C (Section 3.2.4).^{87,97}



Scheme 14. Synthetic pathways A-C to *p*C and D to TPA starting from limonene **39**, α -pinene **40** or eucalyptol **41**.

3.2.1 Limonene to *p*-cymene

Citrus oil is produced as a by-product in the processing of citrus fruits. The main component of citrus oil is limonene, comprising 95% of it.⁷⁵ Limonene is the most common terpene-based starting material for the synthesis of *p*C (Scheme 14, pathway A). Reactions in the gas phase are usually performed in a fixed-bed flow reactor or in an autoclave with metal-impregnated heterogeneous catalysts such as silica, alumina, zeolites or sepiolite, a natural low cost clay. Besides the gas phase systems, several liquid phase reactions have been developed.

Noble metals, such as platinum and palladium, were used in several approaches in the dehydrogenation of limonene. Linstead *et al.*⁷¹ have vaporized limonene over platinumized charcoal. The optimal temperature was 305 °C for limonene yielding 80% of *p*C after 21 h (Table 3). A similar method with either Pd-coated charcoal or alumina was patented by Hull⁷². In the latter, 95% of *p*C was obtained when vaporized limonene was passed over the catalyst at 275 °C (Table 3). Hydrogen formed as a side product in both of these reactions.

Palladium was impregnated on zeolites in the study by Weyrich and Hölderich⁷³. Mildly acidic zeolite H-ZSM-5 ($\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio of 55) was shown to be a better support than strongly acidic H-US-Y ($\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio of 7.6). Almost neutral Na-ZSM-5 was the best platform among those studied. The effect of Pd and Ce in the catalyst, as well as addition of H_2 to the carrier gas, were studied. Full conversion with a *pC* yield of 82% was obtained at 300 °C with a WHSV of 1.3 h⁻¹ when the catalyst was Na-ZSM-5 impregnated with 2 wt% of Ce and 1 wt% of Pd (*Table 3*). The preferred ratio of the carrier gas was 1:1 N_2/H_2 to maintain full limonene conversion for a few days and to avoid catalyst deactivation.

Buhl *et al.*⁷⁴ have studied Pd-doped silica gels as catalysts. The most promising catalyst contained 0.5 wt% Pd on amorphous silica gel with medium pore size (115 Å). With this catalyst, the reaction temperature and H_2 partial pressure were optimized. The best selectivity for *pC* was achieved with pure H_2 as a carrier gas at 300 °C with a WHSV of 2.5 h⁻¹, being up to 96% (*Table 3*). Higher catalyst loading led to the increased formation of *p*-menthane.

At decomposition temperatures, sodium and potassium alkoxides catalyze dehydrogenation of limonene, proceeding by a carbanion mechanism. Pines and Schaap⁸¹ studied these reactions in an autoclave under an N_2 atmosphere. Excellent yields (97% and 95%) were obtained after 9 h with potassium *tert*-pentoxide (*Table 3*) and potassium *tert*-butoxide at 251 °C and 257 °C, respectively. H_2 formed as a side product.

Martin-Luengo *et al.*⁷⁵ have developed a solventless microwave-activated dehydrogenation. The catalyst used in this method was sepiolite which was modified by addition of sodium (SepNa), iron (SepFe), manganese (SepMn) or nickel (SepNi) oxides. Those catalysts were chosen due to their low toxicity or cost compared to most of the catalysts used nowadays in the field. Full conversion of limonene was achieved after 20 min of microwave irradiation at 165 °C. The best yield of *pC* (88%) was obtained with SepFe (*Table 3*). No H_2 was needed for the reaction to proceed; but instead, a mole of it was produced with a mole of *pC*.

Table 3. Comparison of different methods for pathway A (*Scheme 14*) in the gas phase, showing additionally whether H₂ was produced in the reaction or needed as a carrier gas.

Reference	Dehydrogenation catalyst	Yield of <i>pC</i> (%), determination method	H ₂	
			Produced	Needed as a carrier gas
Linstead <i>et al.</i> ⁷¹	Pt/C	80, isolated	yes	no
Hull ⁷²	Pd/C or Pd/Al ₂ O ₃	96, not given	yes	no
Weyrich and Hölderich ⁷³	Ce/Pd/Na-ZSM-5	80, GC	no	yes
Buhl <i>et al.</i> ⁷⁴	Pd/SiO ₂	95, not given	no	yes
Pines and Schaap ⁸¹	<i>t</i> -PeOK	97, UV	yes	no
Martin-Luengo <i>et al.</i> ⁷⁵	SepFe, microwave irradiation	88, GC/MS	yes	no

Liquid phase dehydrogenation reactions normally differ from gas phase reactions in producing higher yields but having lower reaction temperatures and times. In theory, H₂ gas is produced as a side-product in every reaction. Neumann and Lissel⁷⁶ have prepared *pC* by oxidative dehydrogenation with heteropolyacid H₅PMO₁₀V₂₀ (*Table 4*). The acid acted as a catalyst when it was complexed with tetraglyme in 1,2-dichloroethane at 70 °C. To complete the catalytic cycle, O₂ could be used as an oxidant instead of other oxidative reagents, such as quinones. After 20 h, the yield of *pC* was over 98%, but only 70% was isolated.

A zeolite-based catalyst was used also in the liquid phase reaction. Stratakis and Stavroulakis⁷⁷ have supported methyl viologen (MV²⁺) within zeolite Na-Y (*Table 4*). The interior framework of the zeolite forms charge transfer complexes with MV²⁺. Upon photoexcitation, radical cations of MV²⁺ and zeolite are formed. However, in this case, the reaction was successful either in the dark or under ambient light. Limonene was stirred with the catalyst in dry hexane under an argon atmosphere for 1 h, after which moistened THF was added and the stirring was continued for 2 h. The yield of *pC* was 98%, a minor alcoholic component being the only side product.

Aqueous-phase biphasic dehydroaromatization of limonene was studied by Zhao *et al.*⁷⁸ The reaction was performed in an autoclave using acidic water as a solvent in a H₂ atmosphere. Pd nanoparticles were used as a catalyst and polyvinylpyrrolidones (PVPs) with different alkyl chains lengths as stabilizers. The highest molecular weight polymer among those

tested, PVP-K90, prevented the aggregation of the nanoparticles even under more severe conditions (e.g. when temperature was increased from 150 °C to 180 °C). The separation of the product from the reaction mixture was easy due to the hydrophobic nature of *pC*. After 3 h, a conversion of 93% was achieved with a selectivity of 82% for *p*-cymene (*Table 4*). The catalyst could be recycled four times without significant decrease in the conversion or selectivity.

Another approach was designed by Barnes and Buckwalter.⁷⁹ A stoichiometric amount of *N*-bromosuccinimide (NBS) was used for dehydrogenation catalyzed by benzoyl peroxide (BPO) in carbon tetrachloride (*Table 4*). The mixture was refluxed for 2 h. Some unstable bromides formed in the reaction but they were converted almost completely to *pC* upon treating with KOH to obtain a total yield of 80% (*Table 4*).

So far, the most efficient route for generating *pC* is the selective dehydrogenation of limonene in the presence of an alkali metal. Besides high selectivity, almost quantitative yields have been obtained. Pines and Eschinazi⁸⁰ published one of the first alkali metal procedures in which limonene was refluxed for 24 h with sodium and a promotor (*Table 4*). A benzylsodium promotor was made by refluxing Na with *o*-chlorotoluene and toluene. When this compound was reacted with limonene and Na, the soluble residue was used as a promotor in another reaction which yielded 95% of *pC*.

Reggel *et al.*⁸² have performed the alkali metal catalyzed dehydrogenation with lithium in ethylenediamine (EDA). An excellent yield of *pC* (98%) was obtained after 4.5 h (*Table 4*). When Li was replaced with Na, no reaction occurred. Berti *et al.*^{83,84} have patented a similar dehydrogenation reaction in which iron(III) chloride was used with Na in EDA. After 8 h at 100 °C, nearly quantitative yield of *pC* was obtained (*Table 4*). Due to the high selectivity of these reactions, the purification could be done easily by extraction.

Recently, Domingo *et al.*⁸⁵ have proposed a method utilizing iodine for the production of *pC* to avoid the usage of metals or metal salts. The reaction was performed with combination of iodine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene. After 45 min, 82% of *pC* was obtained (*Table 4*).

Table 4. Comparison of the reaction conditions of pathway A (*Scheme 14*) in the liquid phase.

Reference	Conditions		Yield of <i>pC</i> (%), determination method
	Reagents	Atmosphere	
Neumann and Lissel ⁷⁶	H ₅ PMo ₁₀ V ₂₀ , tetraglyme	O ₂	>98, GLC
Stratakis and Stavroulakis ⁷⁷	MV ²⁺ /Na-Y	Ar	>98, GC-MS
Zhao <i>et al.</i> ⁷⁸	Pd nanoparticles (2 mol%)	H ₂ (2 bar)	82, GC
Barnes and Buckwalter ⁷⁹	1) NBS, BPO 2) KOH	air	80, isolated
Pines and Eschinazi ⁸⁰	Na, promotor	air	95, not given
Reggel <i>et al.</i> ⁸²	Li, EDA	air	98, isolated
Berti <i>et al.</i> ^{83,84}	Na, FeCl ₃ , EDA	N ₂	99, isolated
Domingo <i>et al.</i> ⁸⁵	I ₂ (0.5 eq), DDQ (0.5 eq)	air	82, isolated

3.2.2 α -Pinene to *p*-cymene

Besides limonene, α -pinene has been converted to *pC* (*Scheme 14*, pathway B) in the gas phase with several combinations of catalysts and reaction temperatures. These reactions are usually performed in a fixed bed flow reactor using H₂ as a carrier gas to avoid catalyst deactivation. α -Pinene is one of the terpenes that are contained in turpentine oil and tall oil fractions, resulting from the pulping and biorefining industries. Currently, these oils are usually used as an energy supply by burning.⁹⁰

Stanislaus and Yeddanapalli⁸⁶ have dehydrogenated α -pinene with pure chromia gel and three different chromium-doped alumina catalysts. A weakly acidic alumina catalyst containing 1 wt% Na and 6 wt% Cr was the most selective for *pC* production (*Table 5*). When the reaction was performed at 425 °C with a WHSV of 1 h⁻¹, the yield of *pC* was up to 53%, but only 68% of the starting material was converted into aromatics.

Roberge *et al.*⁸⁷ studied the conversion of α -pinene to *pC* in the optimal conditions which they had previously obtained for limonene⁷⁴. Six catalysts of varying acidities were chosen for the dehydrogenation in the gas phase. The results indicated that moderate acid sites

induced the isomerization and that the absence of acid sites were responsible for the hydrogenation and saturation of bicyclic terpenes. The best selectivity was obtained with a moderately acidic catalyst, which was Pd supported either on a silica or an alumina carrier (Table 5). The yields of *pC* were 66% and 67%, respectively, when the reaction was carried out at 300 °C with a WHSV of 6 h⁻¹. The carrier gas had a great impact on the catalyst deactivation: when H₂ was replaced with N₂, the yield of *pC* started decreasing after 1 h. However, the Pd/Al₂O₃ catalyst slowly deactivated even in the presence of H₂. This was probably caused by formation of coke on the acid sites, which was not detected on weaker acid sites of the silica carrier.

One of the tested non-acidic catalysts was Pd on charcoal. Roberge *et al.* found that it had lower selectivity towards aromatics (37% of *pC*) and yielded greater amounts of non-aromatic mono- and bicyclic terpenes instead. When Linstead *et al.*⁷¹ used Pt on charcoal as a catalyst in rather similar conditions at 300 °C, the yield of *pC* was up to 75% after 21 h (Table 5).

As with limonene, the dehydrogenation of α -pinene has been performed on zeolite catalysts. Bazhenov *et al.*⁸⁸ obtained a selectivity of 80% for *pC* when the catalyst was 50% decationized faujasite Y at 150 °C after 2 h (Table 5). The ratio of SiO₂ and Al₂O₃ was not specified. A similar method was patented by Stora Enso Oyj⁸⁹ (Table 5). Several zeolites were used as a catalyst and faujasite Y (SiO₂/Al₂O₃ ratio of 5.2 to 7.5) provided the highest yields of *pC* at 300 °C. N₂ was used as a carrier gas in these reactions. As there was no metal component present, no H₂ was needed for recovering the catalyst.

Golets *et al.*⁹⁰ have studied bimetallic heterogeneous catalysts supported on Al-SBA15. After several optimization reactions, they ended up at the same reaction conditions as Roberge *et al.* A H₂ atmosphere was found to be essential for the metal in the catalyst to maintain its active form. The best yield of *pC* (71%) was obtained with a Pd- and Zn-impregnated Al-SBA15 catalyst with a Pd/Zn ratio of 1:1 (Table 5). By increasing the Pd loading, less side products formed but the yield of *pC* decreased.

Table 5. Comparison of different catalytic systems used in pathway B (*Scheme 14*), showing additionally whether H₂ was produced in the reaction or needed as a carrier gas.

Reference	Dehydrogenation catalyst	Yield of <i>pC</i> (%), determination method	H ₂	
			Produced	Needed as a carrier gas
Stanislaus and Yeddanapalli ⁸⁶	Cr/Na/Al ₂ O ₃	53, GC	no	yes
Roberge <i>et al.</i> ⁸⁷	Pd/Al ₂ O ₃ or Pd/SiO ₂	67, GC	no	yes
Linstead <i>et al.</i> ⁷¹	Pt/C	75, isolated	yes	no
Bazhenov <i>et al.</i> ⁸⁸	Faujasite Y	80, isolated	yes	no
Stora Enso Oyj ⁸⁹	Faujasite Y	80–90, GC-MS	yes	no
Golets <i>et al.</i> ⁹⁰	Pd/Zn/Al-SBA15	71, GC	no	yes

3.2.3 Eucalyptol to *p*-cymene

Eucalyptol (1,8-cineole) is used less as a starting material for *pC* synthesis (*Scheme 14*, pathway C), but its potential for this purpose has gained attention in the past decade. It can be isolated from Eucalyptus oil by steam distillation.⁹³ Leita *et al.*^{91,92} have published several metal-doped γ -Al₂O₃ based catalysts which selectively give *pC* in moderate to good yields. By varying the transition metal component in the catalyst, the selectivity could be driven either towards limonene or *pC*. Transition metals such as Pd, Mo, Ru, Cr and Mn were shown to be selective for the production of *pC*. In addition, the undoped γ -Al₂O₃ catalyst provided selectivity towards *pC*.

The reactions were performed in a down flow tubular reactor system with argon as the carrier gas. Different temperature conditions were tested and the amount of O₂ in the carrier gas was varied. Up to 99.5% yields of *pC* (determined by GC-MS) were achieved when the reaction was performed for 3 h on Pd-doped γ -Al₂O₃ pellets at a fixed temperature of 250 °C with 14.6% of O₂ in the carrier gas. Side products forming during the reaction were mainly water and gases such as H₂ and CO₂.^{92,93}

3.2.4 Terpene mixtures to *p*-cymene

Buhl *et al.*⁹⁷ have used two different kinds of terpene mixtures as starting materials for the production of *p*C. Oulu 405 consisted mainly of 3-carene, α -phellandrene and limonene, while Acintene DP-738 contained limonene, terpinolene, terpinenes, pinenes, and cineoles among other terpenes. The tested catalysts were zeolites (Na-ZSM-5) doped with different combinations of Pd and Ce and Pd-doped silica supports. Zeolitic catalysts provided lower yields than silica-based ones (70% vs. 90% with Acintene DP-738). When H₂ was used as a carrier gas at 300 °C with a Pd/SiO₂ catalyst, Acintene DP-738 gave *p*C yield of 90% while a yield of 60% was obtained with Oulu 405. The method for the determination of the yield was not given.

Crude sulfate turpentine (CST) consists mainly of α - and β -pinenes. It was converted to *p*C on the same Pd/SiO₂ catalyst that was used for pure α -pinene by Roberge *et al.*⁸⁷ (Section 3.2.2) As the CST contained sulfur as a crucial impurity, it had to be washed with aqueous NaOCl solution to avoid catalyst poisoning. Even though the sulfur content was significantly decreased, the catalyst started deactivating immediately. The catalyst activity could be kept stable for 30 min (a 65% yield of *p*C, determined by GC) by adding zinc oxide to the system.

The advantage of zeolite catalysts is that they do not have to contain any metal component, which makes them less sensitive to catalyst poisoning than metal-impregnated silica and alumina catalysts. Hence, they provide the possibility of converting CST to *p*C without washing treatments. In the patent of Stora Enso Oyj⁸⁹, CST was used as a starting material with a faujasite Y catalyst. The conditions were the same as for pure α -pinene (Section 3.2.2). The yield of *p*C was not clearly discussed.

3.2.5 Oxidation of *p*-cymene to terephthalic acid

The second step on the monoterpene pathway is the oxidation of *p*C to TPA (*Scheme 14, pathway D*). An old synthetic process is to oxidize *p*C with chromic acid in the mixture of glacial acetic acid and concentrated sulfuric acid⁹⁸, but due to toxicity and carcinogenicity of hexavalent chromium compounds, this is not a practical approach on an industrial scale.

A more recent approach is a two-stage oxidation, which was reported and patented by Berti *et al.*^{83,84} In the first step, *pC* is refluxed in a mixture of water and nitric acid for 24 h to oxidize the isopropyl moiety. After extraction and the solvent removal, the resulting intermediate is used directly in the second step without purification. To complete the oxidation to TPA, the intermediate is refluxed in an aqueous solution of NaOH and KMnO₄ for 16 h. After filtration on a celite pad, the product is precipitated with sulfuric acid. A good yield of 85% can be obtained over two steps.

In the patent of Perstorp AB⁹⁴, *pC* is oxidized in two steps of which the first step is done in the gas phase and the second in the liquid phase, using very similar conditions to the AMOCO process. The first step is performed in three different temperatures, giving different product distributions. The higher the temperature, the greater is the proportion of TPA in the product mixture. A mixture of Mn(II) and Co(II) acetates is used as a catalyst with NaBr as a promotor in the presence of O₂. The reaction mixtures from the first step are further oxidized in acidic solvent with a metal salt and a promotor. The highest yield of TPA (97%) was achieved in acetic acid and water with the same Mn/Co/Br catalyst as in the first step.

A heterogeneous catalytic system with O₂ was recently developed by Neațu *et al.*⁹⁵ *pC* was oxidized with full conversion to yield 51% of TPA in the presence of a Mn-Fe mixed-oxide catalyst in an autoclave. *pTA* was obtained as a side product in 40% yield. The selectivity to for TPA was increased from 38% to 51% by raising the autoclave volume from 18 mL to 28 mL and splitting the amounts of *pC* and the catalyst into half. This was due to the amount of O₂ being less than the stoichiometric requirement in the former case. Increase of the reaction time did not affect the product distribution. This was probably due to the decreased contact between the reaction mixture and O₂, caused by both the main products being solid. The purification of TPA was not discussed.

Table 6. Reaction conditions of pathway D (*Scheme 14*).

Reference	Conditions			Reaction time	Yield of TPA (%), determination method
	Reagents	Solvent	Temperature		
Ospenson ⁹⁸	CrO ₃ , H ₂ SO ₄	H ₂ O, AcOH	100 °C	30 min	76, isolated
Berti <i>et al.</i> ^{83,84}	1) HNO ₃ 2) KMnO ₄ , NaOH	H ₂ O	reflux	1) 24 h 2) 16 h	85, isolated
Perstorp AB ⁹⁴	1) Mn/Co/Br 2) Mn/Co/Br	1) - 2) AcOH, H ₂ O	200 °C	1) 1 h 2) 2 h	97 wt%, isolated
Neațu <i>et al.</i> ⁹⁵	Mn/Fe/O, O ₂ (20 bar)	-	140 °C	24 h	51, GC

3.2.5 Limonene to terephthalic acid

Direct oxidations of any terpene to TPA were not reported until 2017. Yates *et al.*⁹⁶ used different kind of mixtures of Fe or Mn, Ti and sepiolite as a catalyst with *tert*-butyl hydroperoxide as an oxidant to convert limonene into mixtures of oxidized products. The best conversions were achieved with a Fe- and Ti-impregnated sepiolite catalyst prepared at 500°C (FeTiSep500). The reaction was activated either with conventional heating, or microwave or solar irradiation. For the production of TPA, microwave activation at 120 °C was shown to be the most effective.

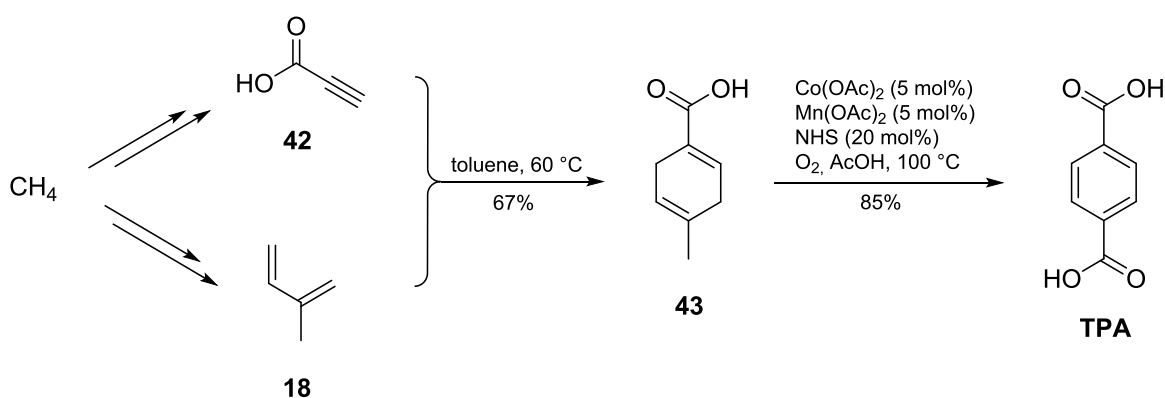
In these conditions, even the highest conversion of limonene was only 35%. The best yield of TPA was also very low (4%, determined by GC-MS) and the major products were actually limonene oxides and other terpenoids. The proportion of TPA increased as the reaction time increased. However, longer reaction times than 70 min were not used under microwave irradiation in order to avoid overoxidation.

The authors stated that the main goal of their study was the development of environmentally-friendly process conditions and catalysts of low toxicity. However, both the conversions and selectivities were very low, and the separation of TPA from the product mixture was not discussed in the paper.

3.3 Other bio-based sources

In addition to the approaches discussed above, there is a constant search for alternative options regarding bio-based TPA production. Recently, a procedure for synthesizing TPA from biogas methane was published.⁹⁹ Annually, $1.2 \cdot 10^{10}$ m³ of biogas is produced from wastewater, landfill or livestock in the United States.¹⁰⁰ While high amounts of methane is already produced by the U. S. chemical industry, biogas production is expected to increase in the following years.⁹⁹

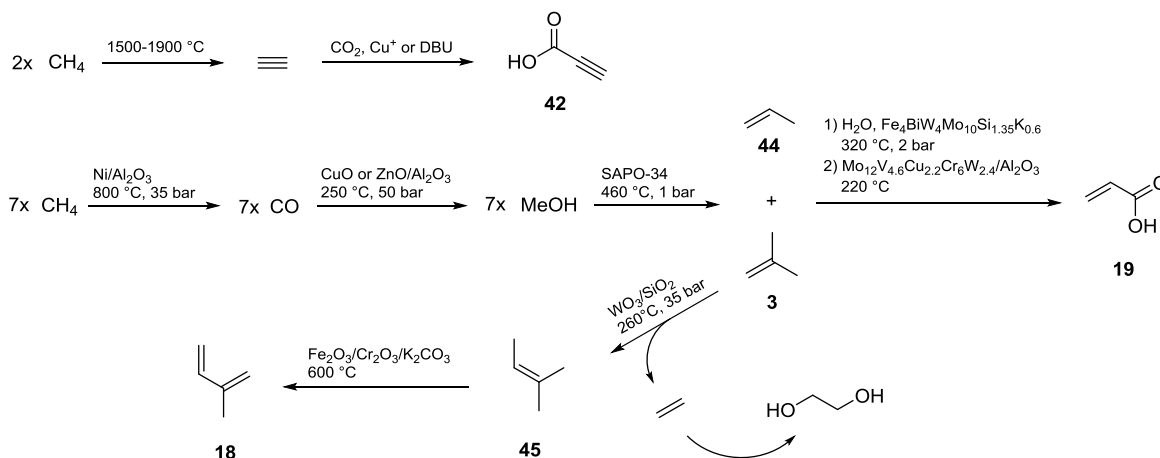
The DA cycloaddition was performed using propiolic acid **42** and isoprene **18** to yield 72% of *p*-adduct **43** and 24% of *m*-adduct when 5 equivalents of isoprene were used. **43** was then crystallized from the mixture in a 67% yield. The aromatization and oxidation was performed with the Ishii-modification¹⁰¹ of the AMOCO oxidation process, using *N*-hydroxysuccinimide (NHS) as the chain carrier in an O₂ atmosphere (*Scheme 15*). A similar reaction can be carried out with acrylic acid instead of propiolic acid (Section 3.1.2.2.3).



Scheme 15. Synthesis of TPA starting from methane.⁹⁹ Isolated yields.

All the three aforementioned starting materials can be synthesized from methane (*Scheme 16*). The syntheses are multi-step pathways requiring harsh conditions. The authors have discussed several options for each step in their article.⁹⁹ In the cross-metathesis of propylene

and isobutylene, ethylene is formed as a side product. It can be collected and converted to ethylene glycol for synthesis of PET.



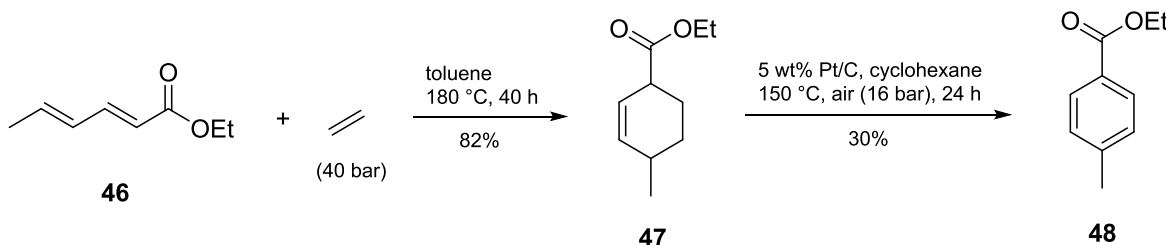
Scheme 16. Syntheses of propiolic acid **42**, acrylic acid **19** and isoprene **18** from methane.⁹⁹

Sorbic acid is another very promising natural source for it can be either extracted from the nonedible berries of *Sorbus aucubaria* or synthesized from bioethanol.¹⁰² Alternatively, glucose can be converted enzymatically to triacetic acid lactone for the preparation of sorbic acid.^{103,104} The current production of sorbic acid is 30 kt/y¹⁰² but the growing market demand has resulted in a fast growth of its production during the past years¹⁰⁵.

The DA approach utilizing sorbic acid and bio-ethylene was studied by Bérard *et al.* (Scheme 17).¹⁰² First, sorbic acid, sorbaldehyde and ethyl sorbate **46** were screened as starting materials for the cycloaddition with ethylene. The cycloadduct **47** was not obtained in the reaction with sorbic acid. The conversions were similar for sorbaldehyde and ethyl sorbate, but the selectivity towards **47** was much higher (27% compared to 90%, respectively) when ethyl sorbate was used. The reaction was performed using toluene as a solvent in a Parr reactor pressurized with ethylene. Using Lewis acids as catalysts failed to activate the reaction. The maximum conversion with nearly quantitative yield of **47** was achieved after 40 h with an ethylene pressure of 40 bar at 180 °C.

The second step was the dehydrogenation of **47**. This was carried out in cyclohexane on a Pt/C catalyst, with various temperature and pressure conditions under air. Even the highest conversion was just 80% with a selectivity of only 41% for ethyl *p*-toluate **48**. Hydrogen transfer was expected to occur between substrates, which caused the formation of aliphatic

4-methyl cyclohexanoate as a major side product.¹⁰² The purification of the product was done by column chromatography, giving a total isolated yield of only 25%.

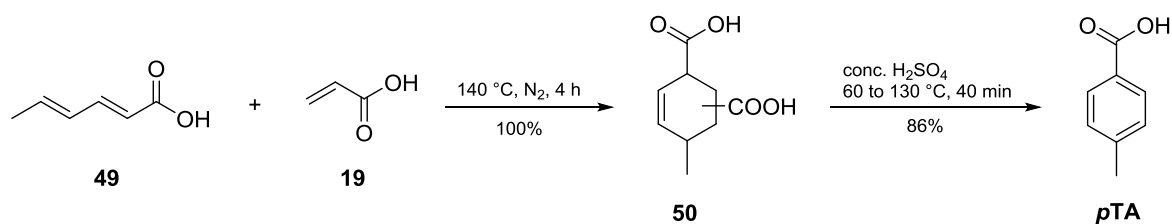


Scheme 17. Synthesis of ethyl *p*-toluate **48** from ethyl sorbate **46** and ethylene.¹⁰² Isolated yields.

Wang and Tong¹⁰⁶ were the first to use sulfuric acid as a dehydroaromatization agent. They performed the reaction with concentrated H₂SO₄ at 100 °C using a free carboxylic acid corresponding to **47** as a starting material. After 45 minutes, 91% of *p*TA was obtained (determined by ¹H NMR). The dehydroaromatization was suggested to occur via a sulfonic acid intermediate, which was formed in an ene reaction. Intramolecular elimination provided sulfur dioxide and a cyclohexadiene intermediate which underwent another ene reaction and elimination. The formation of sulfur dioxide was further evidence for the suggested mechanism.¹⁰⁶

Banella *et al.*¹⁰⁵ have published a milder synthetic route from sorbic acid **49** to *p*TA (Scheme 18). Instead of ethylene, they used 2 equivalents of acrylic acid **19** as a dienophile in the DA cycloaddition. A minimum temperature of 140 °C was necessary when sorbic acid was used in order to maintain it as a liquid. Without solvent, the full conversion of sorbic acid or its methyl ester to *o*- and *m*-diacids **50** (with the ratio of 6:4) was obtained under N₂ in 4 h. The excess of acrylic acid had no influence on the second step so purification of the intermediate **50** was not required.

The aromatization of **50** was performed by adding concentrated H₂SO₄ at 60 °C and then increasing the temperature first to 90 °C over 20 min and then to 130 °C over 5 min. The reaction was kept at 130 °C until no more gas was evolved. This selective decarboxylation of the diacid mixture gave a high yield (86%) of *p*TA.



Scheme 18. Synthesis of pTA from sorbic acid **49** and acrylic acid **19**.¹⁰⁵ Yields determined by ¹H NMR.

4. CONCLUSIONS

Even though no commercial bio-based process for the production of TPA has yet been launched to the author's best knowledge, several promising methods have been developed. Out of the different methods presented here, some selected processes and the companies or research groups that are developing them are listed in *Table 7*. Most of these processes have been performed only on the laboratory scale, but pilot facilities have already been constructed for the processes of Anellotech, Gevo and Virent.²

Table 7. Comparison of different methods for producing TPA from biosources.

Company or research group	Biosourced feedstock	Method	Number of steps	Intermediates
Anellotech Inc. ⁹	Biomass	Pyrolysis	4	<i>pX</i>
Gevo Inc. ^{17,19}	Sugars	Fermentation	5	Isobutanol, isobutylene, diisobutylene, <i>pX</i>
Genomatica Inc. ^{20,21}	Sugars	Fermentation	Multiple	Several, e.g. <i>pTA</i>
Virent ²⁵⁻²⁸	Biomass	Reforming	4	Oxygenates, <i>pX</i>
Honeywell UOP ⁴⁵ , Micromidas ⁴⁹	Sugars	DA reaction	4	HMF, DMF, <i>pX</i>
Toste ⁵⁰	Sugars, acrolein	DA reaction	7	HMF, DMF, cycloadduct, aromatic carboxylic acid, <i>pX</i>
BASF ⁶¹	Ethylene	DA reaction	4	Hexene, cyclohexene, <i>pX</i>
Frost ³⁹ , Tong ⁴³	Isoprene, acrolein	DA reaction	3	Cycloadduct, <i>pTALD</i> or <i>pTA</i>
Kraus ³⁸	Sugars	Fermentation, DA reaction	3	Malic acid, methyl coumalate [#]
Draths Corporation ³³	Sugars	Fermentation, DA reaction	4	<i>ccMA</i> , <i>ttMA</i> , cycloadduct [#]
BP Corporation ⁵¹	Sugars	DA reaction	3	HMF, FDCA
Kasuya ⁵⁶	Sugars	DA reaction	7	Furfural, maleic acid, maleic anhydride, cycloadduct, phthalate
SABIC Innovative Plastics ^{83,84}	Limonene	Dehydrogenation, oxidation	3	<i>pC</i>
Partially funded by the Coca-Cola Company ⁹⁹	Methane	DA reaction	Multiple	Propiolic acid, isoprene, cycloadduct
IFP Energies nouvelles ¹⁰²	Sorbic acid	DA reaction	4	Cycloadduct, <i>p</i> -toluate

[#]The product is DMT or DET

The pyrolysis and reforming processes of Anellotech⁹ and Virent²⁵⁻²⁸ are particularly interesting because lignocellulosic biomass can be used directly as a starting material without first converting it into monomers. Lignocellulose is the most attractive option for the bio-based starting material, as it is both inexpensive, abundant and inedible. In both of the aforementioned processes, the BTX stream is produced from biomass in a single step, making them similar to the current commercial process of producing *pX* from naphtha. The pretreatment of biomass is also simple, as the feedstock requires only grinding and drying. However, the disadvantage is the low selectivity towards *pX* which needs to be improved, for example, through the development of new catalysts.

In the most of the other bio-based processes, sugar-containing feedstock has to be converted to monosaccharides which are subsequently converted to compounds such as isobutanol, HMF and isoprene. The problem in the usage of lignocellulose is mainly the high cost of the pretreatment processes required to separate cellulose, hemicellulose and lignin from each other. Monosaccharides can be readily obtained from other feedstocks such as starch and sucrose, but they also have value in food production. Moreover, converting fructose to HMF is a high-cost process even though high yields of *pX* have been obtained from the cycloaddition routes.^{45,49,50} Considering this aspect, the isobutanol route of Gevo is a preferable option as it does not proceed via HMF intermediate. However, the multiple reaction steps significantly decrease the *pX* yield, the final yield from isobutanol being only about 20% where up to 90% yields can be achieved via cycloaddition routes from HMF.

Besides the sugar-containing feedstocks, other starting materials for TPA synthesis have been considered. Furfural can be produced from agricultural waste materials, but thus far it has been successfully used as a starting material for TPA in only one synthesis, which requires homogeneous catalysts and provides low yield.⁵⁶ One option is to use bioethanol-derived ethylene as the sole feedstock, but multiple steps result in low selectivity towards *pX*.⁶¹

Notable advantages of the limonene-based process are the short route and the particularly high yield and selectivity, providing up to 84% of TPA over three steps.⁸⁴ When suitable heterogeneous catalysts are used for the dehydrogenation of limonene to *pC*, there is also the possibility to collect hydrogen, which is formed as a side-product. Unfortunately, limonene is a value-added chemical itself, having uses in cosmetic products. Moreover, it has restricted

availability since it is produced from the citrus peel waste. The availability is also the limitation of sorbic acid-based syntheses.

Other monoterpenes and especially the mixtures of them, such as turpentine oil and tall oil, provide an option for limonene. However, the sulfur impurities contained in these oils cause the catalysts to deactivate, so further catalyst optimization is required. Using methane as the sole feedstock for TPA production⁹⁹ is an interesting but not very practical option, as harsh reaction conditions are needed, not to mention that methane already has several other applications currently in the chemical industry.

To conclude, the bio-based processes for TPA still need improving in order to reach the low cost of the current fossil-fuel-based process. In the future, the main goals will be the utilization of unpretreated lignocellulose as the feedstock and the development of inexpensive but selective heterogeneous catalysts for the processes discussed here. The desirable catalysts would also be tolerant to ash components and other impurities contained in lignocellulosic biomass.

5. EXPERIMENTAL PART: FUNCTIONALIZATION OF BENZALDEHYDE VIA N-HETEROCYCLIC CARBENE-CATALYZED REACTIVITY UMPOLUNG

5.1 Introduction

The focus of the experimental part is to study whether renewable benzaldehyde¹⁰⁷ could be viable starting material for the synthesis of TPA and other fine chemicals when the functionalization is attempted via umpolung reactions utilizing N-heterocyclic carbenes (NHCs).

NHCs are heterocyclic compounds, containing a divalent carbon and at least one nitrogen atom in the ring structure. In addition, NHCs have some specific structural features. The nitrogen atoms stabilize the singlet carbene by being both π -electron-donating and σ -electron-withdrawing. Further stabilization results from the bulky substituents on the nitrogen atoms and in many cases also from the aromatic backbone of the ring structure.¹⁰⁸ Some examples of NHCs derived from different heterocycles are shown in *Figure 4*.

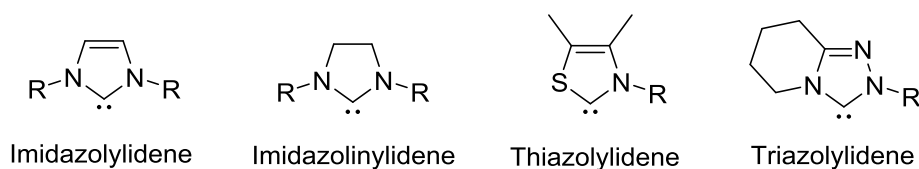
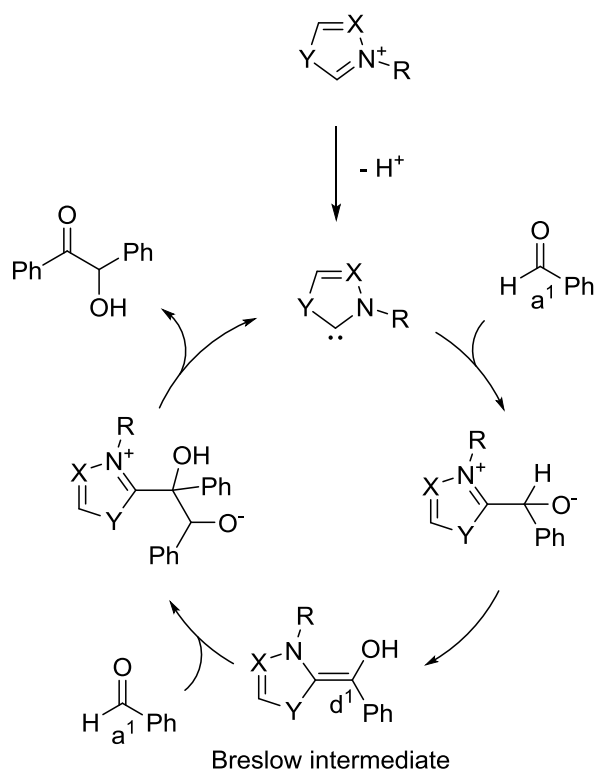


Figure 4. The structures of four different kind of NHCs (R = e.g. adamantyl, mesityl or 2,6-isopropylphenyl).

The major applications of NHCs can be divided in three categories: they can be coordinated either to transition metals or *p*-block elements, or used as organocatalysts.¹⁰⁸ While the first category involves the majority of NHC applications, our focus is on the NHC-mediated organocatalysis.

The reactivity umpolung or polarity inversion is a practical tool for making connections that would otherwise be impossible, for example, a coupling between two electrophilic carbons. Originally, Dieter Seebach has introduced the methods of reactivity umpolung.¹⁰⁹ This can be done by inverting the polarity of a certain functional group typically from an electron acceptor (a) to an electron donor (d). A common example of an umpolung reaction is the

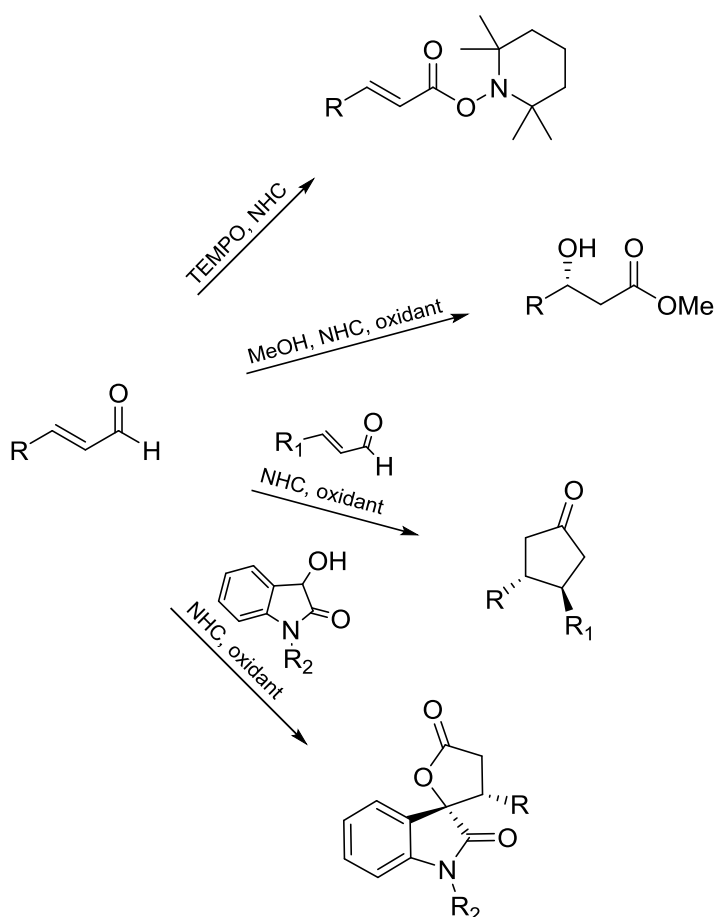
benzoin condensation where the electrophilic carbonyl carbon (a^1) of one benzaldehyde molecule is turned into a nucleophile (d^1), so that a 1,1-connection between two electron acceptors can be made. Traditionally, the reaction is catalyzed by a cyanide anion¹¹⁰ but a more modern method is to use NHCs as the catalysts (*Scheme 19*) as was originally proposed by Breslow.^{111,112} The key intermediate in the catalytic cycle is the electron-rich enaminol called Breslow intermediate.



Scheme 19. The mechanism of NHC-catalyzed benzoin condensation with marked electron acceptors (a^1) and donors (d^1).^{111,112}

Despite their importance in many catalytic transformations, the formation of Breslow intermediates was not confirmed by structural analysis until 2012, when Berkessel *et al.*¹¹³ used imidazolylidenes and imidazolynylidenes together with different aryl aldehydes to generate various 2,2-diaminoenol-type Breslow intermediates which were then characterized by NMR spectroscopy. In addition, they confirmed that the intermediates are able to provide benzoin condensation. A year later, the same group published the crystalline structures of these Breslow intermediates.¹¹⁴

Even though the two-electron oxidations of the NHC-derived intermediates, especially homoenolate equivalents, have been rather well-studied during the past years, the single-electron pathway has gained significantly less attention. However, the single-electron transfer occurs in some biochemical transformations in the nature. These reactions involve a thiazolium NHC precursor, vitamin B₁, which is capable of forming Breslow-type intermediate. This has inspired chemists to develop biomimetic NHC-mediated radical reactions, and a few approaches to functionalize NHC-derived homoenolate equivalents via single-electron transfer have been published during the past decade (*Scheme 20*).¹¹⁵ Besides the novel reactivity, these strategies are also highly enantioselective.



Scheme 20. Different approaches using α,β -unsaturated aldehyde as the starting material.^{116–120}

In this work, our research hypothesis was that the functionalization of α,β -unsaturated aldehydes could be extended to the functionalization to aryl aldehydes via the single electron

pathway. By making the electron-rich Breslow intermediate, the *ortho,para*-deactivating benzaldehyde could be turned into *ortho, para*-guiding (Figure 5).

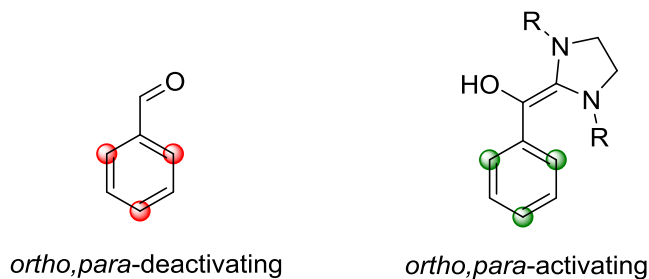
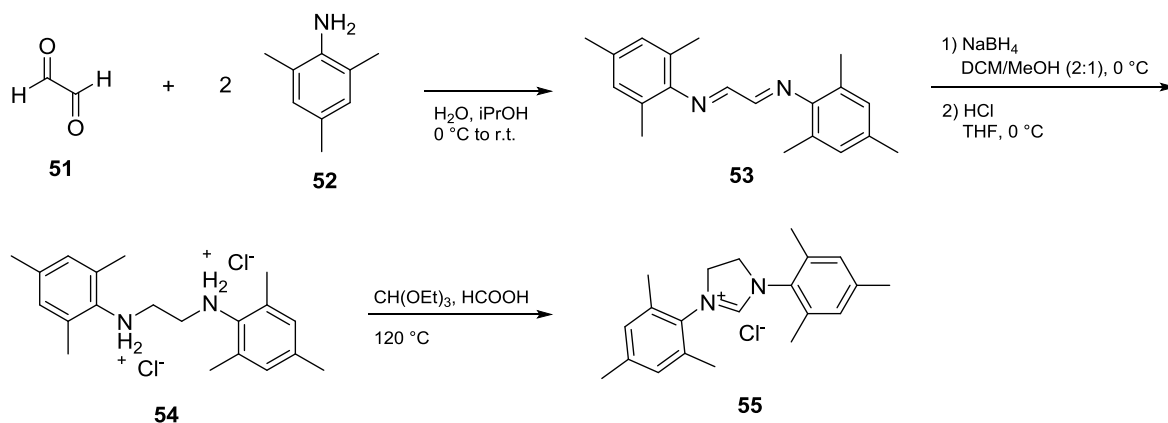


Figure 5. Difference in the activated positions of benzaldehyde and the Breslow intermediate of benzaldehyde.

5.2 Results and discussion

5.2.1 Synthesis of N-heterocyclic carbenes

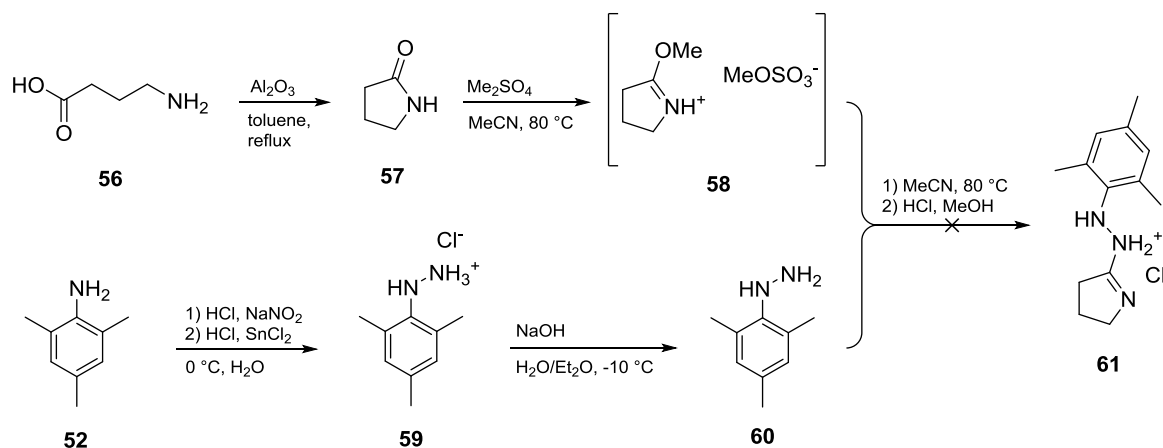
In the beginning of this work, two NHC-precursors were synthesized according to slightly modified literature procedures. The synthesis of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride **55** is shown in *Scheme 21*.¹²¹ The diamine salt **54** was prepared from glyoxal **51** and 2,4,6-trimethylaniline **52** in three steps by reductive amination. The starting materials were stirred in a mixture of water and isopropanol to obtain the bright yellow precipitate **53**. The reduction and salt formation of the diimine **53** was attempted in one pot with sodium borohydride (4 equiv.) and hydrochloric acid in THF, following the patented procedure of Grubbs *et al.*¹²¹ However, it was obtained that the reaction time of 10 min was not long enough to reduce **53** and hence the yield of **54** was very poor (8%). Besides, more sodium borohydride was needed to get a better conversion of the diimine to the diamine. When **53** was stirred in a 2:1 DCM/MeOH solution with 7 equiv. of sodium borohydride for 48 h, purified and treated with hydrochloric acid in THF, **54** was obtained in a 43% yield. The imidazoline ring was successfully closed with triethyl orthoformate in a formic acid catalyzed reaction.¹²¹



Scheme 21. Synthesis of imidazoline-based pre-NHC **55**.¹²¹

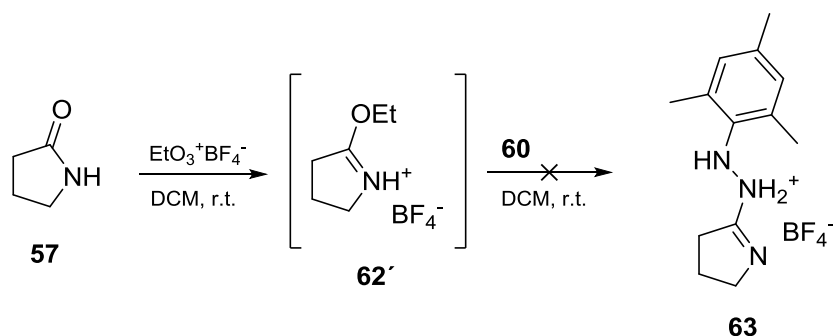
The first attempt to synthesize triazole-based pre-NHC **64** was started by synthesizing pyrrolidin-2-one **57** and 2,4,6-trimethylphenylhydrazine hydrochloride **59** (Scheme 22) according to literature procedures^{122–124}. To get the latter compound, 2,4,6-trimethylaniline **52** was diazotized with sodium nitrite in hydrochloric acid and the resulting diazonium salt was reduced to hydrazine salt **59** with stannous chloride.¹²³ To obtain the free hydrazine **60**, **59** was stirred in a cold solution of sodium hydroxide.¹²⁴ However, the formation of **60** could not be confirmed with ¹H NMR spectroscopy, because it decomposed upon making the NMR sample.

Intramolecular cyclization of γ -aminobutyric acid **56** was carried out on aluminium oxide in refluxing toluene to get pyrrolidin-2-one **57**.¹²² The enol tautomer of **57** was methylated with dimethyl sulfate and the reaction mixture was directly added with free hydrazine **60**.¹²⁵ However, **60** turned out to be extremely labile and seemed to decompose immediately upon exposure to air when adding it to the reaction flask. The product **61** was not obtained from the reaction.



Scheme 22. The first attempt to synthesize **61**.^{122–125}

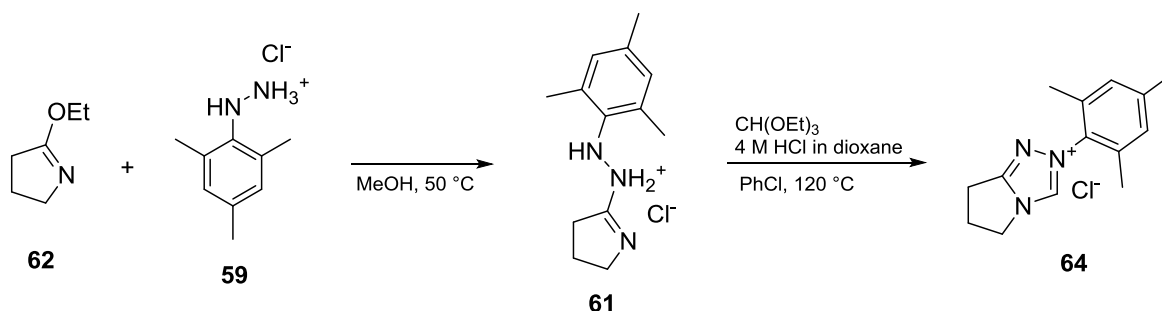
For the second trial to synthesize **63**, **57** and **60** were prepared in the same way as in Scheme 22. The enol tautomer of **57** was then ethylated with triethyloxonium tetrafluoroborate in dichloromethane (Scheme 23). Hydrazine **60** was dissolved in dichloromethane under argon atmosphere to prevent it from decomposing. The reaction mixture containing **62** was directly added with the solution of **60**.¹²⁴ A precipitate formed during the reaction but ¹H NMR spectroscopy revealed that it was not the desired product **63**.



Scheme 23. The second attempt to synthesize **63**.¹²⁴

The problems in the first two synthesis routes were assumed to be caused by the lability of free hydrazine **60**, so in the third pathway, the salt **59** was used instead of **60**.¹²⁶ Pyrroline derivative **62'** was synthesized (Scheme 23) and isolated as a neutral compound **62**. The compounds **62** and **59** were stirred in methanol at 50 °C for an hour, after which the solvent was evaporated to obtain **61** as a white solid (Scheme 24). However, the crude product still

contained **59**, so it was purified by dissolving in acetonitrile to which **59** is insoluble. The triazole ring was finally closed with triethyl orthoformate in an acid catalyzed reaction.¹²⁶ The purification of **64** was carried out by centrifuging and decanting instead of filtration, as **64** seemed to be very hygroscopic and did not remain a solid during filtration.



Scheme 24. The synthesis of triazole-based pre-NHC **64**.¹²⁶

5.2.2 Functionalization of benzaldehyde

Before functionalizing the aryl ring, we performed the benzoin condensation with benzaldehyde and pre-NHC **65** or **66** (Figure 6). The deprotonation of imidazole-based NHC-precursors is usually done with potassium *tert*-butoxide in THF^{127,128}, so the reaction was carried out in these conditions. Benzoin was detected both with **66** and **65**, but in the latter case only when **65** was used in a stoichiometric amount.

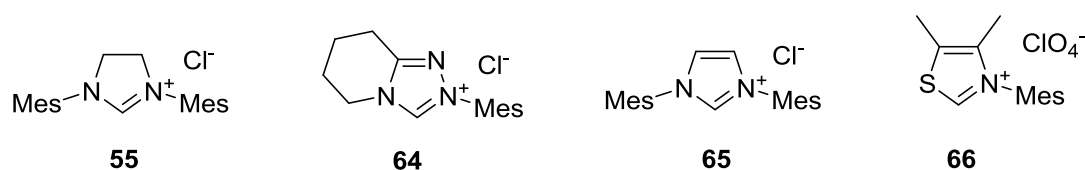


Figure 6. Structures of all four NHC-precursors used in this work. Compounds **65** and **66** were synthesized in our lab prior to this work.

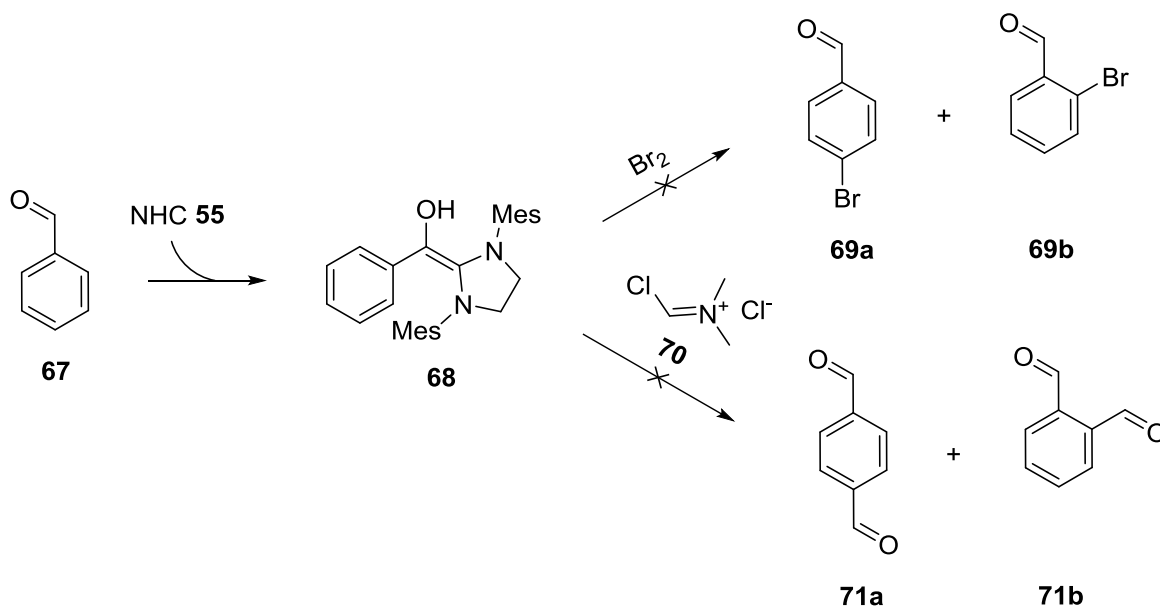
5.2.2.1 Via electrophilic aromatic substitution

Our first target was to induce reactivity on the aryl ring via electrophilic aromatic substitution (Scheme 25). Bromination was chosen as a model reaction because of both its

simplicity and the high usability of aryl bromides as starting materials in organic synthesis. Naresh *et al.* have recently published a mild method to brominate a wide variety of aromatics using ammonium bromide and potassium peroxymonosulfate.¹²⁹ We carried out our reactions at 60 °C. The base and the solvent were potassium *tert*-butoxide and THF, respectively, as in the benzoin condensation. Unfortunately, potassium peroxymonosulfate oxidized benzaldehyde **67** so that the only detected product was benzoic acid, regardless of the NHC used.

Our next approach was to use molecular bromine as the brominating reagent. The reactions were carried out with pre-NHC **55**, **64**, **65** or **66** at room temperature, either in THF or chloroform. Triethyl amine was used as a base with **64**. With the first three NHC-precursors, the only identifiable product was again benzoic acid. In addition, unidentified side products formed in all the reactions. However, with the triazole-based compound **64**, the NHC-benzaldehyde adduct seemed to form based on ¹H NMR spectroscopic analysis, but it did not undergo deprotonation to form the Breslow intermediate and hence no *o,p*-brominated aryl aldehydes **69** (*Scheme 25*) were detected.

Another two-electron approach that was attempted was the Vilsmeier–Haack reaction¹³⁰ to get the products **71** (*Scheme 25*). The reaction was carried out under argon in a flame-dried flask. Benzaldehyde **67**, stoichiometric amount of **55**, potassium *tert*-butoxide and dichloromethane were stirred overnight at room temperature prior to the addition of the Vilsmeier reagent **70**. After stirring the mixture overnight, the only product was benzoic acid. No further experiments were performed with the Vilsmeier reagent.



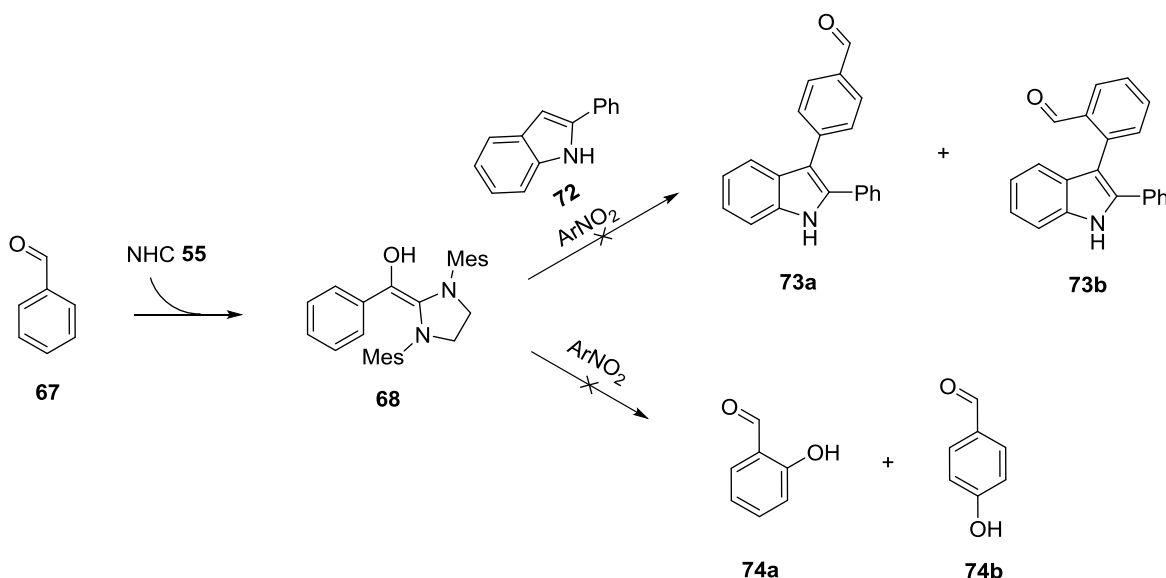
Scheme 25. Attempts to functionalize benzaldehyde **67** via two-electron pathway. The Breslow intermediate of pre-NHC **55** is used as an example.

5.2.2.2 Via single-electron transfer

We started to study the single-electron pathway by attempting a radical coupling between the Breslow intermediate **68** and 2-phenylindole **72** (Scheme 26). The reaction conditions were adopted from Chen *et al.*, using anhydrous toluene as a solvent under argon atmosphere.¹²⁰ All the reactions were done with stoichiometric amounts of pre-NHC **55**, potassium *tert*-butoxide and benzaldehyde **67**. The single-electron oxidant was either nitrobenzene or *p*-nitro-pyridine *N*-oxide (10 mol%). With nitrobenzene, we obtained benzoin as the only product whereas *p*-nitro-pyridine *N*-oxide gave no reaction. However, in all experiments, NHC-derived compound was detected in NMR spectra. Thus, we suspected that the NHC itself could have oxidized and hence we could not get the desired products **73** from benzaldehyde **67**.

Next, we tried hydroxylation in toluene¹¹⁸ under argon atmosphere using anhydrous conditions to get hydroxylated aryl aldehydes **74** (Scheme 26). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base and *p*-nitro-pyridine *N*-oxide as the single-electron oxidant¹¹⁷ in every reaction. The oxidations were performed with benzaldehyde **67**, *o*-anisaldehyde, *m*-anisaldehyde or 1-naphthaldehyde and NHC-precursor **55**, **64** or **65**. Regardless of the starting material, no reaction occurred when **65** was used as

the pre-NHC. All the other experiments produced the corresponding carboxylic acid from the aldehyde. In order to rule out the possibility that the oxidant itself oxidized the aldehyde, control experiments were carried without any pre-NHC or base. No carboxylic acids were obtained.



Scheme 26. Attempts to functionalize benzaldehyde **67** via single-electron transfer. The Breslow intermediate of pre-NHC **55** is used as an example.

5.3 Conclusions

In this work, two NHC-precursors were successfully synthesized, isolated and characterized. Their syntheses were nontrivial and demanded many efforts to find out correct reaction conditions despite the existing literature procedures. It turned out that we needed to, for instance, add purification steps to make their syntheses more viable. Several oxidative benzaldehyde umpolung reactions were attempted via both two-electron and single-electron pathways, but unfortunately those did not result in the desired products. We suspected that this was caused by the instability of the NHCs under our reaction conditions, as in many cases the NMR spectra of the crude product did not show any signals of the NHCs, but some unidentified compound clearly resulting from the NHC. Solely with triazole-based NHC **64**, the formation of NHC-benzaldehyde adduct could be obtained but at least in our conditions, it was not reactive in any of the conducted experiments. The brominations should also have

been tried out under inert atmosphere, to see whether oxygen disturbed the formation of the Breslow intermediate and thus the substitution reaction.

In retrospective, we can also conclude that we should have carried out more extensive base and solvent screening in the early state of the study. The bases that were used in the later experiments, triethyl amine and DBU, seemed to be more effective in deprotonating the NHC-precursors. In order to get better results with potassium *tert*-butoxide, it should probably have been sublimed immediately prior to use.

If this project were to continue, such conditions should be found that benzaldehyde would not oxidize to benzoic acid. Unfortunately, in this project the synthesis of the NHC-precursor **64** consumed a lot of time, which limited the screening of triazole-catalyzed reactions. More research should be made with triazole-based NHCs as they have shown the best results in the single-electron transfer reactions that have been published so far.

5.4 Methods

5.4.1 General methods

All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise mentioned. Diethyl ether and chlorobenzene were dried over 4 Å molecular sieves. Dry methanol was taken from The Vacuum Atmospheres Solvent purification system and used immediately. Water content was measured with Mettler-Toledo DL32 Karl Fischer Coulometer. The reactions were routinely monitored with TLC using Silica gel on TLC Al foils with fluorescence indicator 254 nm by Sigma-Aldrich. The flash chromatographic purifications were performed with Merck Kieselgel 60 (0.040–0.063 mm, 230–400 mesh). The products were dried under reduced pressure with a rotary evaporator or an oil pump.

NMR spectra were recorded on a Varian Mercury 300 MHz (299.95 MHz) NMR spectrometer. ¹³C NMR spectrum was recorded only for compound **61** which has not been previously characterized in the literature. In ¹H NMR, CDCl₃ and DMSO-*d*₆ were used as deuterated solvents with tetramethylsilane (0.00 ppm) and DMSO-*d*₆ (2.50 ppm) as internal

standards, respectively. In ^{13}C NMR, $\text{DMSO-}d_6$ (39.52 ppm) was used as an internal standard. Chemical shifts (δ) are reported in ppm and scalar coupling constants (J) in hertz.

5.4.2 Experimental

1,3-bis(2,4,6-trimethylphenyl)-1,2-ethanediamine dihydrochloride (54). Glyoxal (7.8 mmol, 0.90 ml, 40 wt% in H_2O) was added to a flask with water (20 ml) and isopropanol (10 ml). The mixture was cooled to $0\text{ }^\circ\text{C}$ in an icebath and added with 2,4,6-trimethylaniline (17 mmol, 2.42 ml). The reaction mixture was stirred at room temperature for 24 h. The yellow precipitate was filtered, washed with water and dried in vacuo to yield *N,N'*-bis(2,4,6-trimethylphenyl)ethanediimine **53**.

Diimine was then dissolved in 30 ml DCM/MeOH (2:1) mixture and cooled to $0\text{ }^\circ\text{C}$. Sodium borohydride (55 mmol, 2.09 g) was added and the mixture was stirred at room temperature for 48 h. The solution was washed with sat. aq. NaHCO_3 and the water phase was extracted with DCM (2×10 ml). The combined organics were dried over MgSO_4 and concentrated in vacuo. The crude product was purified with flash chromatography (5:1 hex/EtOAc) to obtain *N,N'*-bis(2,4,6-trimethylphenyl)-1,2-ethanediamine.

The purified diamine was dissolved in THF (15 ml) and cooled to $0\text{ }^\circ\text{C}$. After addition of concentrated HCl (1.28 ml) the mixture was stirred for 20 min followed by dropwise addition of 6 M HCl (36 ml) at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred for further 1.5 h while letting the mixture warm up to room temperature. The resulting white precipitate was filtered, washed with water (40 ml) and 5% acetone (v/v) in diethyl ether (30 ml) and dried in vacuo to obtain *N,N'*-bis(2,4,6-trimethylphenyl)-1,2-ethanediamine dihydrochloride **54** (1.23 g, 43%). The NMR spectroscopic data is in agreement with the literature values.¹³¹

^1H NMR ($\text{DMSO-}d_6$, 300 MHz) δ : 9.13 (bs, 4H), 6.96 (s, 4H), 3.59 (s, 4H), 2.42 (s, 12H), 2.23 (s, 6H).

1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (55). **54** (3.3 mmol, 1.23 g), triethyl orthoformate (23 mmol, 4.0 ml) and formic acid (1 mol%, 1.27 μl) were added to a flask and stirred at $120\text{ }^\circ\text{C}$ for 5 h. After cooling to room temperature, hexane (25 ml) was added and the suspension was stirred for 1 h. The white precipitate was filtered, washed with

hexane and dried in vacuo. The crude product was purified with flash chromatography (10:1 DCM/MeOH) to obtain 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride **55** (0.848 g, 75%). The NMR spectroscopic data is in agreement with the literature values.¹³²

¹H NMR (CDCl₃, 300 MHz) δ : 9.36 (s, 1H), 6.94 (s, 4H), 4.58 (s, 4H), 2.39 (s, 12H), 2.28 (s, 6H).

Pyrrolidin-2-one (57). γ -Aminobutyric acid (21.4 mmol, 2.21 g) and aluminium oxide (70.4 mmol, 7.18 g) were refluxed in toluene (40 ml) for 5 h. Water was collected with Dean-Stark apparatus. The mixture was cooled to room temperature, filtered and washed with DCM/MeOH (9:1) mixture. The liquid was concentrated and dried in vacuo to yield pyrrolidin-2-one **57** (1.71 g, 94%). The NMR spectroscopic data is in agreement with the literature values.¹³³

¹H NMR (CDCl₃, 300 MHz) δ : 6.46 (bs, 1H), 3.41 (t, $J = 6.7$ MHz, 2H), 2.34–2.26 (m, 2H), 2.20–2.07 (m, 2H).

5-Ethoxy-3,4-dihydro-2H-pyrrole (62). **57** (30.0 mmol, 2.28 ml) and triethyloxonium tetrafluoroborate solution (30 ml, 1 M in DCM) were added to a flame-dried Schlenk flask under argon. The reaction mixture was stirred at room temperature for 72 h, diluted with diethyl ether (20 ml) and cooled to 0 °C in an ice bath. Cold sat. NaHCO₃ solution (50 ml) was added slowly. The organic phase was separated, washed with cold sat. NaHCO₃ (50 ml), dried over MgSO₄ and concentrated in vacuo to obtain 5-ethoxy-3,4-dihydro-2H-pyrrole **62** as a colorless liquid (1.50 g, 44%). The NMR spectroscopic data is in agreement with the literature values.¹³⁴

¹H NMR (CDCl₃, 300 MHz) δ : 4.19 (q, $J = 7.1$ MHz, 2H), 3.66 (m, 2H), 2.44 (m, 2H), 2.00 (m, 2H), 1.31 (t, $J = 7.1$ MHz, 3H).

2,4,6-Trimethylphenylhydrazine hydrochloride (59). 2,4,6-trimethylaniline (13.7 mmol, 1.92 ml) was added to a flask with water (3 ml) and concentrated (12.1 M) HCl (3.5 ml). The resulting suspension was cooled in an ice bath while stirring vigorously and a solution of sodium nitrite (15.1 mmol, 1.04 g) in water (2 ml) was added dropwise to maintain the

temperature at 0 °C. After addition, the stirring was continued for 30 min. A solution of stannous dichloride hydrate (34.2 mmol, 7.72 g) in 6 M HCl (11 ml) was added over 1.5 h while keeping the temperature below 5 °C. The brownish slurry was let to stand overnight at room temperature and after that stirred for 23 h. The slurry was cooled in an ice-water bath for 1 h, filtered and washed with brine (5 ml) and diethyl ether (2 × 15 ml). The resulting salt complex was stirred in water (10 ml) and 10 M NaOH (10 ml) was added. The temperature was maintained below 15 °C. After addition, the solution was extracted with diethyl ether (2 × 15 ml). The combined organics were washed with water (15 ml), dried over MgSO₄ and diluted to 40 ml with diethyl ether. 4.8 M HCl in 1,4-dioxane (20 ml) was added to precipitate out the crude hydrazine salt which was then filtered and washed with diethyl ether. The crude product was recrystallized from ethanol to obtain 2,4,6-trimethylphenylhydrazine hydrochloride **59** (0.72 mg, 28%) as pale yellow crystals. The NMR spectroscopic data is in agreement with the literature values.¹²³

¹H NMR (DMSO-*d*₆, 300 MHz) δ: 9.69 (bs, 3H), 6.88 (s, 2H), 6.59 (bs, 1H), 2.34 (s, 6H), 2.21 (s, 3H).

5-(2,4,6-Trimethylphenylhydrazino)-3,4-dihydro-2H-pyrrole hydrochloride (61). **62** (13.2 mmol, 1.50 g) was added to a flame-dried Schlenk flask under argon with dry methanol (50 ml). **59** (13.2 mmol, 2.47 g) was added and the resulting yellow solution was stirred at 50 °C for 1 h. During this time a color change to dark red occurred. Solvent was evaporated and the resulting off-white precipitate was washed with dry diethyl ether and dried in vacuo. The dry precipitate was dissolved in acetonitrile and undissolved **59** was filtered out. The filtrate was concentrated in vacuo to get 5-(2,4,6-trimethylphenylhydrazino)-3,4-dihydro-2H-pyrrole hydrochloride **61** (0.65 g, 19%) as a white solid.

¹H NMR (DMSO-*d*₆, 300 MHz) δ: 10.97 (bs, 1H), 10.06 (bs, 1H), 7.15 (s, 1H), 6.85 (s, 2H), 3.63 (t, *J* = 7.0 MHz, 2H), 2.83 (t, *J* = 7.9 MHz, 2H), 2.24–2.10 (m, 2H), 2.19 (s, 9H).

¹³C NMR (DMSO-*d*₆, 75 MHz) δ: 167.70, 138.61, 133.60, 130.89, 129.31, 46.85, 28.39, 20.82, 20.24, 17.86.

2-(2,4,6-Trimethylphenyl)-6,7-dihydro-5H-pyrrolo[1,2,4]triazol-2-ium chloride (64). **61** (2.6 mmol, 0.65 g), dry chlorobenzene (2.6 ml), triethyl orthoformate (25.6 mmol, 4.3

ml) and anhydrous HCl (0.64 ml, 4 M in 1,4-dioxane) were added to a flame-dried Schlenk flask under argon. The resulting suspension was stirred at 120 °C for 1 h, cooled to room temperature and concentrated in vacuo. The red residue was azeotroped twice with toluene and added with diethyl ether to get the crude product as a light brown solid. The mixture was centrifuged and washed with diethyl ether several times. Ether was decanted out and the solid was dried in vacuo at 80 °C to give 2-(2,4,6-trimethylphenyl)-6,7-dihydro-5*H*-pyrrolo[1,2,4]triazol-2-ium chloride **64** (0.25 g, 37%). The NMR spectroscopic data is in agreement with the literature values.¹²⁴

¹H NMR (CDCl₃, 300 MHz) δ: 11.48 (s, 1H), 7.00 (s, 2H), 4.91 (t, *J* = 7.3 MHz, 2H), 3.26 (t, *J* = 7.7 MHz, 2H), 2.91 (quintet, *J* = 7.6 MHz, 2H), 2.36 (s, 3H), 2.11 (s, 6H).

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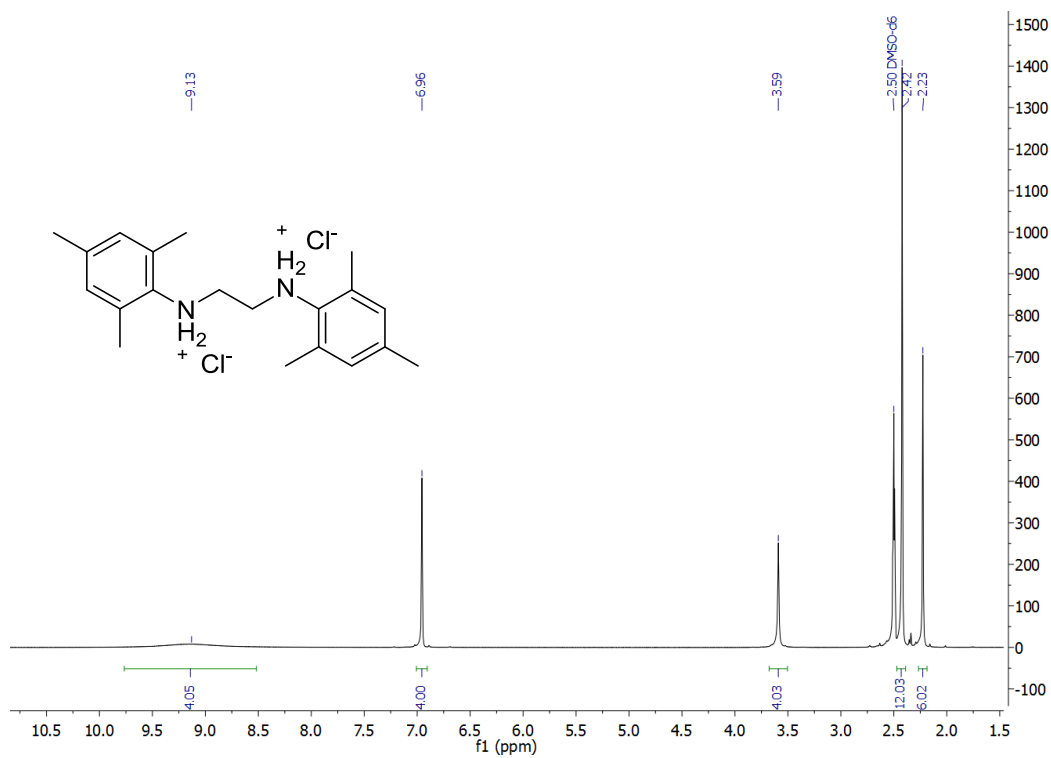
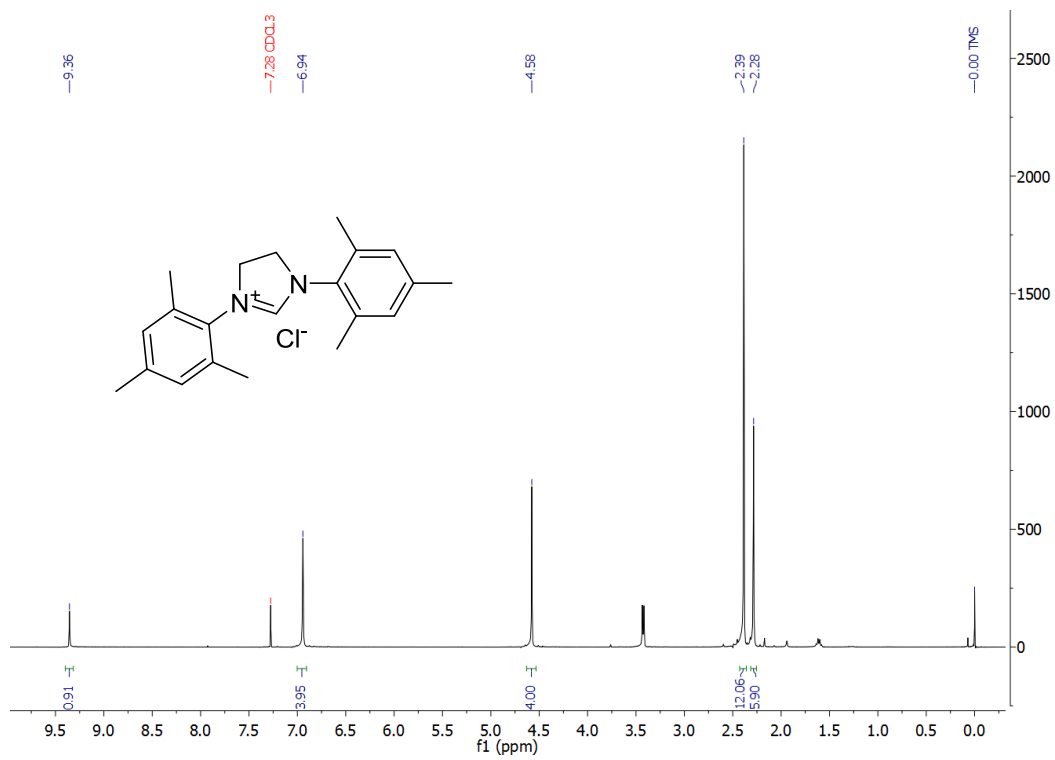
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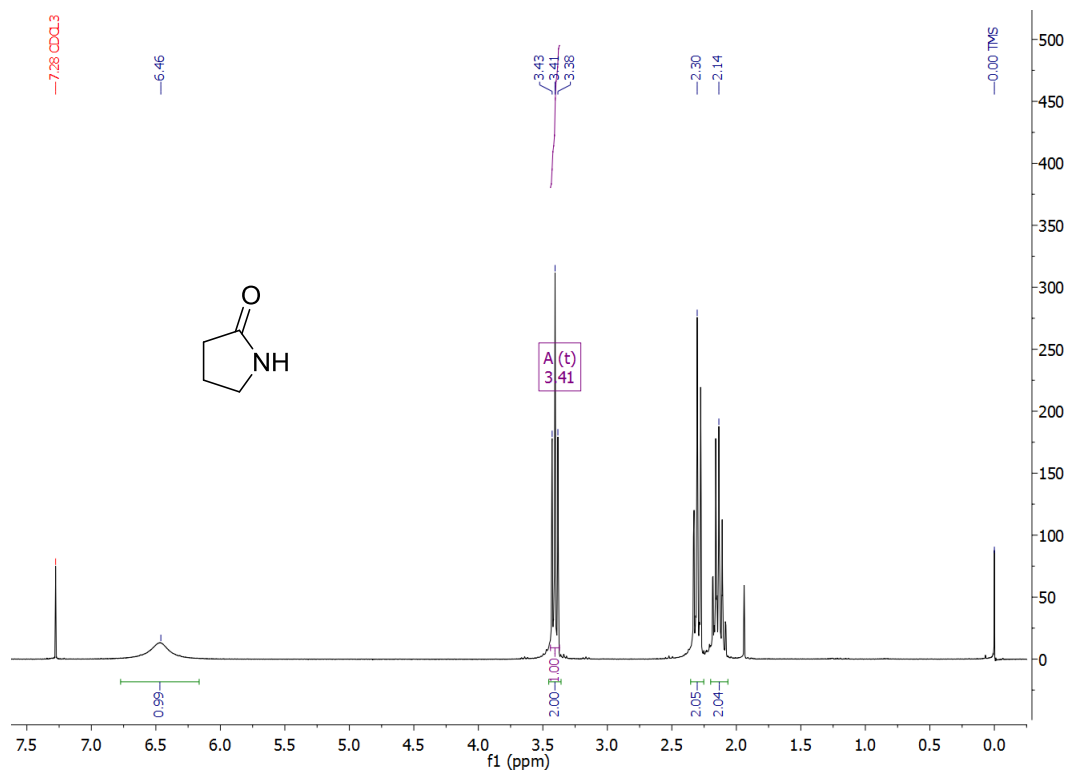
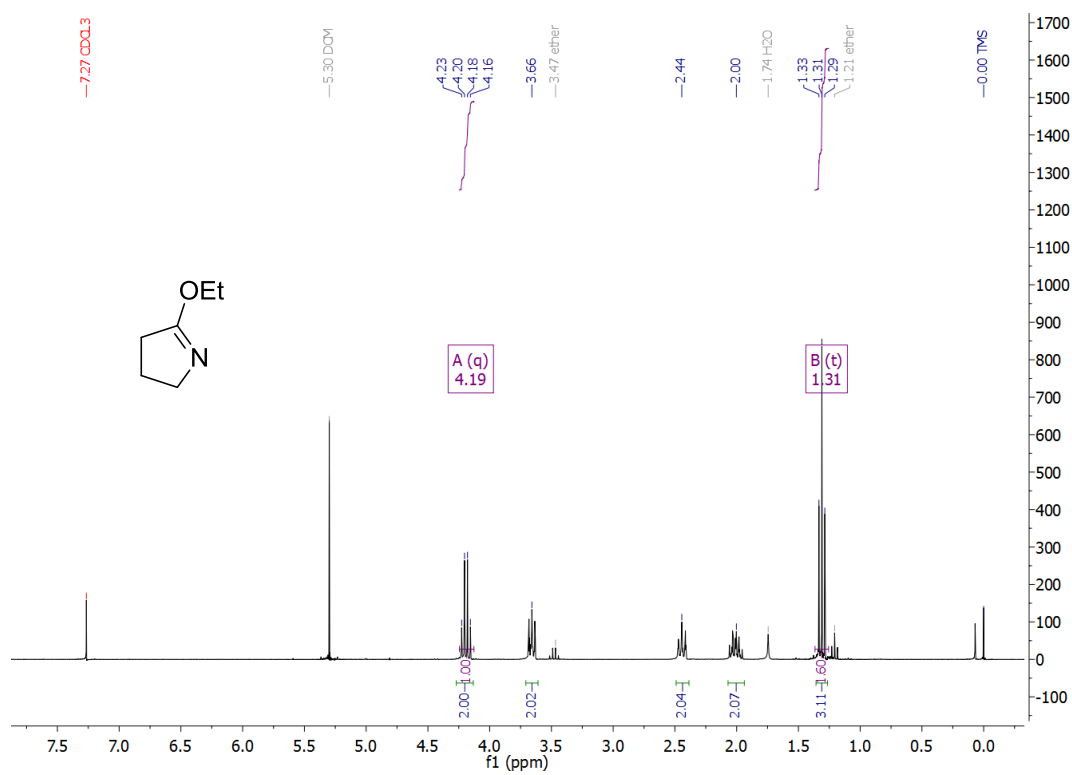
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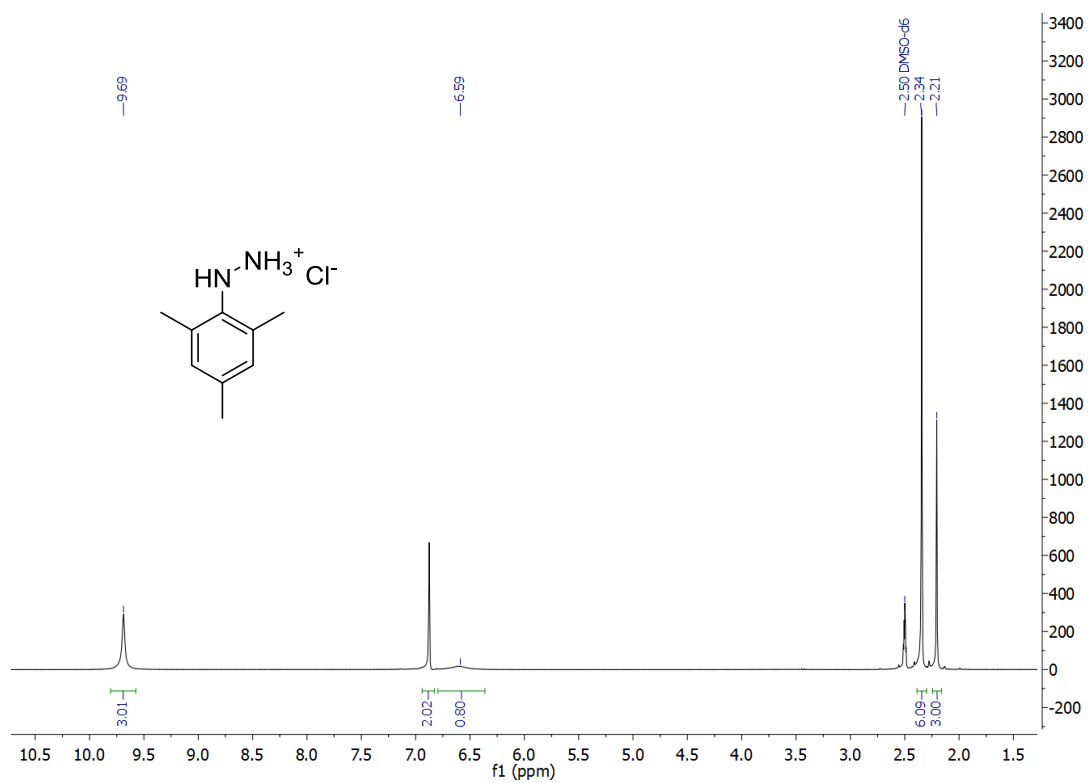
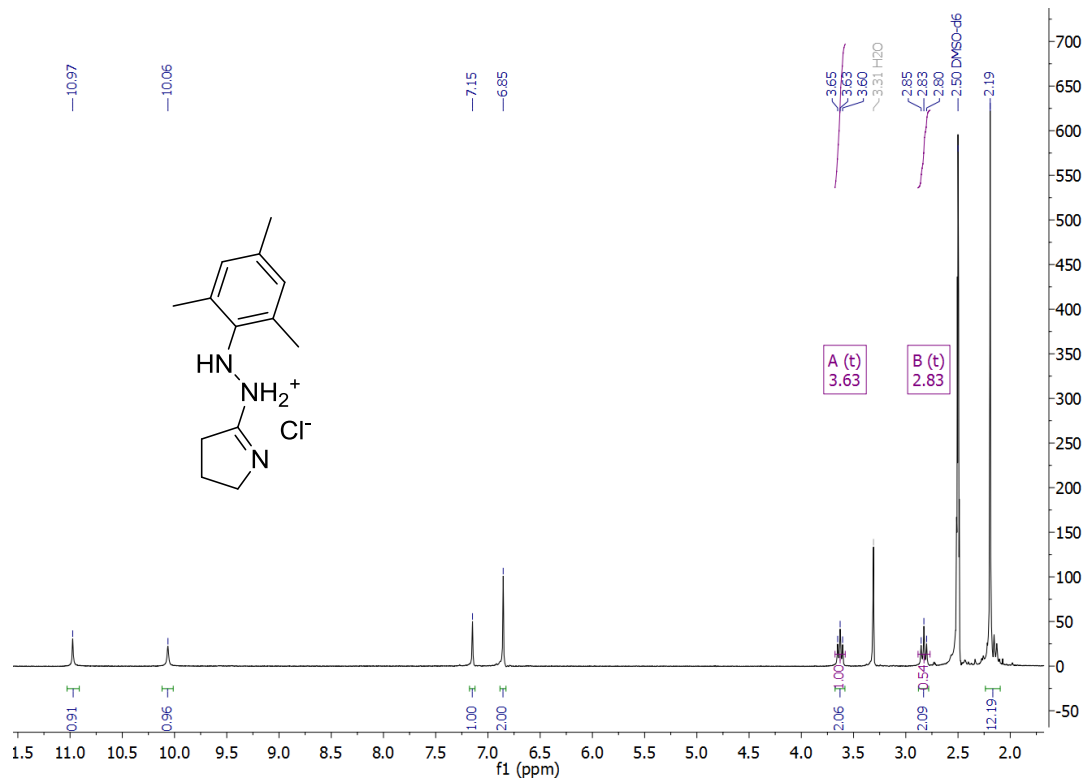
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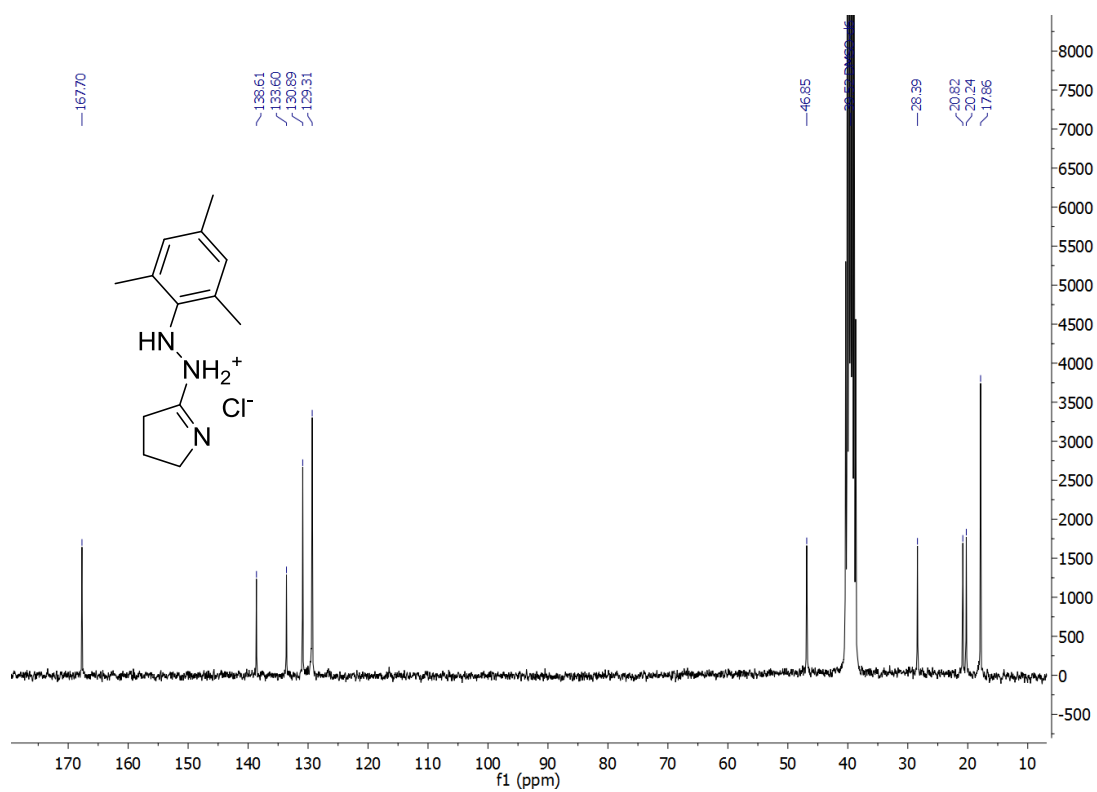
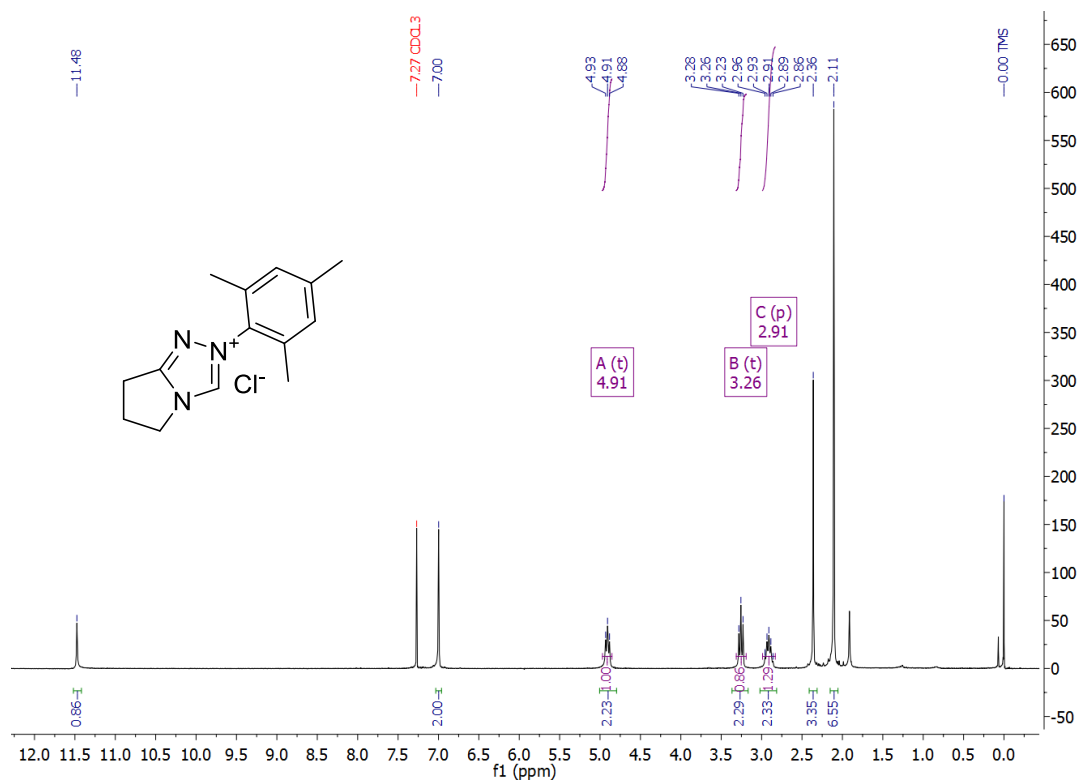
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7. ATTACHMENTS

Attachment 1. ¹H NMR spectrum of 54.Attachment 2. ¹H NMR spectrum of 55.

Attachment 3. ^1H NMR spectrum of 57.Attachment 4. ^1H NMR spectrum of 62.

Attachment 5. ^1H NMR spectrum of **59**.Attachment 6. ^1H NMR spectrum of **61**.

Attachment 7. ^{13}C NMR spectrum of 61.Attachment 8. ^1H NMR spectrum of 64.