Green C_1-Chemistry: Reactions with carbon dioxide and carbon dioxide derivatives

Dissertation

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vorgelegt von

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Abbreviations

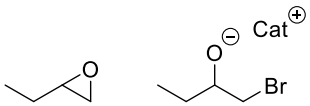
List of abbreviations:

RPM	revolutions per minute
Me	methyl
Et	ethyl
^{i}Pr	*iso*-propyl
^{n}Bu	*n*-butyl
^{t}Bu	*tert*.-butyl
Hex	hexyl
cHex	cyclohexyl
Ph	phenyl
R	generic substituent
dma	dimethyl aminyl
pyrr	pyrrolidinyl
CDP	carbodiphosphorane
TBA	tetrabutyl ammonium
MTO	methyl trioxorhenium
HBD	hydrogen bond donor
BMIM	butyl methyl imidazolium
EMIY	1-ethyl-3-methylimidazol-2-ylidene
TfO^{-}	triflate
AcO^{-}	acetate
X	generic anion
Cat	cation
DBU	1,8-diazabicyclo-[5.4.0]undec-7en
TBD	1,5,7-triazabicyclo-[4.4.0]dec-5en
bp	boiling point
a	year
TON	turn-over number
TOF	turn-over frequency
mp	melting point
NHC	*N*-heterocyclic carbene
IL	ionic liquid
h	hour
T	temperature
p	pressure
rt	room temperature
LA	LEWIS acid
PO	propylene oxide
PC	propylene carbonate
BO	butylene oxide
BC	butylene carbonate
ppb	parts per billion
ppm	parts per million
M	metal cation
HMDS	hexamethyldisilazane
CDI	carbodiimide
DCI	diisopropyl carbodiimide
DCC	dicyclohexyl carbodiimide
$KO^{t}Bu$	potassium *tert*-butoxide
B	base
E	generic chalcogenide
HRMS	high resolution mass spectrometry
NMR	nuclear magnetic resonance spectroscopy

Part I:

Cyclic organic Carbonates from CO_2 and epoxides

Part I: List of compounds



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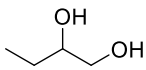

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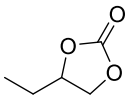

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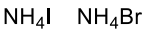
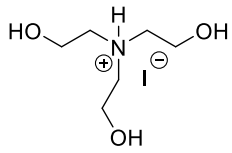


4-I **4-Br**



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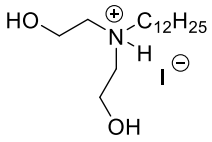

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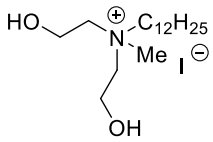

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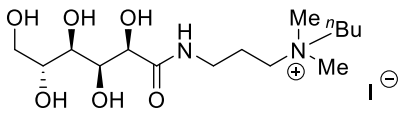

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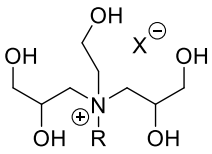
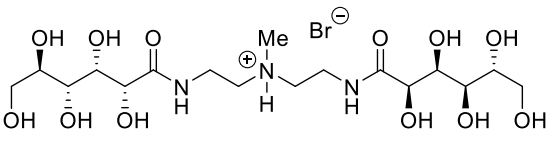
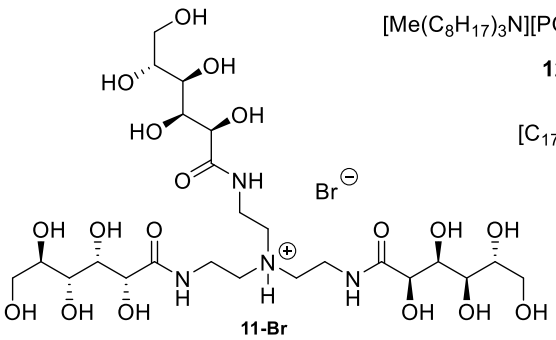


9a-Cl, 9a-Br
9a-I
R= n-Butyl
9b-Br
R= n-Hexyl
9c-Br
R= n-Dodecyl

9*



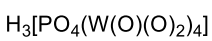
10-Br*



11-Br

$[Me(C_8H_{17})_3N][PO_4(W(O)(O_2)_2)_4]$

12



$H_3[PO_4(W(O)(O)_2)_4]$

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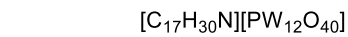

$[C_{17}H_{30}N][PW_{12}O_{40}]$

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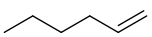

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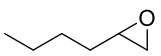

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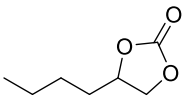

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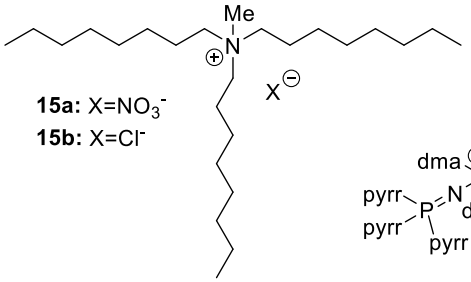
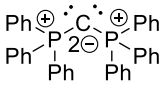


15a: $X=NO_3^-$
15b: $X=Cl^-$



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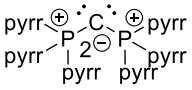

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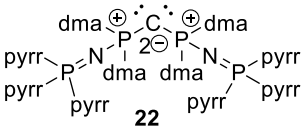

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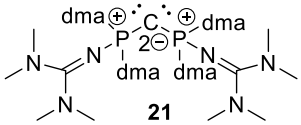

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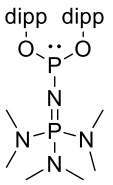

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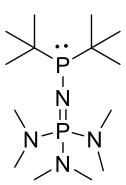

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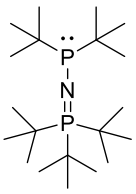

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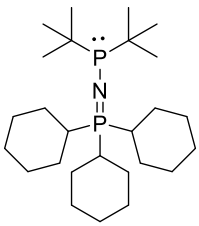

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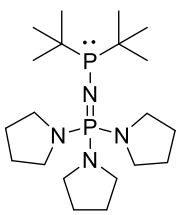

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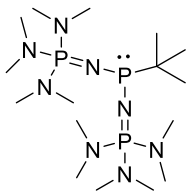

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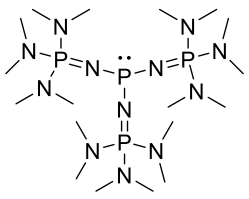

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Compounds marked with * were first prepared in this work. Compounds **19-29** were provided by Igor Martin and Sebastian Wagner

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1 Aqueous two-phase synthesis of cyclic carbonates from epoxides and CO_2

1.1 Theoretical background

1.1.1 CO_2 as chemical feedstock

Carbon dioxide (CO_2) valorisation has gained much attention over the past decades.[1–9] CO_2 is the most abundant C_1-building block on the planet and possesses several properties that make it an attractive raw material for the chemical industry. As the primary waste product of many industrial processes like energy production, fermentation and steam reforming, CO_2 is available in large quantities and varying purity. It is received almost pure from ethanol or ammonia plants and in 14% purity from coal power stations in every industrialized nation and as such the price for carbon dioxide is low (25 $/t in 2013).[6] CO_2 utilization usually takes place near its production as transport is not economically viable.[7] Its non-flammable and non-toxic properties greatly increase inherent process safety. Expansive materials for storage tanks, pipelines and reactors are not required as carbon dioxide is not corrosive. CO_2 is soluble (2-8 mL/g at 20 °C) in most organic solvents, though solubility decreases as temperature increases. Its solubility in water is comparatively low (0.07 mol/kg at rt and 1 atm, Figure 1).

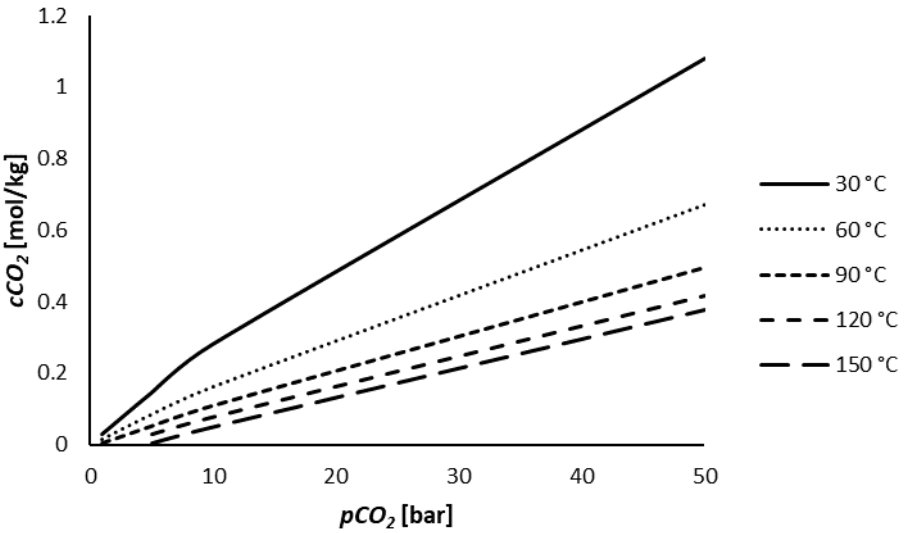


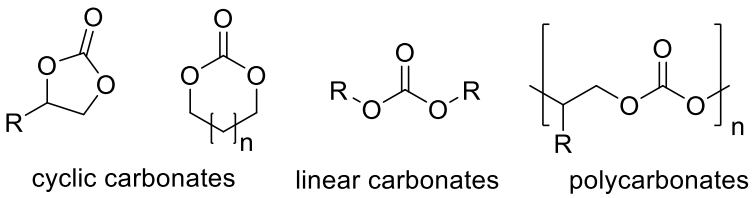
Figure 1: Water-solubility of carbon dioxide at different pressures and temperatures.[10]

CO_2 reacts acidic with water, especially under pressure (pH 5.68 at 1 atm, pH 3.55 at 7 atm).[11,12] Compressed CO_2 greatly increases the volume of many solvents, a phenomenon known as gas expanded liquids or carbon dioxide expanded liquids.[13] It also forms semi-stable adducts with many basic compounds, like amines.[14] This can be exploited for CO_2 capture

and activation. A major hurdle in CO_2-valorisation is the fact that carbon dioxide is, as final product of combustion, an extremely stable molecule ($\Delta G_f°$=-394.2 kJ/mol, $\Delta H_f°$= -393.51 kJ/mol) and its reactions are often kinetically hindered.[12] Reactions involving reduction of CO_2 into methanol or methane require high energy input to overcome the high activation barrier. Reactions without reduction of CO_2 have favourable thermodynamics, as is especially true for reactions with high energy substrates like epoxides and alkynols. Incorporating CO_2 into highly stable products like polymers is also favourable.[15] Estimations for CO_2 utilization range around 200 Mt/a in 2013 compared to 37 Gt/a anthropogenic emission.[15] The largest process by far is the synthesis of urea which accounts for roughly 57% of all CO_2 used and for 66% of CO_2 used as raw material.[15] The second largest demand is the preparation of inorganic carbonates with around 30%. More complex chemicals like polycarbonates and organic carbonates only make up 0.09% of the CO_2 consumed.[15] Nevertheless, they are valuable compounds with many useful applications.

1.1.2 Synthesis, properties and applications of cyclic carbonates

Organic carbonates can formally be described as esters of carbonic acid with alcohols and are primarily distinguished between linear, cyclic and poly carbonates (Scheme 1).



Scheme 1: Different types of organic carbonates.

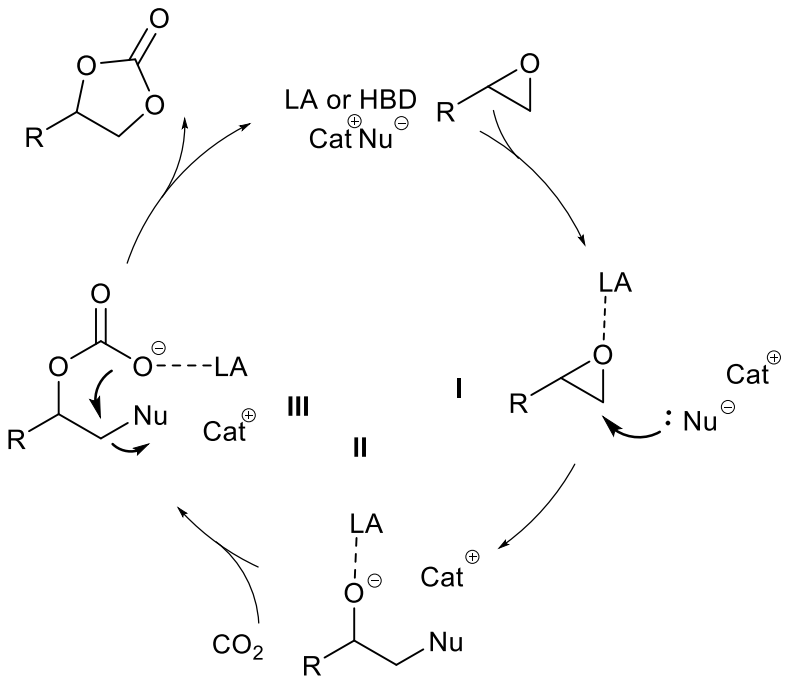
Carbonates with 5-membered rings are the most common cyclic carbonates due to their accessibility and attractive properties:[16] Most used organic carbonates are liquids with exception of ethylene carbonate (m.p. 36.4° C). Propylene carbonate remains liquid from -49 °C to 242 °C at 1 bar. Cyclic carbonates are less volatile than most common organic solvents and have high flash points, making their handling safer. Their viscosity (2.5-3.1 cp) is higher than that of most common used solvents, but still comparable to that of higher alcohols. Cyclic carbonates are polar aprotic solvents like DMSO, DMF or acetonitrile, but display limited miscibility with water. Their dielectric constant ε_R (>60) is higher than that of most organic solvents.[17]

Table 1: Solvent properties of selected cyclic carbonates and other polar aprotic solvents.

Solvent	b.p. [°C]	Vapor pressure (20 °C) [kPa]	ε_R	η [cP]	LD_{50} [mg/kg]	Flash point [°C]	Water solubility [mg/mL]
PC	242	0.13[a]	66	2.5	34920	135	25
BC	260	0.007	n.a.	3.1	>5000	121	7
DMSO	189	0.05	46	1.9	14500	89	indefinite
MeCN	82	9	37	0.38	3800	2	indefinite
THF	66	17	7.8	0.48	1650	-17	indefinite

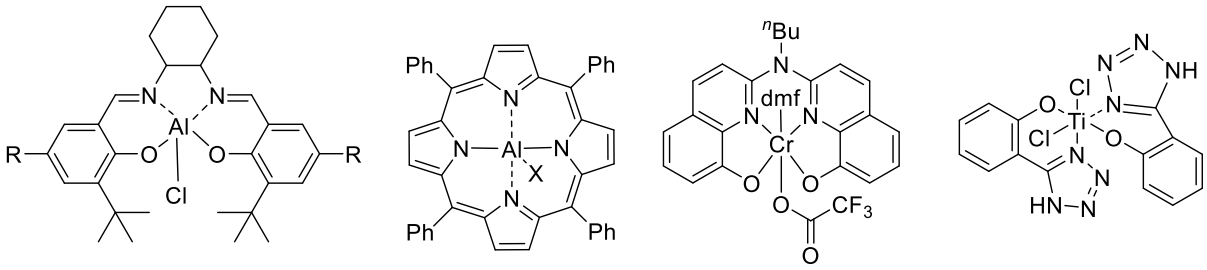
a) 50 °C

Organic carbonates are biodegradable and non-toxic, though ethylene carbonate hydrolyses to harmful ethylene glycol. Due to these attractive properties cyclic carbonates find increasing applications as 'green' solvents. The low toxicity is important for their use in personal care products, cosmetics, paints, lubricants and dyes. Their low ecotoxicity and biodegradability is also relevant for their application in cleaning and paint stripping. They are well suited as a medium for electrochemical applications and battery solvents.[16,18] Their low volatility opens new possibilities in processes requiring high temperature or reduced pressure. Cyclic carbonates are thermally stable but they can hydrolyse in presence of strong acids and react with strong nucleophiles. They are also major intermediates in the preparation of polymers and dimethyl carbonate.[16,17,19] Since their discovery, two major synthetic routes for cyclic carbonate exist: phosgenation of 1,2-diols and the coupling of epoxides and CO_2. The condensation of urea with 1,2-diols or the direct synthesis from CO_2 are currently under investigation but have not been realized yet.[16,20] The synthesis of ethylene carbonate from ethylene oxide was first described in 1939 by IG FARBEN. Active charcoal treated with NaOH was used as catalyst. The carboxylation of epoxides is 100% atom economic, meaning no atom is wasted by formation of by-products.[19] The reaction is thermodynamically favoured but kinetically hindered (E_A= 50-60 kcal/mol), therefor catalysts are regularly employed.[21–25] This chapter focuses on homogenous catalysts. Nowadays, the reaction is performed without additional solvents. Catalysts usually activate the epoxide or CO_2. The epoxide ring is opened by a S_N2 type attack by a nucleophilic catalyst, typically at the less shielded carbon atom of the epoxide [Step I]. The intermediate than rapidly reacts with CO_2 [Step II]. The ring is then closed by internal S_N2 attack of the alkyl carbonate and the nucleophilic catalyst is restored [Step III] (Scheme 2).[26–29]



Scheme 2: Mechanism of the carboxylation of epoxides *via* epoxide activation by a nucleophilic catalyst and an assisting LEWIS acid (LA) or hydrogen bond donor (HBD).

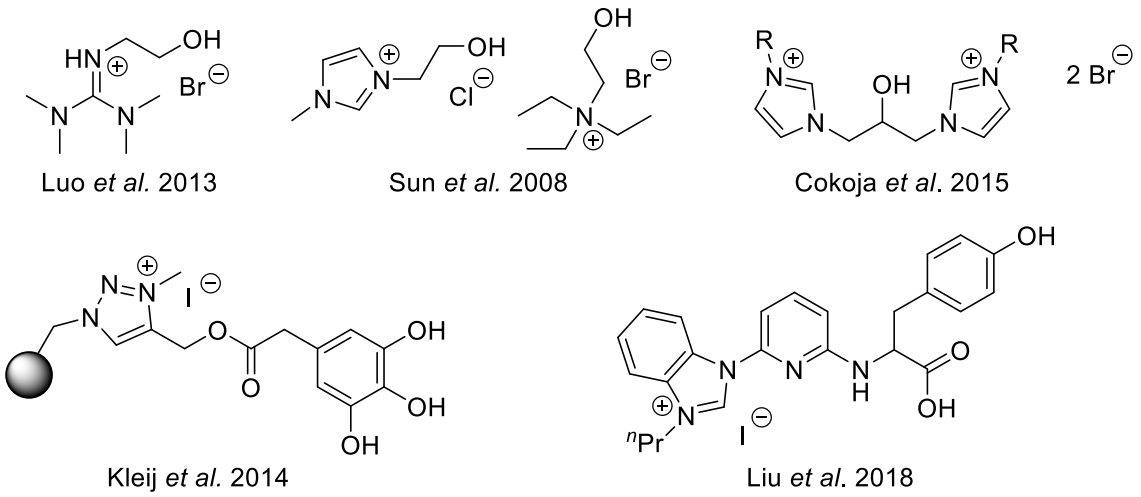
Ring opening can be further assisted by a LEWIS acid (LA) or hydrogen bond donor (HBD) which can activate the C-O bond of the epoxide. In a few special cases an alternative mechanism involving the C-C bond cleavage catalysed by LEWIS acids has been reported.[29]A variety of metal-organic and organic catalysts as well as binary systems are known to the literature. Typical reaction conditions require elevated temperatures >80 °C and pressures >10 bar but room temperature and ambient pressure examples are known. Generally, a nucleophilic species is needed as catalytically active species. Commonly used nucleophiles are Cl^-,Br^-, I^- and less nucleophilic anions like BF_4^- have been utilized as well.[14,30,31] While many highly active LEWIS acid catalysts with excellent TOFs (turn over frequency) and low catalyst loads have been reported, they still require a nucleophile like e.g., I^- as additive or co-catalyst, as these LEWIS acids are not catalytically active on their own whereas the nucleophilic additive is. It can therefore be assumed that the nucleophile is the actual catalyst and the LEWIS acid the co-catalyst. Single component catalysts from metal halide complexes have also seen extensive development (Scheme 3). These types of catalysts are also used in CO_2-epoxide-copolymerisation.



Darensberg *et. al* 2012 | Inou *et al.* 1978 | Sundermeyer *et al.* 2014 | Lee *et al.*2013

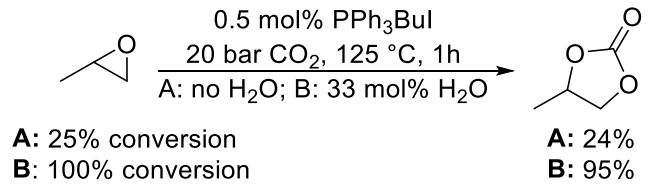
Scheme 3: Metal catalysts for the coupling of CO_2 and epoxides.[32–35]

The most widespread organic catalysts are ammonium-, imidazolium- and phosphonium salts with a naked nucleophilic anion. Organic bases which can be active catalyst themselves are discussed in Chapter 3. The metal-free synthesis of cyclic carbonates has first been reported by NISHIKUBO *et al.* in 1993, who used quaternary onium halides bound on polystyrene beads.[36] In 2006 HE *et al*. first reported that the catalytic activity of ammonium salts increased with the chain length of their substituents.[37] DENG *et al*. were the first to utilize imidazolium ionic liquids as catalysts in 2001.[38] In 2003 SHI *et al.* reported phenol as the first utilized HBD co-catalyst for the coupling of CO_2 and epoxides.[39] HBDs are molecules containing a moiety capable of forming intermolecular hydrogen bonds (e.g. -OH; -COOH; -NH). They assist in epoxide ring opening by bonding at the oxygen atom of the epoxide and polarizing the C-O bonds, analogous to metal LEWIS acid activation.[21] By incorporating HBD moieties into ILs SUN *et al*. created single component organic catalysts that were significantly more active than their non-HBD containing counterparts.[40] These type of bifunctional catalysts (Scheme 4) are among the most active organic catalyst for the coupling of CO_2 and epoxides, some of which are effective even at room temperature. Since then many HBDs have been reported, including protonated superbases, polyphenols and natural compounds like amino acids, sugars, cellulose and ascorbic acid.[21,41,42]



Scheme 4: Multifunctional organic catalysts for the coupling of CO_2 and epoxides.[30,40,42–44]

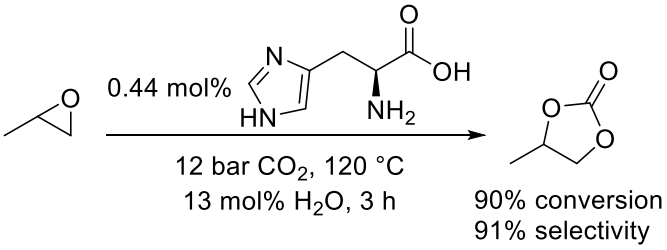
Externally added hydrogen bond donors are very attractive co-catalysts if they are obtainable from a renewable, easily accessible source.[45] Water has been used as efficient medium for epoxide ring opening for several decades. The presence of water greatly enhanced the reaction of epoxides with various nucleophiles, in some cases making reaction possible which could not be performed in organic solvents.[46] It was reported on multiple occasions that the pH of the reaction medium greatly affects the reaction. In the azidolysis of 1,2-epoxides the regioselectivity of the nucleophilic attack could be reversed by switching from a basic to neutral to acidic medium.[46,47] SUN *et al*. first reported the use of water reaction medium for the synthesis of cyclic carbonates from epoxides and CO_2 in 2009.[28] They observed that the TOF of several alkali, phosphonium and imidazolium salts was 4 to 100 times higher in presence of water than in absence. PPh_3BuI for example reached 24% conversion of propylene oxide after 1 h with 96% selectivity if the reaction was performed neat. If water was added, propylene oxide conversion reached >99% with 95% selectivity (Scheme 5).[28]



Scheme 5: Example for the rate enhancing properties of water on the carboxylation of epoxides.[28]

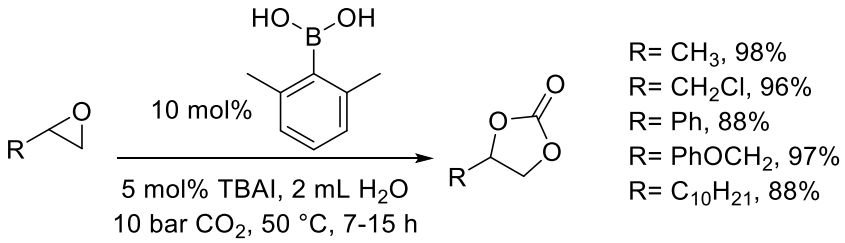
Simple alkali halides such as NaI only produced traces of cyclic carbonate under dry conditions. In presence of water the yield reached up to 68%, a more than 100-fold increase in TON. Additionally, they noted that the anions order of activity changes in presence of water, from Br^-> Cl^-> I^- in absence of water to I^-> Br^-> Cl^- in presence of water. They compared the effect of water with other known HBDs and found it was superior in all cases.[28] The selectivity however

is slightly lower compared to conventional organic solvents due the hydrolysis of propylene oxide to 1,2-propane diol. The conversion of other epoxides profited similarly from the presence of water, though conversion was lower for more hydrophobic substrates like 1,2-epoxy hexane and styrene oxide. Conversion of cyclohexene oxide was especially slow with only 49% conversion after 6 h. In 2019, PESCARMONA and ALASSMY investigated the influence of water and organic catalysts under mild conditions.[48] At 60 °C and under 10 bar of CO_2 1,2-epoxy hexane was nearly quantitatively transformed to the 1,2-hexane carbonate in 48 h. They noted that small amounts of 1,2-diols were formed (0.3-1%) which could act as HBDs themselves. While 1,2-diols did enhance the conversion of propylene carbonate, the effect is significantly lower than that of water (9% yield without HBD, 31% with 1,2-diol as HBD and 55% with water). Water was also found to be less effective as HBD than other organic HBDs so that a higher molar loading of water was required. PARK *et al.* investigated the catalytic activity of 20 naturally occurring α-amino acids in the coupling of CO_2 and epoxides (Scheme 6).[49] At 120 °C and 12 bar CO_2 and with 0.44 mol% amino acid no conversion of propylene oxide was observed. In presence of 13 mol% water, the conversion ranged from 3% for glutamic acid to 90% for histidine. The selectivity reached 69% to 91%.



Scheme 6: L-Histidine as catalyst for the carboxylation of epoxides.[49]

Increasing the amount of water led to a drastic decrease in selectivity. Other terminal epoxides were transformed with a selectivity of >80% and good rates of conversion (>79%). Only the internal epoxide cyclohexene oxide performed poorly. ZHANG and WANG describe the synergistic effect of boronic acid HBDs and water in 2016.[50] Glycidyl phenyl ether was reacted with 10 bar of CO_2 at 50 °C with 5 mol% of tetrabutylammonium iodide (TBAI) and 10 mol% of 27 different boronic acids (Scheme 7). The rate of conversion was greatly enhanced compared to water alone. Even at room temperature 82% conversion with a selectivity of <99% could be achieved. If solvents other than water were used, the rate of conversion was greatly diminished. They attributed this to the tendency of boronic acids to aggregate under anhydrous conditions which greatly reduces their potency as HBDs.

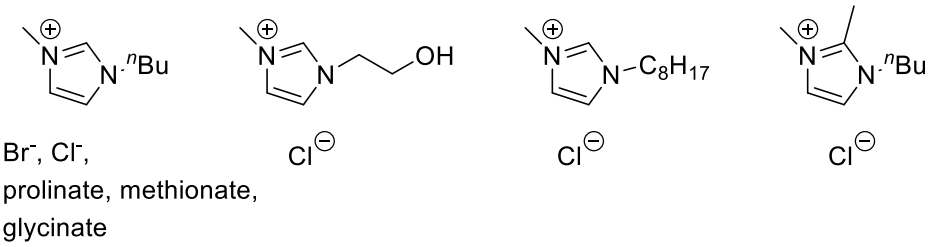


Scheme 7: Boronic acids as catalysts for the carboxylation of epoxides.

Other epoxides were similarly efficiently transformed at 50 °C, though no internal epoxides were tested. A polystyrene supported boronic acid was also successfully used, achieving 60% conversion at full selectivity. It remained stable over 6 runs. The ammonium catalyst, TBAI, however was not recycled. In 2020 DONG *et al.* published an in-depth theoretical study on the effect of anions, cations and water on the coupling of CO_2 and epoxides.[51] [BMIM]Br and propylene oxide were used as model compounds. In absence of water, the reaction path consists of three distinct steps. The energy barrier ΔE for the first step, the ring opening, was calculated to be 38.7 kcal/mol. The energy barrier for the insertion of CO_2 was determined as 12.9kcal/mol. For the final ring closure, the energy barrier was calculated as 15 kcal/mol. As such, the epoxide ring opening was determined to be the rate-determining step of the reaction. $\Delta E_{\text{ring-opening}}$ is dependent of the nucleophilicity of the anion: the higher the nucleophilicity, the lower $\Delta E_{\text{ring-opening}}$. Correspondingly, $\Delta E_{\text{ring-closing}}$ decreases if the leaving ability of the anion increases. If water is present as solvent $\Delta E_{\text{ring-opening}}$ decreases to 24.2 kcal/mol. This can be further reduced to 15.3 kcal/mol if three molecules of water participate by active hydrogen bond formation. This effect was attributed to a polarizing effect on the epoxides C-O bond. This also effected the CO_2 insertion, decreasing $\Delta E_{CO2\text{-}insertion}$ to 5.8 kcal/mol. Furthermore, by polarisation of the alkyl carbonate intermediate, $\Delta E_{\text{ring-closing}}$ was reduced to 8 kcal/mol. Water therefore actively participates in all steps of the catalytic cycle. Additionally, more than one water molecule may participate. While many highly efficient catalysts have been developed, efficient recycling has not been the main focus of development. In many cases catalyst recycling involves isolation and purification of the used catalyst. Methods include thermal separation of the carbonate product or precipitation of the catalyst by addition of large quantities of non-polar solvent.[42,43,52,53] This is often followed by washing and vacuum drying of the catalyst. Another common method is the immobilisation of the catalyst on solid support.[54] This is achieved by covalent binding to a polymer[55,56] or as SILP (supported ionic liquid phase)[57,58]. This generally reduces catalytic activity leading to

harsher reaction conditions.[59] Preparation of these heterogenized catalyst can be rather tedious as well. More advanced concepts incorporate additional functionalities, like HBDs into the solid catalyst. KLEIJ *et al.*'s catalyst contained a 1,2,3-trihydroxybezene moiety as HBD and a methyl triazonium iodide moiety as nucleophile on a polystyrene support (Scheme 4).[44] Over 70% yield of 1,2-hexane carbonate were obtained under mild conditions (45 °C, 10 bar CO_2, 18 h, 4 mol% catalyst). The catalyst remained stable over 5 runs and could be regenerated after performance dropped in the sixth run. Other terminal epoxides produced high yields as well, though most internal epoxides reacted sluggish.

Recently, a concept similar to the one presented in this work was published by NAVARRO *et al*. in 2021 and 2022.[60,61] They used an water-soluble amino acid based IL [BMIM][Gly] as catalyst and were able to achieve propylene carbonate conversions up to 91% in presence of water, though no selectivity was given. They determined the extractive properties of a propylene carbonate-IL-water system and found that the IL could be readily extracted into the aqueous phase at low IL concentrations. They also simulated a continuous process where the catalyst was recovered by liquid-liquid extraction with water as extracting solvent.[60] A year later, they performed these investigations for 8 different commercially available ILs known for their use as catalyst for the synthesis of cyclic carbonates (Scheme 8).



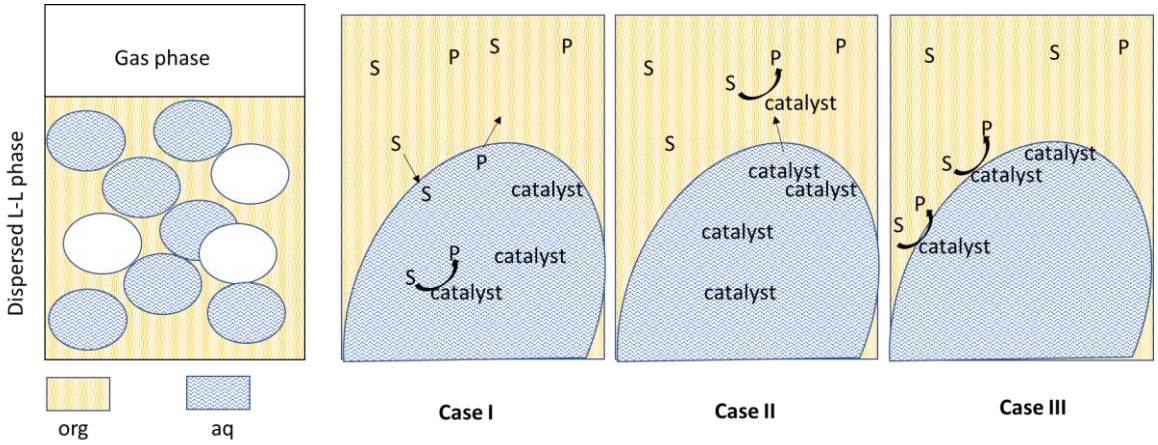
Scheme 8: ILs investigated for recyclability by NAVARRO *et al*.[61]

The extractive properties of the IL and its distribution in model propylene carbonate/water systems was investigated. They found that the amount of IL recovered depends on its hydrophilicity and on its concentration. The more hydrophobic the IL the more remained in the propylene carbonate phase. The distribution also became less favourable with an increase in IL concentration. The more hydrophilic the IL the better the distribution of IL between aqueous and organic phase. This means a higher catalyst load could be theoretically used.[61] Additionally, the specific energy consumption for the simulated process was calculated. If the traditional separation methods (e.g. vacuum distillation) was used the consumption was around 2.4 $kWh/kg_{product}$. If the liquid-liquid-extraction was used, energy consumption

dropped to around 1.2 $kWh/kg_{product}$, demonstrating the feasibility and economic value of such a process.[60] The concept of multiple phase processes is discussed in greater detail in the following chapter.

1.1.3 Multiple phase catalysis

Technically, all reactions that involve more than a single homogenous solution with all components completely dissolved are multiple phase reactions. These include but are not limited to gas-liquid, liquid-liquid and solid-liquid reactions. This chapter and this work focus on liquid-liquid-systems, though in most cases a gas-liquid-liquid-system is actually present. Phase transfer catalysis is also excluded, as catalyst and product are in this case located in the same phase. While homogenous catalysts are generally associated with higher activity, milder reaction conditions and other benefits over their heterogenous counterparts,[62] one major flaw often prevents their use on an industrial scale: laborious catalyst-product separation. Many methods for efficient catalyst recovery have been developed, including immobilisation on solid support or nanofiltration. One of the most elegant methods however is multiple phase catalysis.[54,63–65] Multiple phase reactions are reactions in which at least two liquid phases are present during and/or after the reactions. These phases separate substrates, products, reactants and catalyst from one another. The epoxidation of olefins with aqueous hydrogen peroxide is an obvious example: The olefin substrate and later the epoxide product is located in an organic phase and H_2O_2 in the separate aqueous phase. Multiple phase catalysis is a special case in which product and catalyst are selectively dissolved in different liquid phases at the end of the reaction.[66] Thus, the catalyst retains its homogeneous properties in terms of reactivity but is heterogenous relative to the product. During the reaction a dispersion is usually created through agitation. If an aqueous phase and an immiscible organic phase are present during the reaction, then the chemical transformation can take place in three different places: the aqueous bulk phase (case I), the organic bulk phase (case II) or at the phase interface (case IIIa;b). For the example in Scheme 9, we assume that the aqueous phase (**aq**) contains the catalyst and the organic phase (**org**) the substrate/product (**S** and **P**).[67–71]



Scheme 9: Different mechanisms for aqueous organic two-phase reactions.

In **Case I**: The **S** is partially soluble in the aqueous phase and fully soluble in the organic phase. Following the concentration gradient, **S** crosses the phase interphase from the organic phase into the aqueous phase. The rate of this transfer and the amount that is transferred depend primarily on the water solubility of **S** and the surface area of the interface. In the aqueous bulk phase **S** can react with the catalyst to form **P**. Depending on the water solubility of **S** and the concentration of the catalyst, the ratio between the catalyst and **S** can vary. If the solubility of **S** is limited, the effective catalyst load is higher than in a purely homogenous system. **P** is then transferred to the organic phase, the rate of which depends on the same factors as **S**. The catalyst remains in the aqueous phase during the entire process and can be recovered with the aqueous phase. Effective mass transport of **S** is crucial for an efficient process.

In **Case II**: The catalyst is fully soluble in the aqueous phase and partially soluble in the organic phase. Its transfer is analogue to **S** in case 1. The effective catalyst load is lower compared to the purely homogenous system as most of the catalyst remains separated from **S** in the aqueous phase. Additionally, a portion of the catalyst is lost with organic phase. This reduces the aqueous phase simply to a reservoir of the catalyst, rendering this scenario undesirable.

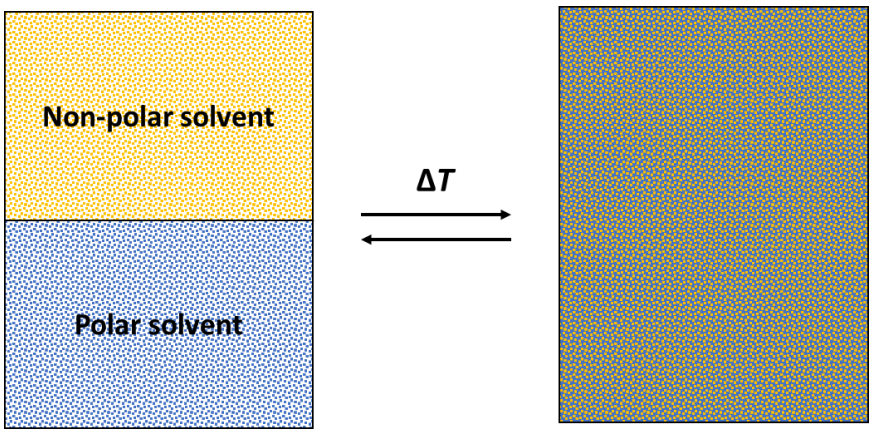
In **Case IIIa**: **S** and the catalyst are located in the organic and aqueous bulk phase respectively. If the reaction takes place at the phase interface, **S** does not need to cross into the aqueous phase to react with the catalyst. This greatly reduces the influence of the water solubility of **S** and mass transfer limitations. The phase interface's surface areas impact is however greatly increased, as it determines how many molecules of the catalyst and **S** are in contact. Stirring is the most common method of increasing the interface area.

As a special **Case IIIb**: The catalyst is concentrated at the phase interface. This occurs when the catalyst is a surfactant for example. The size of the phase interface surface area becomes

irrelevant once the interface is saturated with the catalyst because all of the catalyst is located were the reaction takes place. Therefore, case IIIb has the highest effective catalyst load. As the catalyst has at least some amphiphilic properties in this scenario, leaching may become an issue.

It should be noted that these examples are simplified and dependent on the mutual solubility of the components, reality is more complex. For example, while a system may be biphasic at the start and the end, a single-phase system may be present under reaction conditions.

Thermomorphic solvent systems or temperature dependent multi-component solvent systems (TMS) are systems containing multiple solvents whose miscibility is dependent on temperature.[69,72] The idea is, that under reactions conditions, which frequently require heating, all components mix and form a homogenous system. The reaction then proceeds analogously to its homogenous counterpart without the issues associated with multiple phase systems. After the reaction is finished and the system is cooled down, the components separate into distinct phases (Scheme 10).



Scheme 10: Working principle of temperature dependent multi-component solvent systems.

Product and catalyst are located in different phases and catalyst recovery is achieved by simple phase separation. Usually, three solvents are used to form a TMS. A polar solvent and a non-polar solvent which are close to immiscible contain the product and catalyst respectively. A third solvent whose polarity lies in between is often added as solubility mediator (e.g. hexane, dioxane and propylene carbonate form a TMS). Depending on the ratios between these three solvents, full miscibility can be achieved at certain temperatures.[73]

Separation can also be achieved by introducing a gas to the system. Pressurized CO_2 can greatly affect the polarity when introduced to a solvent. Several water-miscible solvents (e.g.

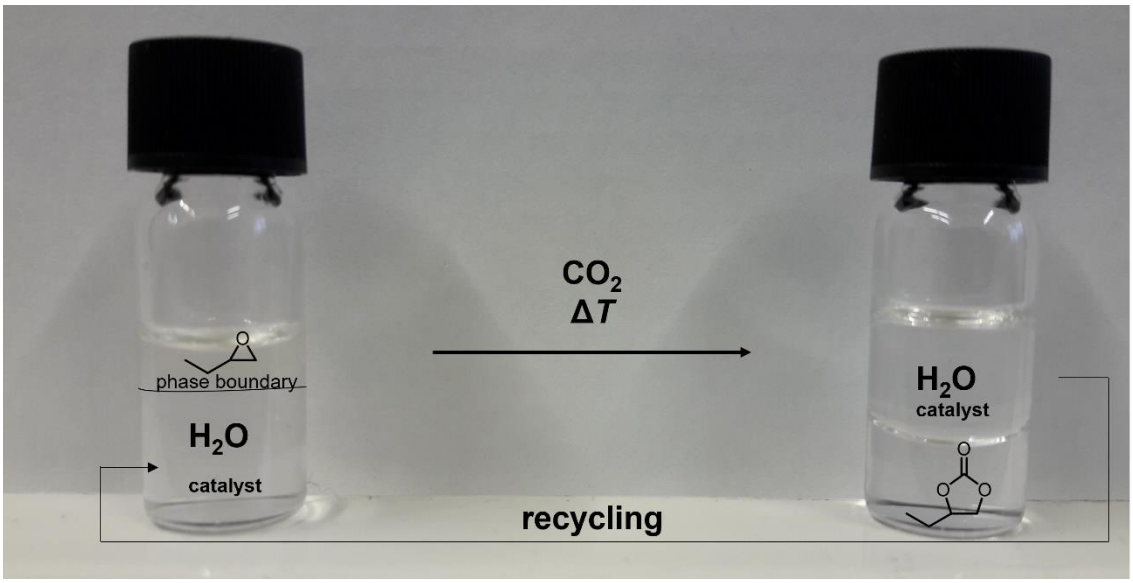
THF, acetonitrile) separate from water when exposed to pressurized CO_2.[74] Additionally, additives like amines can be added to a solvents mixture which drastically increase the polarity of the system in presence of CO_2.[74–77] The concept of multiple phase catalysis has already proven itself on an industrial scale. Introduced in 1977, the SHELL HIGHER OLEFIN PROCESS (SHOP) was the one of first industrial process utilizing multiple phase (liquid-liquid-gas) catalysis.[78,79] Ethen is oligomerized and the products are subsequently isomerized to from α-olefins with a chain length of 4-20 carbon atoms. The Ni-phosphine catalyst is immobilized in a polar 1,4-butandiol phase. The formed olefins are insoluble in this polar phase and can easily be separated. Its capacity today is around 1 Mio t/a. The RUHRCHEMIE/RHÔNE-POULENC oxo process was the first industrial process utilizing aqueous biphasic catalysis. It was introduced in 1984.[80] Rather unusual, the process was realized before aqueous-biphasic catalysis gained traction as research subject. Short olefins (≤ C_4), CO and H_2 are transformed into aldehydes *via* [Rh] catalysed hydroformylation. Water is used as the solvent and the catalyst is retained in the aqueous phase through the highly water-soluble tris(3-sulfophenyl)phosphine trisodium salt (TPPTS). The short olefins have a very limited solubility in the aqueous phase (≈200 ppm), so the reaction takes primarily place at the interphase region, rather than in the bulk aqueous phase. As such special stirrers are used to increase the interphase area. The produced aldehydes are somewhat soluble in water (71 g/l for butanal) and form a separate organic phase at higher concentrations. After the reaction the organic phase and a small part of the aqueous phase are transferred to a separator unit, with the bulk of the aqueous phase remaining in the reactor. The catalyst containing aqueous phase is recycled into the reactor after separation. The catalyst retention is high with a [Rh] concentration in the organic product phase in ppb range. With a butanal production capacity of 600.000 t/a it is one of the most relevant hydroformylation processes.[80]

1.2 Aim of this chapter

This chapter aims to develop an effective catalyst system that is simultaneously efficiently recyclable. This should be achieved by utilizing the reaction enhancing properties of water as well as the miscibility gap between water and most cyclic carbonates. The core design principle of the catalysts presented in this work is their hydrophilicity. They were specifically and deliberately designed to be as water soluble as possible and as insoluble in the organic carbonate product as possible. Additionally, catalyst longevity and high selectivity towards the cyclic carbonate are the main priorities.

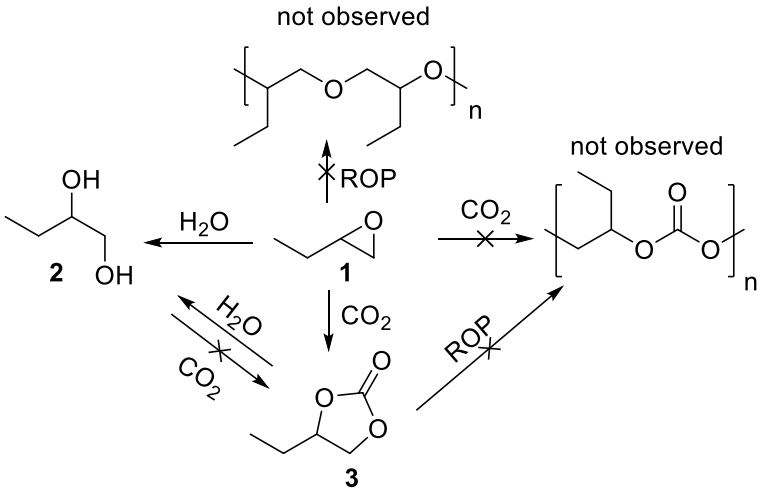
1.3 Results and discussion

The unactivated butylene oxide **1** was chosen as model substrate due to its simpler handling and similarity to the industrial relevant but more volatile propylene oxide. Scheme 11 displays the concept: The neat product (and the substrate) and water form separate phases, whereby the catalyst is fully located in the aqueous phase.



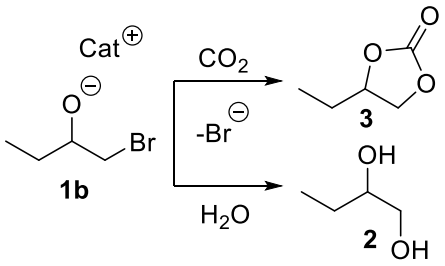
Scheme 11: Concept of the aqueous organic two-phase system for the carboxylation of epoxides.

After the reaction is finished both phases are separated and fresh substrate is added to the catalyst containing aqueous phase. Isolation of the catalyst is not necessary for recycling. [See Chapter 1.1.3 for a more comprehensive theoretical background]. At the time the project began, no such system was reported in the literature. During the reaction four products can theoretically be formed (Scheme 12).



Scheme 12: Possible reaction products of the carboxylation of BO under aqueous conditions and their formation.

No oligomerisation products have ever been observed when the reaction is performed in presence of water. The organic product phase consists in all cases of butylene carbonate **3** (**BC**), 1,2-butane diol **2** and unreacted butylene oxide **1** (**BO**). The carbonate is formed *via* CO_2 insertion into the epoxide. No C-O bond is formed from 1,2-butane diol and CO_2 under the conditions of the carboxylation of **BO**, as proven by a control experiment. The undesired side product 1,2-butane diol can be formed by epoxide hydrolysis and to a lesser degree by hydrolysis of butylene carbonate. They epoxide hydrolysis might occur uncatalyzed or *via* hydrolysis of the halohydrin intermediate **1b** (Scheme 13).



Scheme 13: Possible reaction paths of the halohydrin intermediate.

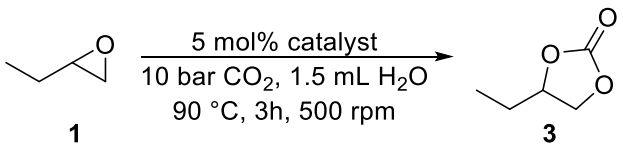
1.3.1 Catalyst design

In order to obtain a viable aqueous two-phase system, the catalyst must fulfil three criteria:

- **Water solubility**
- **Stability**
- **Selectivity**

If the catalyst is not fully dissolved in the aqueous phase during the separation step, part of it will be lost, greatly reducing recycling efficiency. Likewise, if the catalyst is not stable over multiple cycles, efficiency is greatly reduced. Low selectivity towards the desired product is the most obvious course of inefficiency. Additionally, the formation of large amounts of 1,2-diol by-product enhances the miscibility of aqueous and organic phase to the point where only a single phase remains. This renders efficient recycling impossible, even if the other criteria are met. As previously discussed, in the coupling of epoxides and CO_2 the catalyst can activate CO_2, the epoxide, or both. This approach focusses on the activation of the epoxide with a nucleophilic anion, forming the aforementioned intermediate. It benefits greatly from the presence of a hydrogen bond donor like water. Furthermore, an ionic catalyst should be more hydrophilic than a comparable neutral one. With these goalposts established, it was now possible to move onto the design of the actual catalyst.

Water not only interacts with the epoxide during the reaction but also has a profound effect on the catalytically active anion as well. Solvation, protonation and the forming of strong hydrogen bonds greatly affect the anions nucleophilic properties and in turn its catalytic performance.[81–84] To determine which anions are suitable catalysts in presence of water an anion screening was performed (Table 2, Scheme 14). The anions were chosen based on their nucleophilic properties or previous reports of catalytic activity in the coupling of epoxides and CO_2. Additionally, the anion's leaving group ability is known to play a crucial role in this reaction. For this reason, nucleophiles that form highly stable C-X (e.g. F^-, CN^-) bonds were not investigated. They were used as more lipophilic salts to supress effects resulting from miscibility and solubility issues.



Scheme 14: General scheme for anion screening under aqueous conditions.

Table 2: Anion screening under aqueous organic conditions.

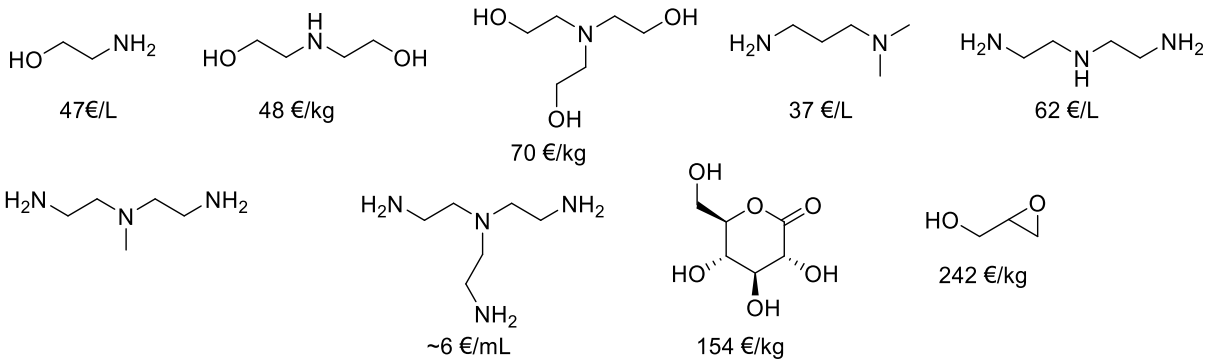
Entry	Cation	Anion	Conversion BO [%]	Yield BC [%]	Selectivity BC [%]
1	TBA	Cl^-	97	88	90
2	TBA	Br^-	93	87	94
3	TBA	I^-	98	98	99
4	TBA	NO_3^-	58	11	19
5	TBA	HCO_3^-	nd	0	0
6	TBA	OH^-	nd	0	0
7	TBA	PF_6^-	nd	0	0
8	TBA	TfO^-	nd	0	0
9	R_3N	-	nd	0	0
10	TMA	N_3^-	nd	trace	0
11	TMA	$MeCO_3^-$	nd	trace	0
12	BMIM	AcO^-	nd	0	0

Conditions: 1 g butylene oxide **1**, 5 mol% catalyst, 1.5 mL H_2O, 90° C, 10 bar CO_2, 3 h, 500 rpm, yields determined *via* GC-FID.

As expected, Cl^-, Br^- and I^- (Entry 1-3) perform best with a conversion >90% while maintaining high selectivity (90%) towards the carbonate **3**. The order of activity is I^-> Br^-≈Cl which is consistent with the nucleophilicity of halides in aqueous solutions.[81] NO_3^- (Entry 4) is the only other anion exhibiting any significant selectivity (19%) under these conditions. As it is known to effectively open epoxide in aqueous solutions, its poor performance is likely due to its poor leaving ability.[85–87] With all other anions a mixture of unreacted butylene oxide **1** and 1,2-butylene diol **2** was obtained. This means that these anions are under these conditions either not active or not active enough to compete with the epoxide hydrolysis side reaction or actively promote hydrolysis of the epoxide **1** or carbonate **3**. HCO_3^- (Entry 5) performs poorly under aqueous conditions. OH^- and any amine (Entry 6, 9) form HCO_3^- under these conditions and therefore react in the same way. Triflate and hexafluorophosphate have been used as catalysts but cannot compete with the hydrolysis side reaction under these conditions.[88,89] Similar to nitrate, azide opens epoxides in aqueous solutions. However, the

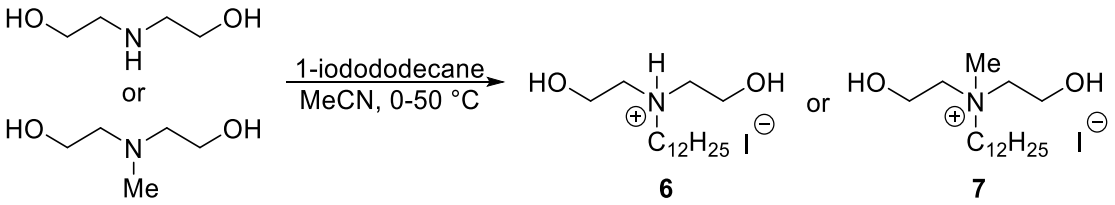
resulting intermediate has been reported to be highly stable which explains its poor performance (Entry 10).[90] Being salts of weak acids $MeCO_3^-$ and acetate (pK_A 3.6-6.4) could be partially protonated under these conditions, as the acidity of the aqueous phase rises with increasing CO_2 pressure.[11] Through the formation of strong hydrogen bonds with surrounding water molecules their nucleophilicity is strongly diminished compared to the naked anion. For $MeCO_3^-$ catalytic hydrolysis is also likely. Bromide and iodide were primarily chosen for further investigations due to their excellent selectivity. Most of the water-solubility of the catalyst derives from the cation. Ammonium salts were chosen as primary candidates as these are among the most effective organic catalysts for the coupling of CO_2 and epoxides.

Salts containing multiple hydroxy groups as well as amphiphilic cations and simple small cations were investigated. These cations need to be mostly insoluble in butylene carbonate and they must be thermally and chemically stable. Quaternary onium salts of tertiary amines should be more stable than simple base HX adducts as they cannot act as nucleophiles after deprotonation. Ethanol amines and polyamines represent attractive precursors: they are commercially available and relatively cheap (Scheme 15). However, while hydrophilic amine precursors are easily accessible, quaternization of these precursors presented a major synthetic challenge.



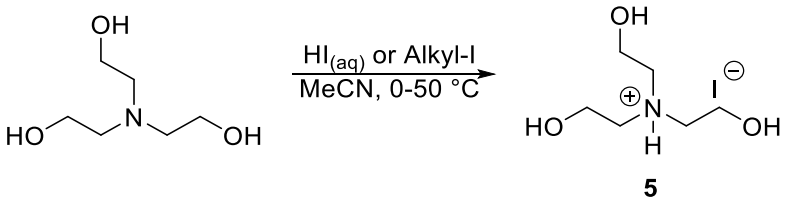
Scheme 15: Precursors for water-soluble catalyst and their cost.[91]

Triethanolamine, diethanolamine and methyl diethanolamine were the first precursors considered. By alkylation with a lipophilic electrophile like 1-iodododecane, surface active compounds can be obtained (Scheme 16). These were envisioned to be more effective catalysts than purely hydrophilic compounds.



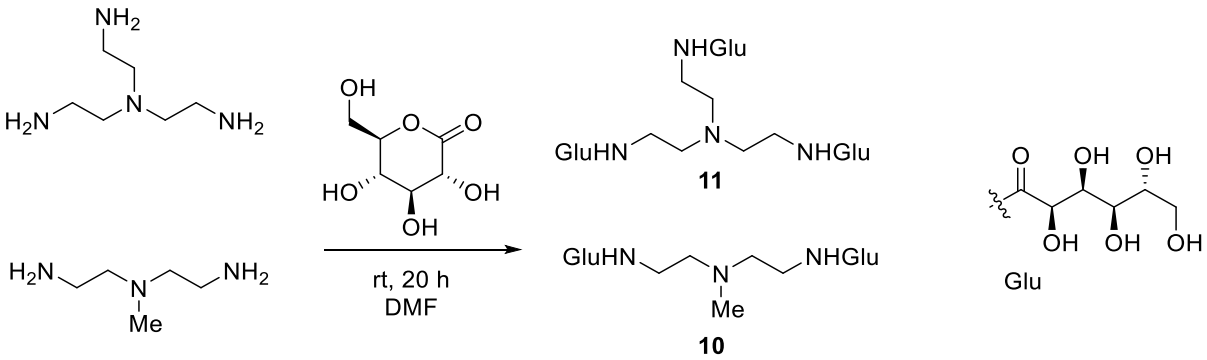
Scheme 16: Synthesis of catalysts 6 and 7 *via* alkylation of ethanol amines.

However, with triethanolamine only HI salt **5** was obtained reliably with 1-iodobutane and 1-iodododecane (Scheme 17).



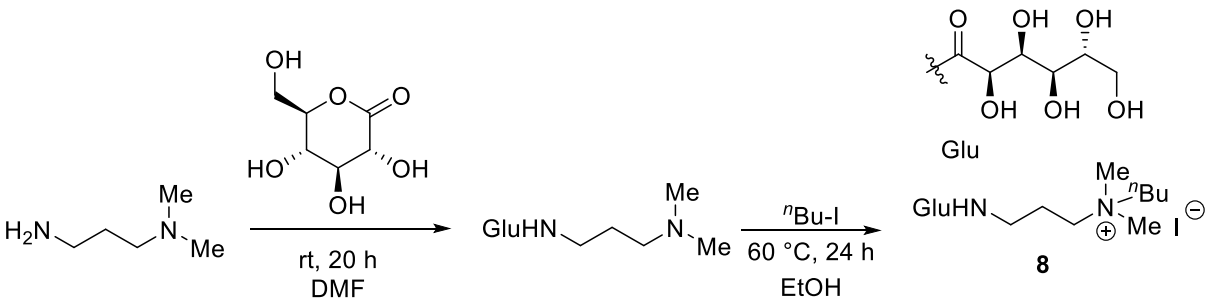
Scheme 17: Synthesis of 5 from triethanolamine and iodides.

Adding a long alkyl chain to the water-soluble amine resulted in a surface-active catalyst. This can be desirable [see Chapter 1.1.3] but also increased the solubility in the organic phase. This can lead to increased leaching (~80 mg/mL solubility in butylene carbonate for **6** and **7**). To further enhance water solubility and reduce the solubility butylene carbonate, more hydroxy moieties were introduced. Therefore, compounds **8, 10** and **11** were prepared from polyamines and *D*-glucono lacton (Scheme 18).[92]



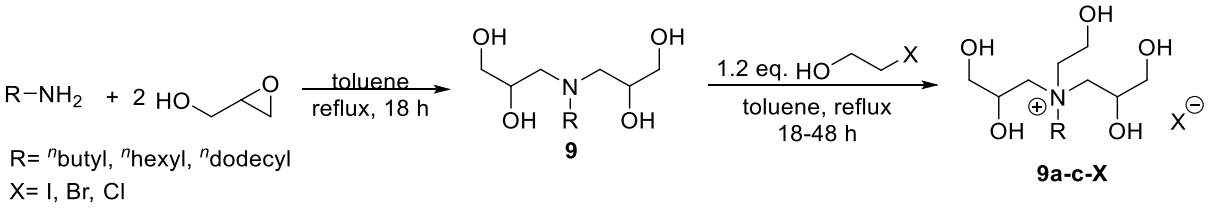
Scheme 18: Synthesis of precursors 10 and 11.

These were by far the most hydrophilic compounds investigated in this work. Unfortunately, these tertiary amines were poor nucleophiles and only **8** could reliably be synthesised (Scheme 19).



Scheme 19: Synthesis of catalyst 8.

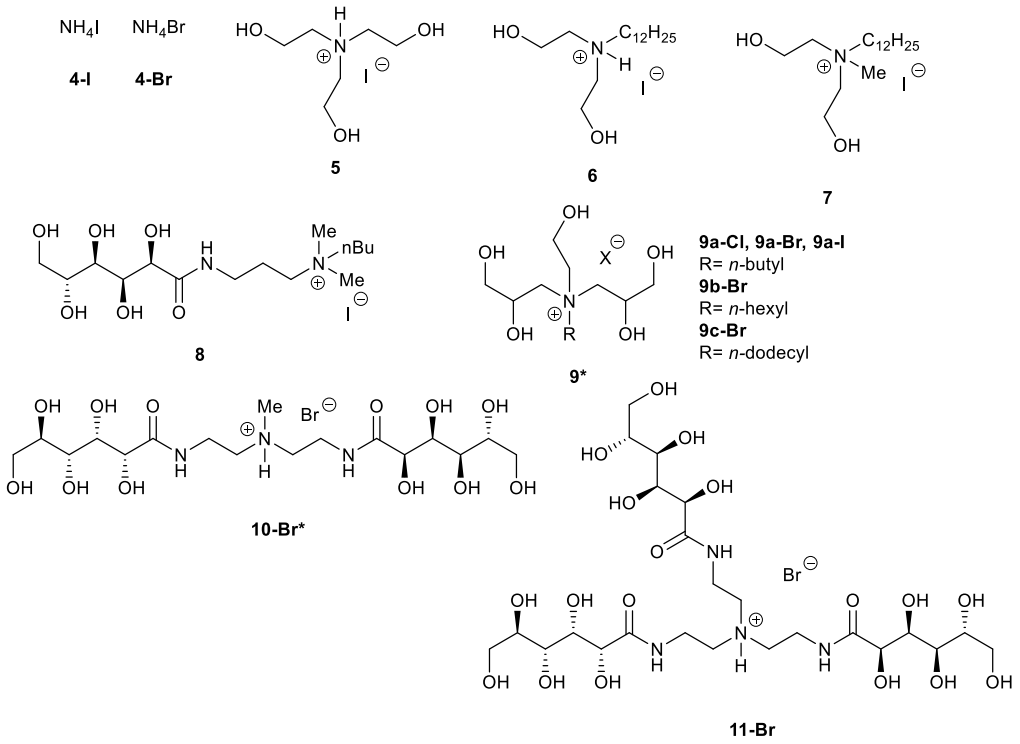
The insolubility of precursors **10** and **11** in organic solvents as well as the high steric hindrance at the central *N* atom are the likely reason for their low nucleophilicity towards alkylation agents. Alternative routes involving protection of the primary amine moieties and quaternization prior to introduction of the hydrophilic parts were unsuccessful. Therefore, their HBr salts, **10-Br** and **11-Br**, were investigated instead. The precursors **9a-c** were obtained from primary amines and glycidol[93], followed by quaternization with halohydrins (Scheme 20).



Scheme 20: Synthesis of catalyst 9a-c with I^-, Br^- and Cl^- anion.

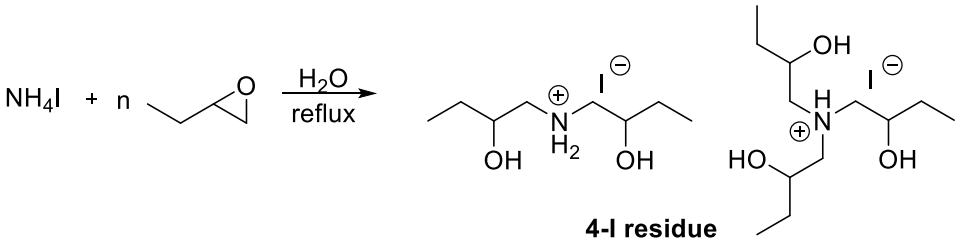
By using primary amines with varying alkyl chain length, hydrophilic precursors with varying amphiphilic character can be obtained. Most importantly, these precursors can be reliably quaternised. This enables a high degree of modifiability, which can be useful when adapting to different substrates with varying polarity [see Chapter 1.3.4]. **9a-Cl, 9a-Br** and **9a-I** are also insoluble in butylene carbonate.

The screening results for these hydrophilic ammonium salts (Scheme 21) are listed in Table 3.



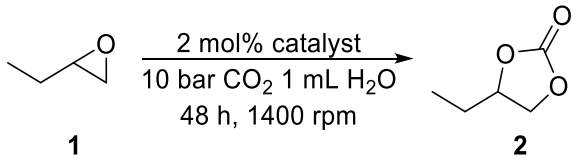
Scheme 21: Investigated water-soluble catalysts for the carboxylation of BO.

The simplest ammonium salts, NH_4I (**4-I)** and NH_4Br (**4-Br)**, exhibit remarkably high activity (97 % and 98% conversion) and selectivity (98% and 96%) towards butylene carbonate **3.** However, their recyclability is poor. After recycling, 1,2-butan diol **2** is formed as major product instead of the desired butylene carbonate **3** (Table 3, Entry 3). A control experiment showed that these ammonium salts react with butylene oxide to different amino butanols which are much more lipophilic than NH_4^+ (Scheme 22).



Scheme 22: Formation of a lipophilic catalyst from NH_4I and butylene oxide.

This mixture, **4-I-residue**, was as effective as catalyst as NH_4I itself (Table 3, Entry 4). This suggests that NH_4I and NH_4Br act merely as water-soluble precursor to a more lipophilic catalyst. The catalysis then takes place in the organic phase. As a result, the aqueous phase is mostly devoid of active catalyst at the end which makes recycling impossible.



1 2

Scheme 23: General conditions for the screening of water-soluble catalysts.

Table 3: Screening of water-soluble catalysts according to Scheme 10.

Entry	Catalyst	Conversion BO [%]	Yield BC [%]	Selectivity BC [%]
1	4-I	97	97	98
2	4-Br	98	95	96
3[d]	4-Br	>90	trace	n.d
4	4-I residue	98	95	96
5[b,c]	5	40	37	92
6	5	52	49	93
7[b,c]	6	64	62	95
8	6	77	71	92
9[d]	6	8	4	50
10	7	70	65	92
11[d]	7	41	31	74
12	8	59	56	94
13	9a-Br	93	85	92
14[d]	9a-Br	94	86	93
15[e]	9a-Br	93	84	90
16[f]	9a-Br	91	53	58
17[g]	9a-I	99	97	98
18[d,g]	9a-I	99	94	95
19[e,g]	9a-I	88	57	65
20[h]	9a-Cl	73	19	26
21	10-Br	58	46	80
22	11-Br	97	89	91

General conditions: 2 g butylene oxide, 2 mol% catalyst, 1 mL H_2O, 110 °C, 10 bar CO_2, 48 h, 1400 rpm, yields determined by GC-FID. b) 500 rpm, 5 bar c) 4 h, d) aqueous phase reused, e) aqueous phase reused for a second time, f) third reuse; g) 5.81 g butylene oxide, 2 mol% catalyst, 6 mL H_2O, 110 °C, 5 h, 20 bar CO_2 h) 2 mol% catalyst, 20 bar CO_2, 5 h

Moving from the primarily hydrophobic TBAI (Table 2, Entry 3) to the primarily hydrophilic **5** lead to a sharp drop in conversion from 98% to just 40%. Notably the selectivity towards the

carbonate is still >90%. Conversion could be increased slightly to 52% by stronger agitation of the reaction mixture and a prolonged reaction time. The surfactant type catalyst **6** performed significantly better, reaching 64% conversion at 95% selectivity in 4 h. By raising agitation and the reaction time the conversion was increased to 77% with a small drop in selectivity. Recycling of **6** failed, only 8% conversion was observed when the aqueous phase of the previous run was reused. [Catalyst recycling and decomposition is discussed in greater detail in chapter 1.3.3]. For catalyst **7**, the ammonium is methylated instead of protonated. The catalyst performance is similar with 70% conversion at 92% selectivity. Recyclability is notably better for **7** with 41% conversion at 74% selectivity in the second run (Entry 10-11). Amphiphilic catalyst **8** has a more hydrophilic headgroup and shorter tail. While selectivity is high with 94% the conversion is low reaching only 59% after 48 h (Entry 12). Similarly, catalysts **9a-Cl**, **9a-Br** and **9a-I** have a more hydrophilic headgroup with three additional hydroxy moieties and a significant shorter butyl tail. While for **9a-Cl** the conversion does reach 73% the selectivity towards the carbonate is with 26% much lower than for its hydrophobic counterpart TBACl (Table 2, Entry 1 and Table 3, Entry 20). Being the least effective halide catalyst, the low solubility of the catalyst in the organic phase might exacerbate the problem. **9a-Br** and **9a-I** on the other hand showed promising results. Conversion reached 93% for **9a-Br** and was near quantitative for **9a-I** with 92% and 98% selectivity respectively. The recyclability for both catalysts was also notably better: **9a-Br** remained stable for 3 runs and **9a-I** for 2 runs. For further runs a significant deterioration in performance was observed (Table 3, Entry 13-20). Nevertheless, this proves that recycling of **9a** by recycling of the aqueous phase is viable. The two purely hydrophilic HBr salts **10-Br** and **11-Br** exhibit vastly different activities. **10-Br** reaches only 58% conversion after 48 h were as **11-Br** reaches 97%. Despite their excellent water solubility, **10-Br** and **11-Br** were not recyclable, likely due to thermal instability as indicated by a strong coloration of the reaction mixture. The better performance of **11-Br** could be related to a higher stability or stronger dissociation of HBr. Catalysts **9a-Br** and **9a**-I high activity and selectivity towards the carbonate as well as their recyclability make them the most suitable subjects for further investigation in the following chapters. **9a-Br** was chosen over **9a-I** despite lower activity as **9a-I** was less stable, showing a significant loss of selectivity in the third run. For **9a-Br** a significant loss of selectivity was observed after the fourth run. **9a-I** also visibly darkens upon prolonged storage and the presence of I_2 was detected *via* iodine-starch test.

1.3.2 Optimization of reaction conditions

Reactions for the optimization were performed in duplicate to ensure reproducibility and additional experiments were performed if the discrepancies were larger than 5%. To establish a reasonable timeframe for the reaction a time-conversion measurement was performed (Figure 2).

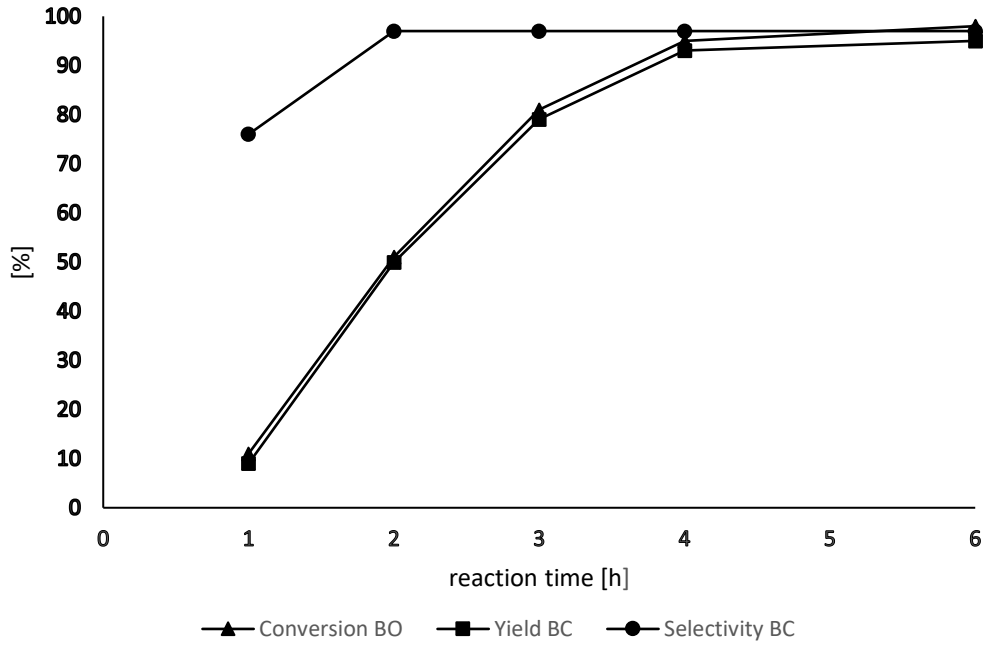


Figure 2: Reaction time profile of the carboxylation of butylene oxide.

Conditions: 27.7 mmol butylene oxide, 2 mol% **9a-Br**, 1 mL H_2O, 10 bar CO_2, 110 °C, 1400 rpm, yields determined by GC-FID.

Most of the conversion is finished after 3 h and almost quantitative conversion is achieved after 6 h. Interestingly, the selectivity after 1 h is with 76% much lower than during the rest of the reaction with 97%. In addition, the selectivity is also lower after 48 h with 92%. This suggest that the side product 1,2-butan diol **2** is primarily formed at the beginning of the reaction and then much slower through hydrolysis of butylene carbonate **3**. A control experiment showed that butylene carbonate is not formed from 1,2-butan diol **2** under these conditions. Carbonate formation likely overtakes the hydrolysis side reaction after a short induction period (<1 h). A possible reason is the low temperature at the start of the reaction. While the heating block is preheated to the desired temperature, the autoclave and its contents start out at room temperature. If lower temperatures favour the hydrolysis, the rate of side product formation should be at its highest at this point. The temperature profile supports this hypothesis (Figure 3).

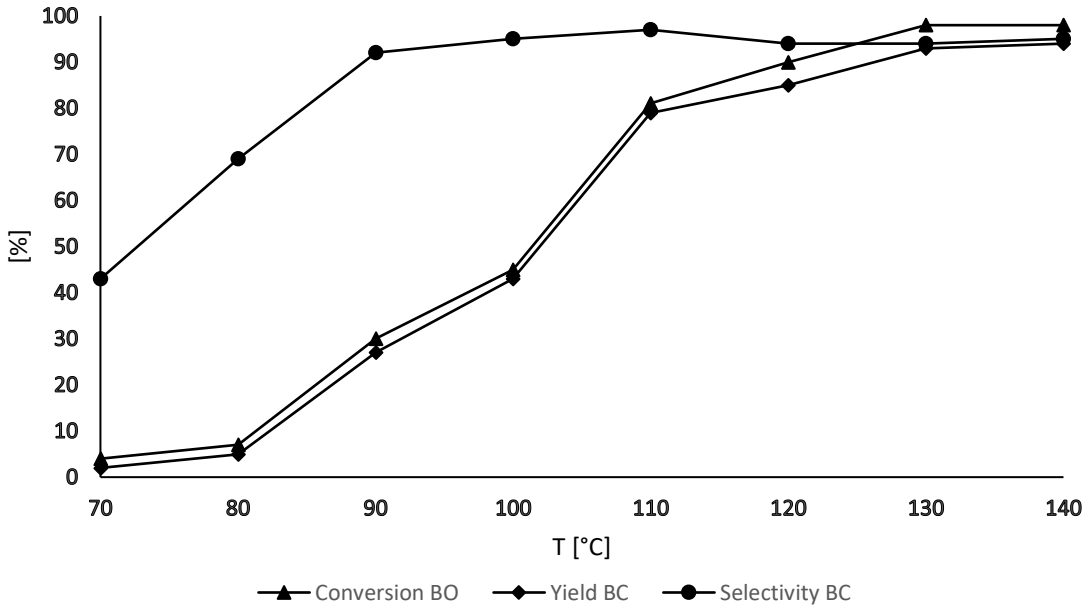


Figure 3: Influence of temperature on the carboxylation of butylene oxide.

Conditions: 27.7 mmol butylene oxide, 2 mol% **9a-Br**, 1 mL H_2O, 10 bar CO_2, 3 h, 1400 rpm, yields determined by GC-FID.

At 70 °C the reaction is slow with only 4% conversion after 3 h. The selectivity is also low with 43%. While the reaction is still slow at 80° C, selectivity already reaches 69%. At 90 °C the selectivity towards butylene carbonate **3** reaches 92%. A further increase in temperature mainly affects the conversion, though the selectivity reaches its maximum of 97% at 110 °C. While the reaction is overall exothermic, the sluggish conversion at lower temperatures can be explained by the relatively high activation barrier of 24-36 kJ/mol[51] for the ring opening step. Though ring opening is the first step for both hydrolysis and CO_2 insertion, the latter benefits more from higher temperatures. The decline in selectivity at temperatures above 110 °C might be due to increased hydrolysis of **3**. Alternatively, hydrolysis of the epoxide **1** could also be accelerated. As the solubility of **1** in water increases with rising temperatures, phase transfer is enhanced. This allows more substrate to be in contact with the catalyst. If the concentration of **1** in the aqueous phase increases too much, hydrolysis is also increased. Solubility of CO_2 in water also decreases with temperature, reducing the amount of CO_2 available in the aqueous phase.

Next, the effect of the CO_2 pressure on the reaction was investigated (Figure 4). Starting at 5 bar, conversion of BO **1** reaches 78% with selectivity of 88% towards BC **3**. This means that the CO_2 concentration the of solution is already high enough to favour CO_2 insertion over hydrolysis.

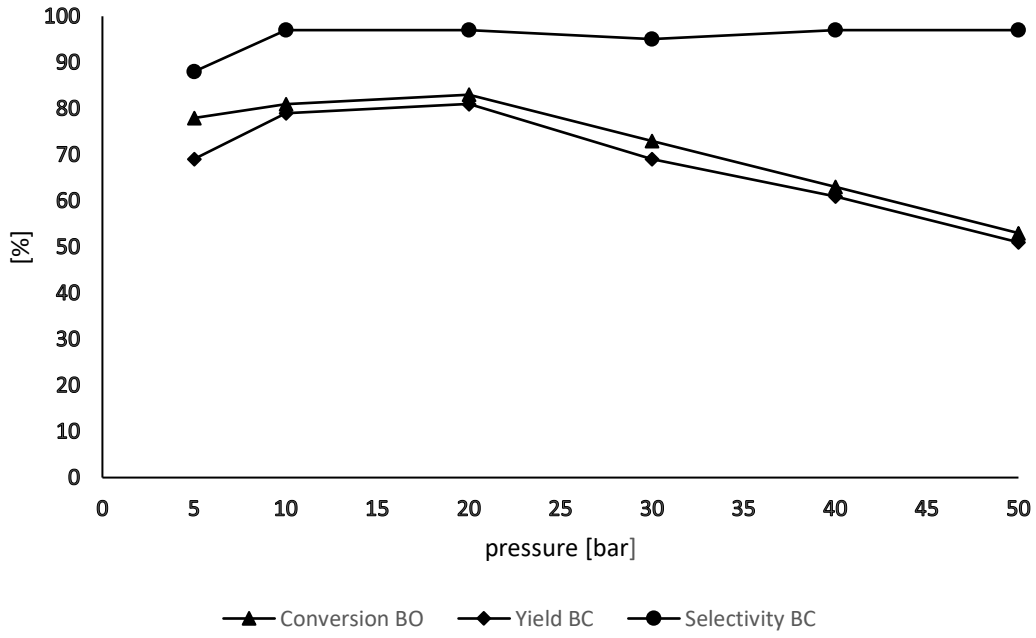


Figure 4: Influence of CO_2 pressure on the carboxylation of butylene oxide

Conditions: 27.7 mmol butylene oxide, 2 mol% **9a-Br**, 1 mL H_2O, 110 °C, 3 h, 1400 rpm, yields determined by GC-FID.

At 10 bar the selectivity already reaches its maximum of 97% and a slight increase in conversion. At 20 bar a slightly higher conversion is achieved. As the acidity of the aqueous phase and therefore the H_3O^+ concentration increases with pressure, the increase in conversion could be due to the fact that oxonium is a stronger hydrogen bond donor than H_2O. Any further increase in pressure leads to a significant decrease in conversion. As the presence of CO_2 can have a profound effect on the solubility of organic compounds in water, it is likely that that the mass transfer between the two phases is inhibited by high CO_2 concentration [see Chapter 1.1.3]. This effect becomes more pronounced with higher pressure. The hydrolysis side reaction should also be affected by this, explaining the retention of the high selectivity. Notably, the fact that >80% selectivity can be achieved at pressures ≤ 5 bar is quite interesting from an engineering standpoint. Reactor concepts with more efficient ways to introduce gaseous reactants could further reduce the amount of CO_2 required.

Mass transfer between two separate phases is greatly affected by the size of the surface area at the phase boundary [see Chapter 1.1.3]. This means the reaction should be greatly affected by the agitation provided by the stirrer (Figure 5).

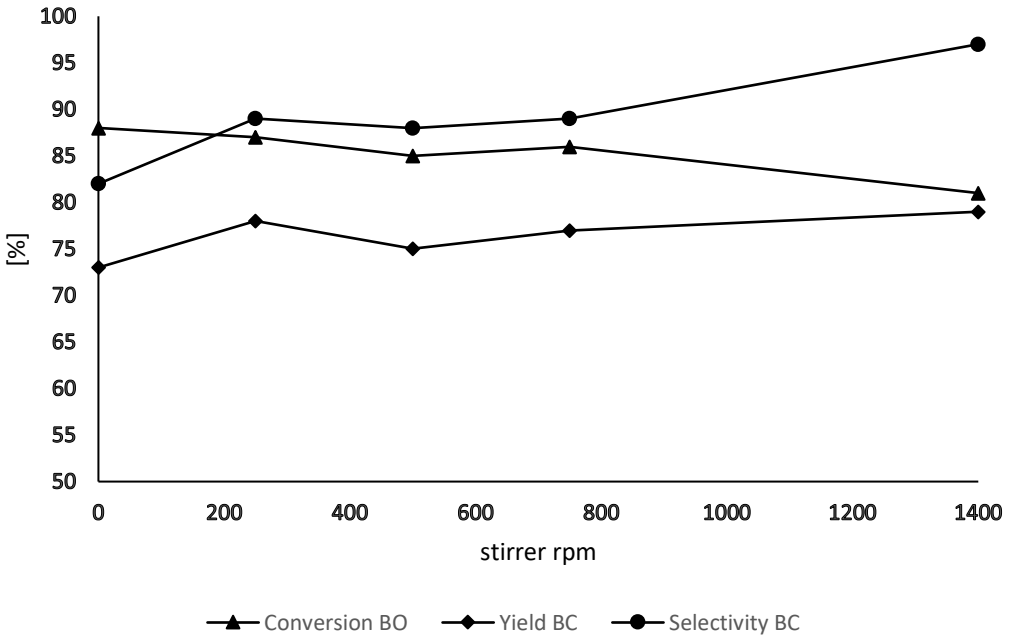


Figure 5: Influence of agitation on the carboxylation of butylene oxide

Conditions: 27.7 mmol butylene oxide, 2 mol% **9a-Br**, 1 mL H_2O, 110 °C, 20 bar CO_2 3 h, yields determined by GC-FID.

Surprisingly the agitation has little impact on the overall performance. Even without any stirring 88% of BO is transformed with high selectivity. With stirring the selectivity increases to 89%. Between 250 rpm and 750 rpm the performance remains largely unchanged. Due to the substrates relatively high (59 g/L) and the products low (7 g/L) solubility in water mass transfer might be fast enough even without an enhanced surface area. While the butyl chain of **9a-Br** is too short to be considered as a true surfactant, it could still act as short chain amphiphile increasing its concentration at the interface. These compounds sometimes act as hydrotrope, meaning **9a-Br** could increase the solubility of butylene oxide in the aqueous phase.[94] Another possibility is the formation of a single-phase system during the reaction. As the solubility of butylene oxide in water should increase with temperature, thermomorphic behaviour might be the culprit. However, a control experiment in a glass autoclave revealed that the reaction system retained its biphasic properties throughout the reaction. Increasing the agitation further to 1400 rpm finally resulted in another increase in selectivity. At this speed the mixture is more turbid than at lower speeds, indicating a finer microemulsion of the two phases (Figure 6).

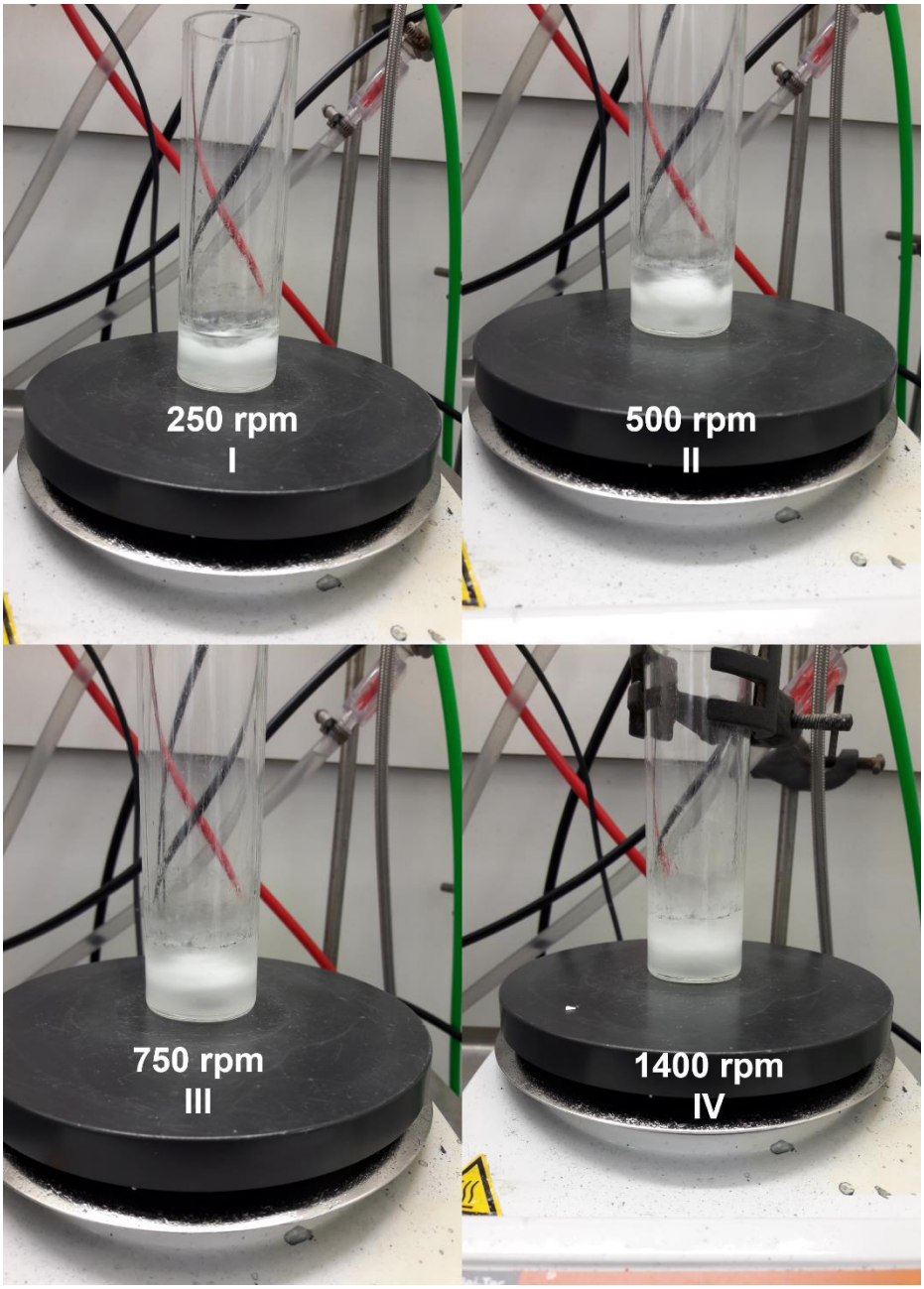


Figure 6: Butylene oxide/water mixture at 250; 500; 750 and 1400 rpm.

As seen in Figure 6, at 250 rpm (I) and 500 rpm (II) two distinct phases are visible: a turbid emulsion in the aqueous phase and a clear butylene oxide phase. At 750 rpm (III) the phases are mostly dispersed and at 1400 rpm (IV) full dispersion was achieved. The resulting emulsion is unstable and completely separates within 30 min. Next, the influence of the water/substrate ratio and catalyst load was investigated (Table 4).

Table 4: Influence of catalyst load and water/substrate ratio.

Entry	9a-Br concentration [mol%]	Water/Substrate ratio [V/V]	Conversion [%]	Yield [%]	Selectivity [%]
1	0.1	4/5	23	5	20
2	0.5	4/5	32	21	69
3	1	4/5	77	72	95
4	2	4/5	81	79	97
5	2	6/5	77	75	97
6	2	2/5	81	77	95
7	2	1/5	92	86	93

Conditions: 27.7 mmol butylene oxide, 110 °C, 20 bar CO_2 3 h, 1400 rpm, yields determined by GC-FID.

At very low catalyst concentration the hydrolysis of the epoxide **1** is the dominant reaction (Entry 1), since it can occur without **9a-Br**. With 0.5 mol% catalyst a selectivity of 69% is achieved with one third of the substrate consumed. This indicates that the catalysed carbonate formation is much faster than the epoxide hydrolysis. An excellent selectivity of 95% and 77% conversion are already obtained at 1 mol% catalyst load. A further increase to 2 mol% nets only a small increase in conversion and selectivity. However, as high selectivity is crucial for efficiency and **9a-Br** is not an expensive catalyst, 2 mol% were chosen as standard. Lowering the water to substrate ration slightly decreases selectivity while increasing conversion, indicating that more hydrolysis took place. A smaller water phase (and therefore smaller catalyst phase) would mean that the water phase gets saturated faster with butylene oxide, limiting the amount of butylene oxide that can participate in the catalytic cycle at any given time. This slowed the epoxide conversion down while the hydrolysis can proceed uncatalyzed with water dissolved in the organic substrate phase. Increasing the water to substrate ratio slightly slows the conversion, possibly due to dilution effects.

As previously discussed [Chapter 1.1.1], CO_2 reacts acidic with water. Higher pressure further increases the acidity and epoxide hydrolysis is catalysed by protons. To investigate if this impacts the systems selectivity, *N,N,N*-tris-(ethane)-D-gluconamide **11**, the free base form of catalyst **11-Br**, was added. Under reaction conditions an ammonium hydrogen carbonate is formed which should act as a buffer. This base was selected due to its high hydrophilicity and it is completely insoluble in butylene carbonate. Additionally, it is non-nucleophilic as

demonstrated by unsuccessful alkylation attempts [see Chapter 1.3.1]. The results are listed in Figure 7. Reaction time was increased to 5 h for higher conversion.

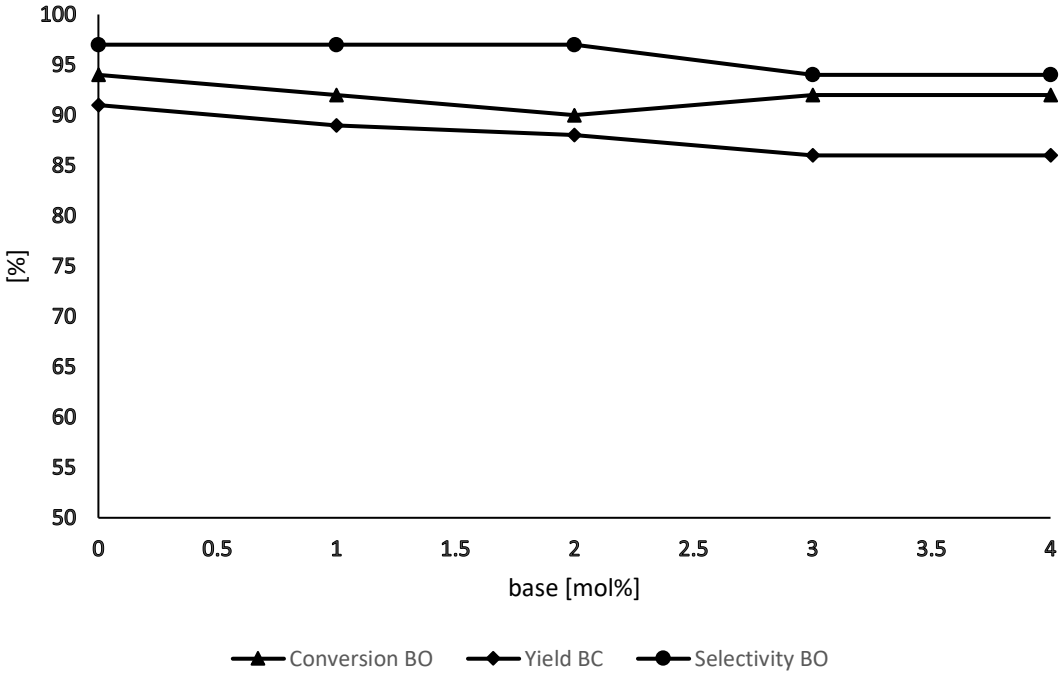


Figure 7: Influence of base additive on the carboxylation of butylene oxide.

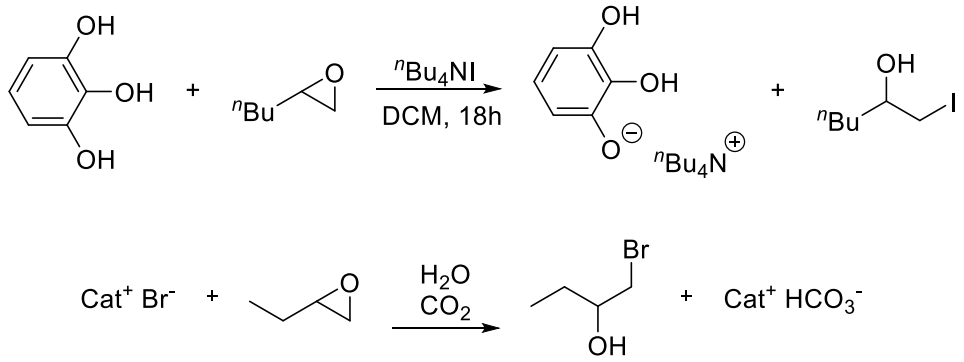
Conditions: 27.7 mmol butylene oxide, 2 mol% **9a-Br**, 2 mol% *N,N,N*-tris-(ethane)-D-gluconamide **11** added, 2 mL H_2O, 110 °C, 20 bar CO_2, 6 h, yields determined by GC-FID.

The impact of this buffer was small. Selectivity remained unchanged until a base load of 3 mol% was reached, where it dropped from 97% to 94%. The presence of the base also very slightly decreased conversion. The low impact of the reaction mixtures acidity can be attributed to the comparatively high stability of terminal epoxides towards hydrolysis.

After these investigations the optimal conditions were determined as: 2 mol% catalyst load with **9a-Br**, 110 °C, 20 bar CO_2, 5 h reaction time, 1400 rpm stirring speed and a water to butylene oxide ratio of 4/5. Under these conditions conversion of the butylene oxide **1** was 94% at 97% selectivity, resulting in 91% yield of butylene carbonate **3**. With catalyst and conditions established, catalyst recycling and decomposition was investigated in more detail.

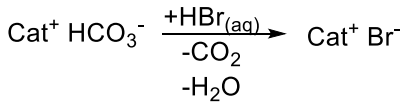
1.3.3 Catalyst recycling

While the recycling of **9a-Br** and **9a-I** *via* reuse of the aqueous catalyst phase was successful, the catalysts show signs of significant catalyst deactivation after the third and second reuse, respectively. Thermal decomposition, leeching and loss of the nucleophilic anion were investigated as the most likely culprits. Thermal analysis shows that **9a-Br** starts to decompose at 221 °C, much higher than the reaction temperature (see experimental section for details). Additionally, stirring **9a-Br** for 24 h in water at 110° C under 20 bar CO_2 prior to addition of butylene oxide does affect the performance: conversion drops from 94% to 90% and selectivity drops from 97% to 93%. No change in colour was observed after reactions with **9a-Br** unlike with **10-Br** and **11-Br**. To combat potential leeching, diethyl ether was added to the organic phase to decrease polarity and in turn decrease the solubility of the catalyst as well as the miscibility with the aqueous phase. This did however not resolve the issue. Loss of the nucleophilic anion can occur in the final step of the catalytic cycle.[44] This would result in a HCO_3^- species which is a poor catalyst as previously established (Scheme 24).



Scheme 24: (Top) catalyst decomposition in presence of hydrogen bond donor reported by KLEIJ[44] and (bottom) potential catalyst deactivation path in this work.

A similar catalyst deactivation path was reported by SERRA[95] and KLEIJ[44] when quaternary ammonium salts were used as epoxide carboxylation catalysts in presence of hydrogen bond donors. The effect should only be noticeable after several runs, as catalyst **9a-Br** remains highly selective at lower catalyst concentrations (Table 4, Entry 2-3). This effect might be more pronounced if HX adducts are used instead of quaternised ammonium salts. The quaternary catalysts investigated were generally more stable than the HX catalysts (Table 3, Entry 9 and 11). Addition of a small amount of HBr should be sufficient to regenerate the catalyst (Scheme 25). Batch size has been increased to reduce the effect of potential incomplete recovery of the aqueous phase.



Scheme 25: Potential catalyst regeneration with HBr.

Indeed, by addition of 0.5 mol% HBr (48 %wt in H_2O, 25% of catalyst load) after each run, the catalyst degradation is greatly slowed down (Figure 8 and 9, Run 1-6). As HBr itself is poor catalyst (Figure 8), the restored activity should be attributed to **9a-Br**.

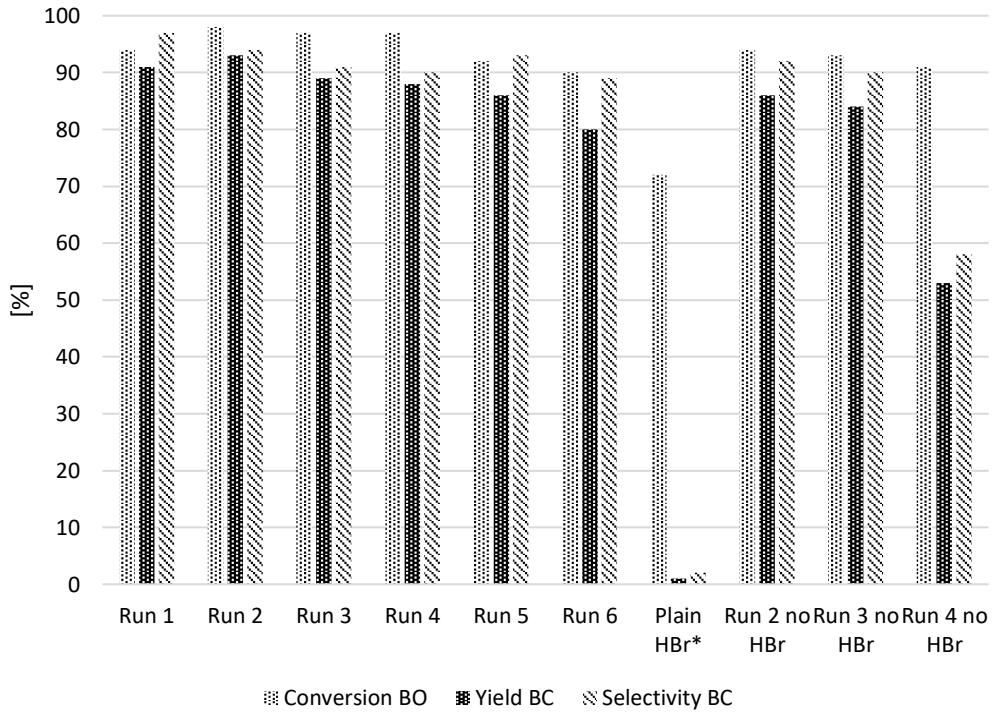


Figure 8: Catalyst recycling with and without regeneration *via* HBr addition.

Conditions: 80.7 mmol **1**, 2 mol% **9a-Br**, 20 bar CO_2, 110 °C, 1400 rpm, 5 mL H_2O, 5 h,*) 48%wt in H_2O, yields determined by GC-FID.

Taking the regeneration into account an accumulative TON of 263 is achieved over 6 runs and an average TON of 44.

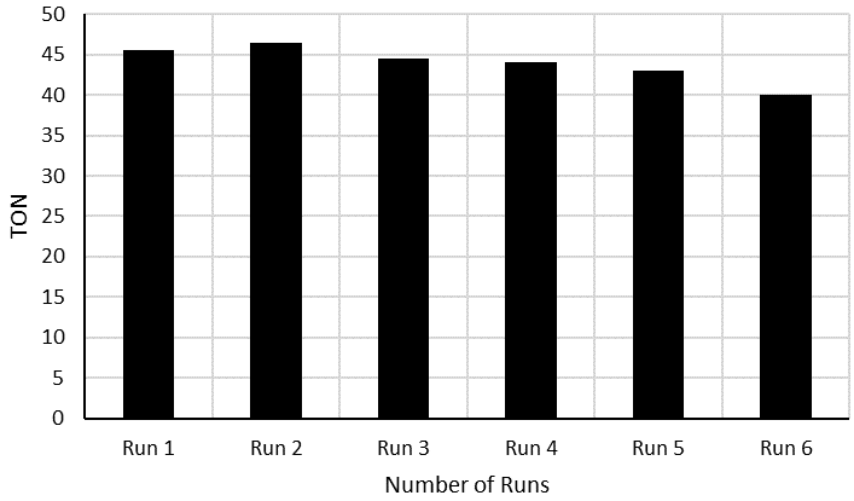


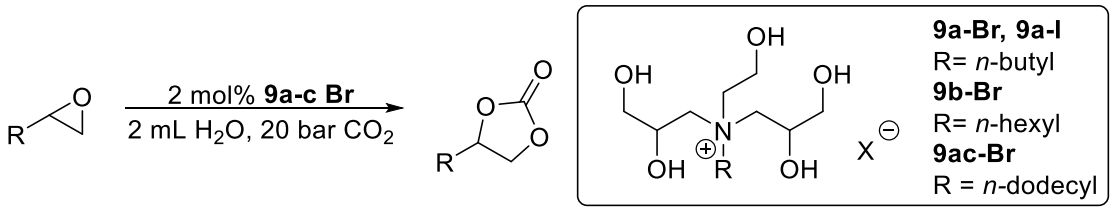
Figure 9: TON per Run with catalyst regeneration by HBr.

Conditions: 80.7 mmol **1**, 2 mol% **9a-Br**, 20 bar CO_2, 110 °C, 1400 rpm, 5 mL H_2O, 5 h,*) 48%wt in H_2O, yields determined by GC-FID.

The remaining degradation might be due to leaching or simply non-quantitative recovery of the catalyst containing aqueous phase. The latter is likely to occur, as the experimental setup is a discontinuous system. Having shown that the system is recyclable as well as the ability of the catalyst to be regenerated, the scope of this method was further investigated.

1.3.4 Substrate Scope of the developed biphasic system

Industrially relevant propylene oxide and three increasingly hydrophobic epoxides (1,2-epoxy hexane, 1,2-epoxy dodecane and 1,2-epoxy hexadecane), glycidol, epichlorohydrin and styrene oxide as functionalized epoxides as well as cyclohexene oxide as internal epoxide have been chosen for evaluation of the substrate scope (Scheme 26, Table 5).



Scheme 26: General reaction conditions of the substrate scope.

Table 5: Carboxylation of various epoxides under aqueous biphasic conditions.

Entry	Catalyst	R	Carbonate yield [%]	Selectivity [%]
1[k]	**9a-Br**	Me	94	95
2[h]	**9a-Br**	Ph	60	60
3[b]	**9a-I**	Ph	38	38
4[b,c]	**9a-I**	Ph	51	71
5[c]	**9a-Br**	Ph	13	61
6[i]	**9a-Br**	Ph	22	80
7	**9a-Br**	*n*-C_4H_9	15	67
8[d]	**9a-Br**	*n*-C_4H_9	84	85
9[e]	**9b-Br**	*n*-C_4H_9	48	92
10[f]	**9c-Br**	*n*-C_4H_9	46	97
11	**9a-Br**	*n*-$C_{10}H_{21}$	0	99
12[g]	**9a-Br**	*n*-$C_{10}H_{21}$	26	90
13[f]	**9c-Br**	*n*-$C_{10}H_{21}$	48	75
14[e]	**9b-Br**	*n*-$C_{10}H_{21}$	78	92
15	**9a-Br**	*n*-$C_{14}H_{29}$	0	99
16[f,g]	**9c-Br**	*n*-$C_{14}H_{29}$	trace	99
17[k]	**9a-Br**	CH_2Cl	45	61

General conditions: 27.7 mmol epoxide, 2 mol% **9a-Br**, 20 bar CO_2, 2 mL H_2O, 3 h, 1400 rpm; yield determined by NMR; b) 2 mol% **9a-I**; c) 80 °C; d) 48 h; e) **9b-Br**; f) **9c-Br**; g) 20 h; h) 10 bar, 3 h; i) 2 mol% *N,N,N*-tris-(ethane)-D-gluconamide; k) yields determined by GC-FID.

Propylene oxide (PO) shows very similar results to the model substrate (BO) even though its water solubility is significantly higher. Propylene carbonate (PC) is obtained in 94% yield (Entry 1). As the length of the epoxide chain R increases the water-solubility decreases. This limits the substrates mass transfer into the aqueous catalyst phase and results in slower conversion of the substrate. Higher yields can be obtained by employing surfactant style catalysts **9b-Br** (R=6) and **9c-Br** (R=12) (Entry 7-14). These increase the amount of available catalyst at the surface interface were in this case most of the reaction with hydrophobic substrates should take place (see Chapter 1.1.3). Changing the alkyl chain of **9a-Br** from butyl to hexyl (**9b-Br**) and dodecyl (**9c-Br**) increase yields of hexene carbonate from 15% (Entry 7, **9a-Br**) to 48% (Entry 9, **9b-Br**) and 46% (Entry 10, **9c-Br**) and the selectivity increases greatly from 67% (**9a-Br**) to 92% (**9b-Br**) and 97% (**9c-Br**) respectively (Entry 7; 9; 10). For 1,2-epoxy

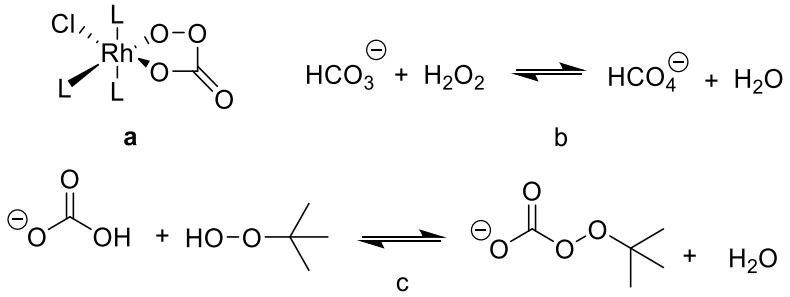
dodecane, no conversion is observed after 3 h when **9a-Br** is used. Utilizing the surfactant catalyst **9b-Br** the 1,2-dodecane carbonate is formed with 78% yield and 92% selectivity (Entry 11-14). 1,2-epoxy hexadecane did not react at all under biphasic conditions. Epoxides prone towards hydrolysis are expectably transformed with lower selectivity with acid catalysed epoxide hydrolysis as side reaction (Table 5, Entry 2-6; 17). It is accelerated under the present conditions as CO_2 reacts with water by formation of carbonic acid. At higher CO_2 pressures the pH value decrease to 3. The pH of the aqueous medium has been reported to have a significant effect on the regioselectivity of the ring opening of epoxides by nucleophiles, which in turn could affect the rest of the catalytic cycle. In order to test if this has a profound effect on catalyst performance, some of the substrates in this scope were tested under different conditions. These include lower temperatures and pressure as well as the use of a base as buffer. In case of butylene carbonate no significant change in performance has been observed in presence of a base. Full conversion of styrene oxide with 60% selectivity towards styrene carbonate was achieved with **9a-Br** in 3 h under 10 bars of CO_2 (Table 5, Entry 2). With **9a-I** only 38% selectivity was achieved. However, lowering the temperature to 80 °C led to an increase in selectivity to 71% and yield to 51% for styrene carbonate. Addition of 2 mol% *N,N,N*-tris-(ethane)-D-gluconamide **11** further increased selectivity to 80% but reduced the yield to 22%, due to lower conversion. If **9a-Br** is used with a base yield drops to 13% with no change in selectivity (Entry 3-6). The oxonium ion is a better hydrogen bond donor than H_2O and accelerates the ring opening step, explaining the difference in epoxide conversion. If the CO_2-insertion is not fast enough, protonation of the HBD stabilized halohydrin intermediate is more likely under acidic conditions leading to lower selectivity.

2 Direct Synthesis of cyclic Carbonates from Olefins, H_2O_2 and CO_2

2.1 Theoretical Background

2.1.1 Epoxidation with H_2O_2

Hydrogen peroxide is an attractive oxidant for green oxidations. It produces only water as by-product and is less dangerous and easier to activate than oxygen.[96] As such it has gained much attention as an oxidant for epoxidation reactions. Various catalysts have been developed: solid titan silicalite catalysts like TS-1[97–99], polyoxometalates[100,101], W and Mo based catalysts[102], Mn based catalysts[103,104] and other metal catalysts[105] like methyl trioxorhenium (MTO).[105,106] The presence of CO_2 and hydrogen carbonate salts can also have a major impact on epoxidation reaction as pointed out by ARESTA *et al*. in 1987. With a Rh-catalyst in THF styrene was transformed into styrene carbonate in 20% yield under a mixed CO_2/O_2 atmosphere. They postulated that a Rh-peroxocarbonate species was the active catalytic species.[107] In 2000 YAO and RICHARDSON described the epoxidation of various olefins with hydrogen peroxide catalysed ammonium bicarbonate (Scheme 27).[108]



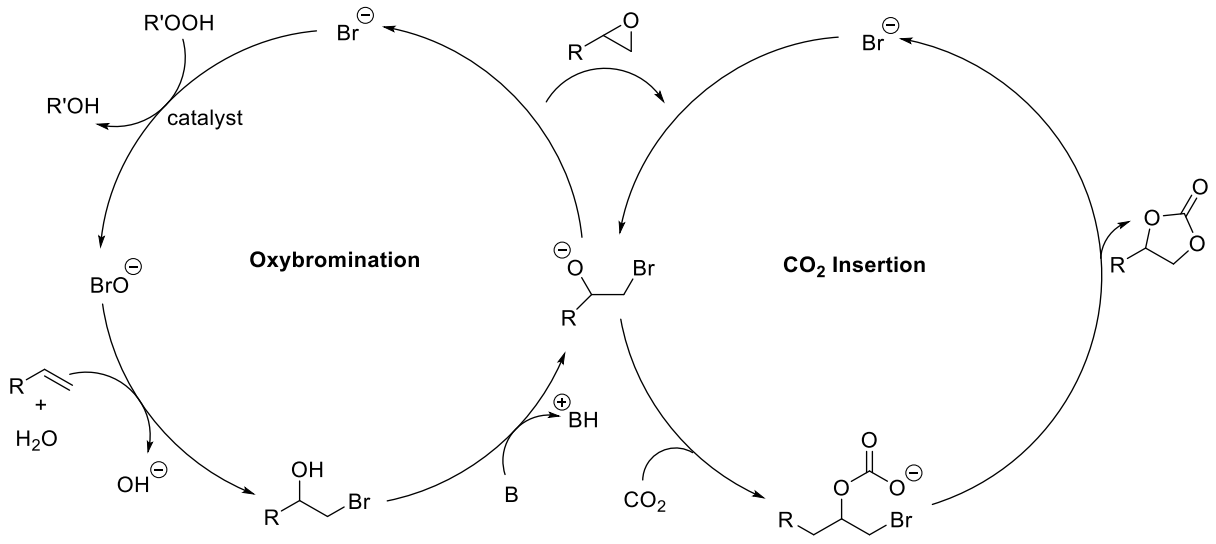
Scheme 27: Various proposed peroxocarbonate species and their formation.[107,108]

Conversion of the olefins was 20-90% and only trace amounts of epoxide products were observed in absence of bicarbonate. Even though the reaction was performed in acetonitrile, the authors claimed that no PAYNE oxidation *via* peroxycarboximidic acid took place as no acetamide was detected. On the other hand, during MIELBY and KEGNÆS investigations, it was observed that acetamide was formed and that none of the employed bicarbonate salts were active in absence of acetonitrile.[109] BURGEES *et al*. reported in 2002 that $MnSO_4$ is an effective epoxidation catalyst with H_2O_2 in DMF when a $NaHCO_3$ buffer was present.[103] The effect of CO_2 on the oxidation of cyclohexene to cyclohexenons with H_2O_2 was investigated in greater

detail by AUOISSI *et al.* in 2017. They found that an increased CO_2 pressure would lead to an increase in cyclohexene conversion from 53% to 70%.[110]

2.1.2 Synthesis of cyclic carbonates from olefins, CO_2 and oxidants.

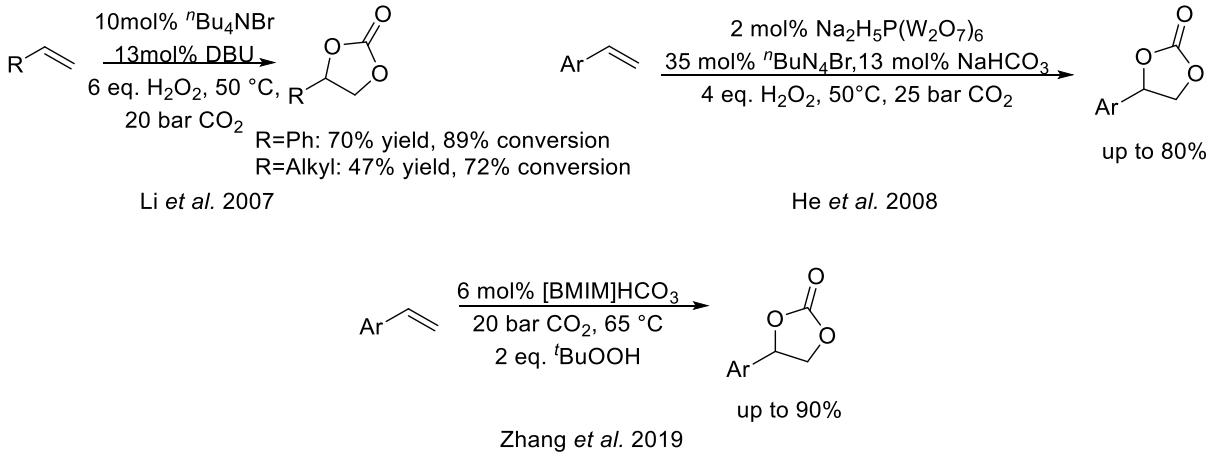
As previously established in Chapter 1.1.2 the coupling of CO_2 and epoxides is an efficient and simple method for CO_2 valorisation. However, epoxides are very reactive, toxic and cancerogenic substrates. A process that would avoid the isolation of epoxides as intermediate product is therefore very desirable. While some one-pot systems for the preparation of cyclic carbonates from olefins have been reported, only a few use H_2O_2 as green oxidant.[111,112] A major challenge for these systems is the lack of compatibility of species involved in the epoxidation step and the carboxylation step as most catalysts for the coupling of CO_2 with epoxides (e.g. iodide) are unstable in the presence of H_2O_2. Instead, *tert*-butyl hydroperoxide (TBHP) is often used in excess as an oxidant in most cases.[103,108,113–118] In some instances, the epoxidation and CO_2 insertion are performed subsequently to avoid the simultaneous presence of CO_2, oxidant and halide containing catalyst. In an opposite approach, bromide salts were used as the catalyst. A halohydrin intermediate, formed *via* oxybromination, participates in the CO_2-insertion (Scheme 28, compare Scheme 2, Chapter 1.1.2).



Scheme 28: Catalytic cycle of the oxybromination and subsequent CO_2-insertion.[112,117,118]

In 2004, ARAI *et al.* used TBABr as catalyst for the one-pot synthesis of styrene carbonate from styrene, CO_2 and TBHP.[118] With 1.5 eq. of oxidant and 11 mol% TBABr a styrene conversion of 94% and a styrene carbonate yield of 38% was achieved under mild conditions, however benzaldehyde, oligomers and other unidentified by-products were also produced in large

quantities. When H_2O_2 was used as the oxidant, only traces of styrene carbonate were formed. LI and HE improved that concept and managed to obtain higher yields of cyclic carbonate with H_2O_2.[117,119] LI used DBU as a base to deprotonate the halohydrin intermediate (Scheme 28). This greatly enhanced the CO_2-insertion step.[119] HE *et al*. used a phosphotungstic acid catalyst and 35 mol% of TBABr as co-catalyst and $NaHCO_3$ as base for the same purpose.[117] Both groups used H_2O_2 in large excess (Scheme 29).



Scheme 29: Examples for the preparation of cyclic carbonates from olefins, CO_2 and oxidants.

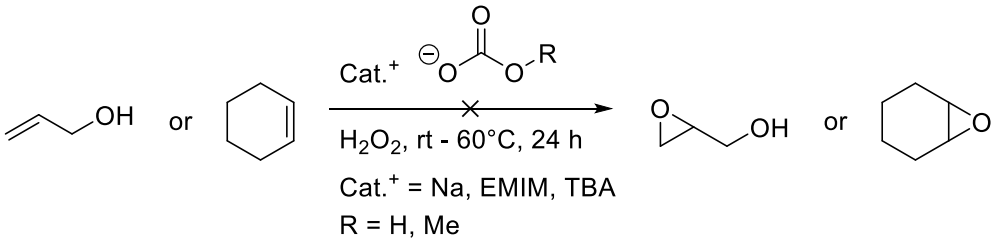
HE *et al*. also reported that styrene carbonate was the main product in presence of CO_2 and $NaHCO_3$ while phenacyl benzoate was selectively formed in absence of $NaHCO_3$. ZHANG *et al*. reported the use of $[BMIM]HCO_3$ as epoxidation catalyst in 2019.[114] With 2 eq. of anhydrous THBP as oxidant, aromatic olefins were transformed into the corresponding organic carbonates with up to 90% yield.

2.2 Aim of this chapter

The goal of this chapter was the development of a one pot synthesis for cyclic carbonates from olefins, aqueous H_2O_2 and CO_2. The explicit goal is to maximize the H_2O_2 efficiency. The oxidant is the more valuable reactant as unreacted olefin can be simply recycled, while decomposed H_2O_2 is simply lost. Therefore, an excess of H_2O_2 is avoided in most reactions presented in this chapter. The potential activation of H_2O_2 by CO_2 [see Chapter 2.1.1] and the rate enhancing effect of water in the coupling of CO_2 and epoxides might offer a unique opportunity for an efficient one pot reaction.

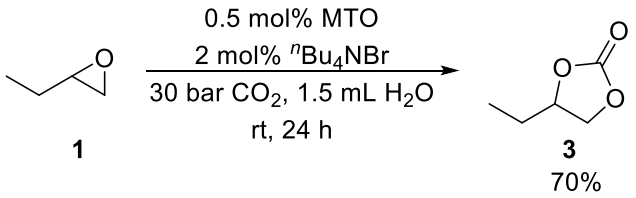
2.3 Results and discussion

More oxidation-stable nucleophilic anions as catalyst for the CO_2-insertion were investigated as a possible solution to the general lack of compatibility between the most active catalysts for the coupling of CO_2 and epoxides (e.g., Br^-, I^-) and H_2O_2. It was found that the catalytic activity of these anions is greatly diminished by oxidation to Br_2 and I_2. Accelerated H_2O_2 decomposition is reducing the resource efficiency of the system and requires an excess of H_2O_2. Therefore, as a first step, a stable catalyst system needs to be found. As HCO_3^- salts have been described as active catalysts for epoxidation reactions, several HCO_3^- and $MeCO_3^-$ ammonium salts have been investigated for their epoxidation ability (Scheme 30).



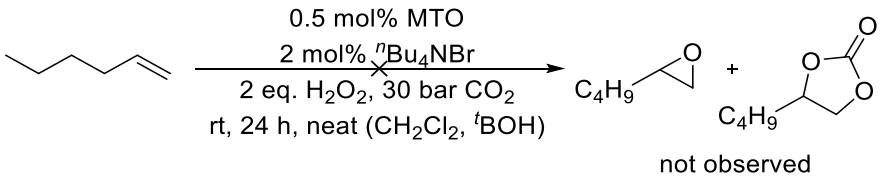
Scheme 30: Attempted epoxidation catalysis with methyl carbonate catalysts.

Unfortunately, none of the used salts exhibited any catalytic activity. Temperature might play a role in the previously discussed H_2O_2 or Br^- decomposition. Therefore, methyl trioxorhenium (MTO) was chosen catalyst. It was anticipated that next to its high epoxidation efficiency under mild conditions, its LEWIS acidity might enhance the CO_2 insertion into the epoxide *via* known mechanisms [Scheme 2, Chapter 1.1.2]. Indeed, by addition of 0.5 mol% MTO, 70% of butylene carbonate was obtained after 24 h at rt (Scheme 31).



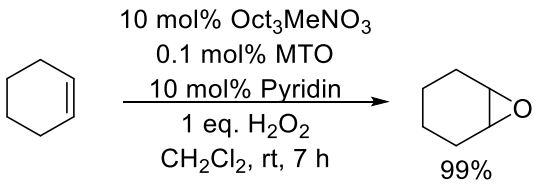
Scheme 31: Carboxylation of BO with MTO as LEWIS acid co-catalyst.

However, a one-pot epoxidation-carboxylation tandem reaction of 1-hexene was not successful (Scheme 32).



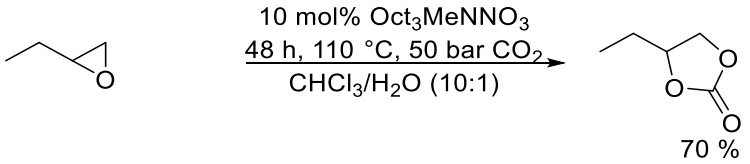
Scheme 32: Attempted one-pot synthesis with methyl trioxorhenium.

As changing the epoxidation catalyst did not solve the problem, the nucleophilic anion required in the carboxylation step was investigated next. While Br^- and I^- are the most active, Cl^- and NO_3^- exhibited some catalytic activity in prior screening [Table 2, Chapter 1.3.1]. Both are far less susceptible to oxidation by H_2O_2 and don't catalyse its decomposition. The addition of 10 mol% of trioctylmethylammonium nitrate **15a** has no negative impact on the epoxidation with MTO (Scheme 33).



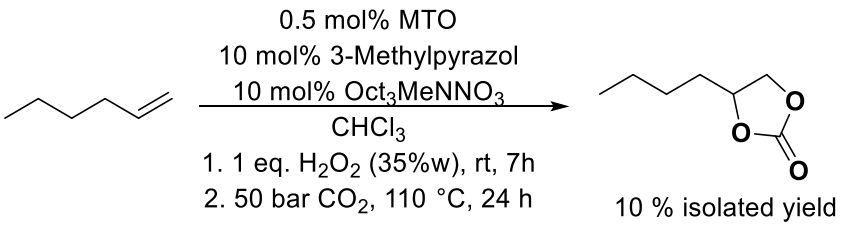
Scheme 33: Epoxidation of cyclohexene with MTO in presence of nitrate.

Additionally, it exhibits satisfying activity for the coupling of CO_2 and epoxides (Scheme 34).



Scheme 34: Carboxylation of BO with nitrate as nucleophilic catalyst.

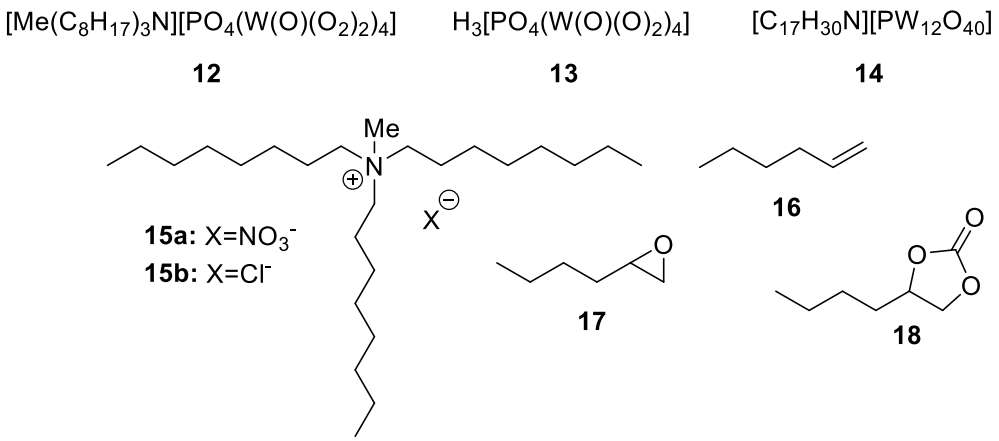
Combining the two reactions into a two-step one pot reaction revealed however, that the solution is not so simple (Scheme 35). Nevertheless, this was the first investigated system to produce any carbonate product.



Scheme 35: One pot synthesis of hexene-carbonate with methyl trioxorhenium and a quaternary ammonium nitrate catalyst.

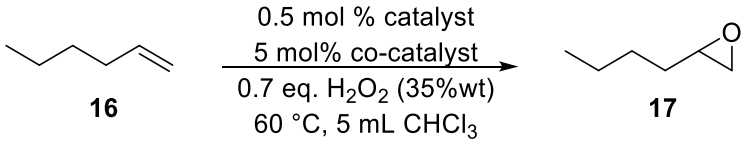
While MTOs LEWIS acidity enhances epoxide ring opening, it is also known to accelerate epoxide hydrolysis. Therefore, other epoxidation catalysts were investigated. Especially polyoxometalates might be interesting since they have been reported to show some activity

in the coupling of epoxides and CO_2.[120–122] The performance of three epoxidation catalyst (**12**-**14**) in presence or absence of tandem catalyst **15a** were investigated first (Scheme 36 and Table 6).



Scheme 36: Investigated epoxidation catalysts and reaction products.

1-Hexene **16** was chosen as model substrate as it is a terminal aliphatic olefin like the industrial relevant propene while also having a sufficiently high boiling point for easy handling. In table 6 the yields of 1,2-epoxy hexane **17** after 30 min, 60 min, 3 h and 19 h according to Scheme 37 are being displayed.



Scheme 37: Epoxidation of 1-hexene with catalyst 12-14 and co-catalyst 15a.

Table 6: Screening of epoxidation catalysts and the influence of 15a.

Entry	Catalyst	Co-catalyst	Yield 17 after 30 min [%]	Yield 17 after 60 min [%]	Yield 17 after 180 min [%]	Yield 17 after 1140 min [%]
1	**12**	**15a**	13	24	56	68
2	**12**	-	34	48	68	98
3	**13**	**15a**	34	48	55	61
4	**13**	-	0	0	0	0
5	**14**	**15a**	0	0	2	49
6	**14**	-	0	0	0	1

Conditions: 6 mmol 1-hexene **18**, 0.7 eq. H_2O_2 (35w%), 0.5 mol% catalyst, 5 mol% co-catalyst, 60 °C, 5 mL $CHCl_3$, yields based on H_2O_2 and determined by GC-FID.

Catalyst **12** shows the highest activity of all screened epoxidation catalysts, reaching 68% yield after 3 h and almost quantitative yields after 19 h (Entry 1). The presences of tandem catalyst **15a** significantly hinders the epoxidation: After 30 min and 60 min the yield is less then or half as large as in the absence of **15a**. The difference is less dramatic after 3 h, though it takes 19 h to match the yield obtained after 3 h in absence of **15a** (Entry 2). The opposite is observed for catalyst **13**, no epoxide is formed in absence of **15a** (Entry 4). In presence of tandem catalyst **15a** 34% yield is obtained after 30 min and 48% after 60 min (Entry 3) which is comparable to **12**. However, after 3 h and 19 h the yield of **17** is noticeably lower. As **13** is insoluble in nonpolar organic solvents, its lack of activity is easily explained. In presence of **15a** catalyst **12** is formed *via* anion exchange, explaining their similar performance. Despite its solubility in the organic phase **14** only shows a significant amount of epoxide in presence of **15a** and after 19 h (Entry 5,6). These results showed that strong agitation is not sufficient to facilitate the reaction with a hydrophilic catalyst. The lower yield after 19 h in presence of **15a** might hint on catalyst, H_2O_2 or product decomposition caused by **15a**. Catalyst **12** was chosen for further investigation. Next, the influence of the substrate ratios was investigated (Table 7).

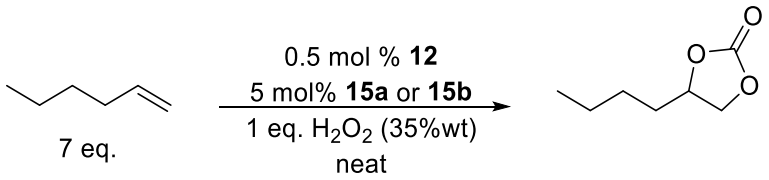
Table 7: Influence of the H_2O_2 concentration and substrate ratio on the epoxidation of 1-hexene.

Entry	Concentration of the added H_2O_2 solution [wt%]	1-hexane excess in respect to H_2O_2 [eq.]	Yield of epoxide 17[%]
1	17.5	1.3	19
2	23.3	1.3	32.4
3	35	1.3	56
4[a]	35	1.3	3
5[a]	35	7	82
6[a]	35	14	50

General conditions: 0.5 mol% **12**, 5 mol% **15a**, 60 °C, 3 h, 5 mL CH_3Cl a) no additional solvent; yields are based of H_2O_2 as limiting component and determined by GC-FID.

Diluting the same equivalents of H_2O_2 from 35 wt% to 23.3 wt% and 17.5 wt% greatly reduces the reaction rate and yields drop from 56% after 3 h to 32% and 19%, respectively. If no solvent is used, hardly any conversion takes place. By using an excess of 1-hexene however, the reaction can be performed neat. At a 7-fold excess of 1-hexene the reaction proceeds fast, yielding 82% hexene oxide after 3 h. The reaction begins to slow down again if a 14-fold excess

of 1-hexane is used. Epoxide hydrolysis is not observed under these conditions. Having established suitable conditions for the epoxidation step, the one pot reaction including CO_2 was investigated next under different conditions (Scheme 38, Table 8).



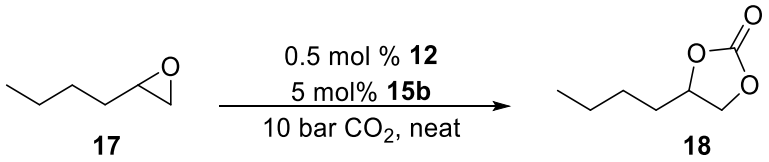
Scheme 38: One pot synthesis of hexane carbonate from 1-hexene.

Table 8: One pot synthesis of hexane carbonate from 1-hexene under different conditions.

Entry	tandem catalyst	*T* [°C]	*t* [h]	P_{CO2} [bar]	Yield of carbonate 18 [%]
1	**15a**	110	3	50	10
2	**15a**	110	39	50	13
3	**15a**	60	3	50	3
4	**15a**	60[a];110[b]	3[a];18[b]	0[a];50[b]	22
5	**15b**	110	39	50	22
6[b]	**15b**	60[a];110[a]	3[a];18[b]	0[a];10[b]	19

Conditions: 7 eq. 1-hexene **16**, 1 eq. H_2O_2 (35wt%), 0.5 mol% **12**, 5 mol% **15a** or **15b**, b) Yield based on H_2O_2 and determined by GC-FID, a) epoxidation step, b) carboxylation step.

If **15a** is used as co-catalyst at 110 °C for both reaction steps, then the carbonate yield is poor with 10%. Increasing the reaction time to 39 h has little effect and performing the reaction at a lower temperature (60 °C) yields only 3% carbonate. The yield can be doubled by performing both steps under different conditions: a) the epoxidation at 60 °C under air and b) the CO_2 coupling at 110 °C and under 50 bar CO_2. The same result is obtained when the reaction is performed with chloride **15b** at 110 °C. Performing the reaction under the same conditions as entry 4 has little effect. Despite high yields during the epoxidation step, the total yield of the one pot reaction is low. As conversion of the epoxide seems to be the critical issue, the second reaction step was investigated (Scheme 39, Table 9).



Scheme 39: Carboxylation of 1,2-epoxy hexane by 15b in presence of 12.

The CO_2 coupling was performed with **12** and **15b** (Entry 1). Additionally, the reaction was performed in presence of H_2O_2 (Entry 2) and after **12** and **15b** have been treated under the conditions of the first reaction step prior to use (Entry 3).

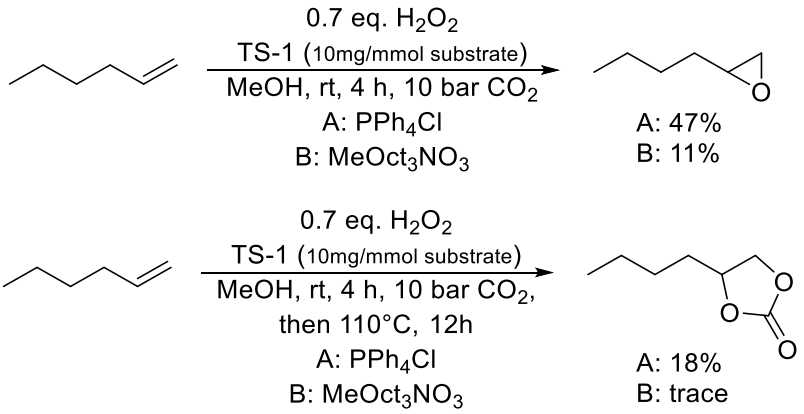
Table 9: Effect of H_2O_2 and preforming on the insertion of carbon dioxide into 1,2-epoxy hexane.

Entry	Conditions	Yield of carbonate 18 [%]
1	110 °C (3 h), no H_2O_2 added	60
2	60 °C (3 h) - 110 °C (3 h), 0.7 eq. H_2O_2	55
3	60 °C (3 h), 0.7 eq. H_2O_2, then addition of epoxide **17**, 110 °C (3 h)	50

Conditions: 10 mmol 1,2 epoxy hexane, 0.5 mol% **12**, 5 mol% **15b**, 10 bar CO_2, 0.5 mL H_2O, yield determined by GC-FID.

Under standard conditions, 1,2-hexane carbonate **18** is obtained in 60% yield after 3 h (Entry 1). If H_2O_2 is present the yield drops slightly, indicating a slow decomposition (Entry 2). If both catalysts are treated under conditions of the first reaction step the yield decreases further to 50% (Entry 3). A negative impact of H_2O_2 on the carboxylation step is present, however it alone can't be responsible for the poor performance of the one pot system. Total one pot yields should be around 41%, 82% yield in the first step and 50% in the second. Yet, achieved yields are 22% and 19%. Catalyst decomposition during the first reaction step could lead to poor results in the second step. As the anions Cl^- and NO_3^- should be stable under these conditions, cation decomposition was put under scrutiny. If the tri(octyl)methyl ammonium cation and H_2O_2 are present in the same reaction system, the formation of side products is observed. Comparison with authentic sample shows that these are not direct oxidation products of 1-hexen like aldehydes or acids. Additionally, they do not appear if either the ammonium cation or H_2O_2 are absent. Therefore, these side products are either decomposition products of the ammonium cation or products formed by these. The side products were isolated by column chromatography and analysed. The ^{1}H-NMR spectrum shows remarkable similarity to the cation. So does the ^{13}C-NMR spectrum, however many very similar signals can be seen suggesting a mixture of chemically similar compounds. Two of these compounds were identified *via* mass spectrometry: dioctylmethyl amine and trioctyl amine. As previously demonstrated in Chapter 1.3.1 amines can catalyse epoxide hydrolysis or react with the epoxide itself to form a variety of compounds. Oxidation of the amines is also possible. Furthermore, the employed epoxidation catalysts perform poorly when they are not kept in

the organic phase by a lipophilic cation. As a more stable alternative, the heterogenous titanium silicalite catalyst TS-1 was briefly investigated as an epoxidation catalyst (Scheme 40).



Scheme 40: Epoxidation and carboxylation of 1-hexene as one-pot synthesis with TS-1.

With PPh_4Cl as the nucleophilic tandem catalyst the carbonate is obtained with 18%. No remaining epoxide was detected by GC-FID and the primary side product is 1,2-hexane diol compared to the multitude of unidentified side products which were obtained with **15a**. This suggest that the system is indeed more stable, even though the yield is still unsatisfying and the use of methanol as solvent is required.

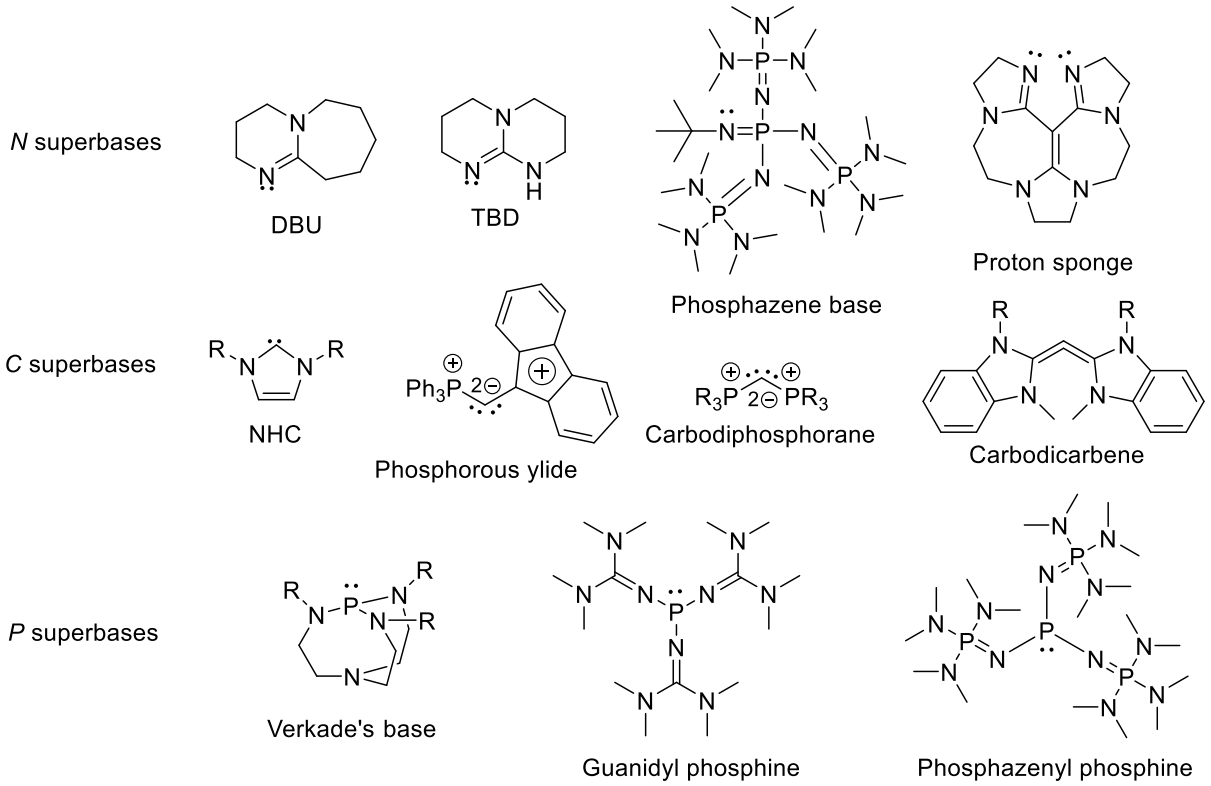
Unfortunately, it was not possible to identify a set of conditions that allows a one pot orthogonal tandem catalysis for the epoxidation-carboxylation of 1-hexene with a yield higher than 22%. The reasons are the decomposition of the catalyst and the different temperature regimes preferred by each reaction step.

3 Synthesis of cyclic carbonates from CO_2 and epoxides with organic superbases

3.1 Theoretical background

3.1.1 Organic superbases

While there is no clear definition for what an organic superbase is, most have a pK_{BH+} >18.6 or combine multiple functionalities to enhance basicity e.g. charge delocalization.[123–126] They can be roughly divided in three categories based on the centre of basicity: nitrogen based, carbon based and phosphorous based (Scheme 41).



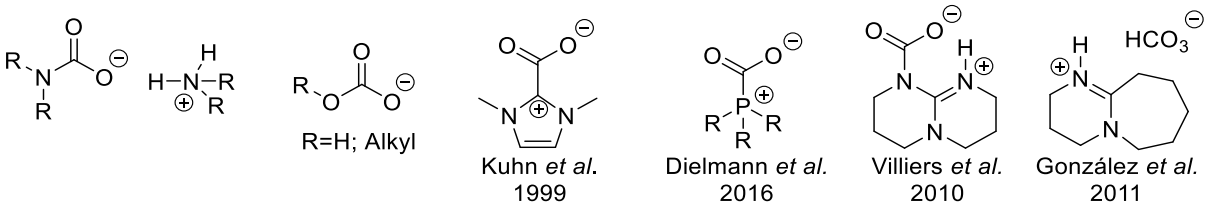
Scheme 41: Overview for different types of organic superbases.[124,125,127–129]

Nitrogen superbases are the most common super bases. These include cyclic amidines like DBU, cyclic guanidines like TBD and phosphazenes such as SCHWESINGER bases.[123] Carbon superbases include phosphorous ylides, carbodiphosphoranes and carbenes, though these are usually used for their electron donating properties as ligands rather than for their basicity.[127,130–133] Phosphorous superbases include VERKADE's base and the highly basic class of phosphazenyl phosphines.[134,135] Owing to their solubility in organic media and their tuneable electronic and steric properties, organic superbases have found several interesting applications as organocatalysts. Organic superbase catalysed reactions include but are not

limited to double bond isomerization, *N*-alkylation, hydroamination and other hydrofunctionalisations as well as the activation of small molecules like CO_2.[123,136,137]

3.1.2 Organic bases as catalysts for the coupling of CO_2 and epoxides

Carbon dioxide activation is an alternative to epoxide activation in the synthesis of cyclic carbonates. CO_2 forms adducts of varying stability with strong bases like OH^-, alkoxides, amines, carbenes and phosphines (Scheme 42). These adducts have been isolated and characterized in the literature.[138–141]

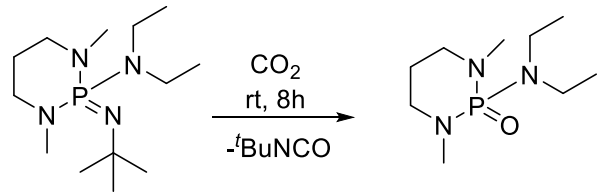


Scheme 42: CO_2-adducts of different bases in absence and presence of water (last entry).

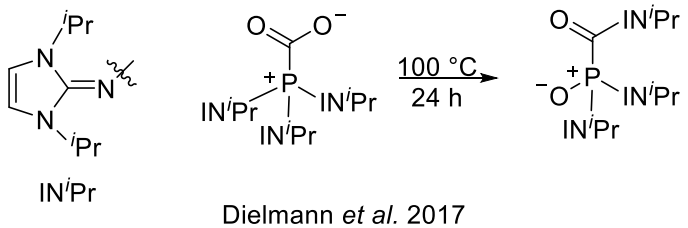
The carboxylation of NHCs with CO_2 is known to be reversible.[142] These NHC-CO_2 adducts are more stable under CO_2 atmosphere and decarboxylate readily upon warming or in presence of CO_2 acceptor substrates like epoxides[143]. In case of neutral bases, the adducts can differ in presence or absence of water: under anhydrous conditions a zwitterionic carboxylate is formed and in presence of water an onium bicarbonate salt is formed (Scheme 42). The formation of these adducts is reversible and their parent bases or CO_2 adducts have been reported to be active catalysts for the coupling of CO_2 and epoxides. These CO_2 adducts have also been used in combination with LEWIS acids or onium salts as part of multifunctional catalytic systems:

In 2003 SARTORI *et al*. used the cyclic guanidine 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-en (MTBD) as effective catalyst.[144] Various carbonates were obtained with 60-98% yield under relatively harsh conditions (120 °C, 50 bar, 20 h, 4 mol% catalyst load, MeCN). LU *et al.* first used NHCs as organocatalysts for the carboxylation of epoxides in 2008.[143] They achieved quantitative yields of propylene carbonate with low catalyst loadings (0.5 mol%) though conditions were still harsh (120 °C, 20 bar, 24 h, CH_2Cl_2). Since then, many similar systems in presence or absence of co-catalysts and solvents have been reported. In 2015 ZHOU *et al.* demonstrated that phosphorous ylides were active catalyst for the synthesis of propylene carbonate under very mild conditions (25 °C, 1 bar, 5 mol% catalyst load, neat).[145] Reversible

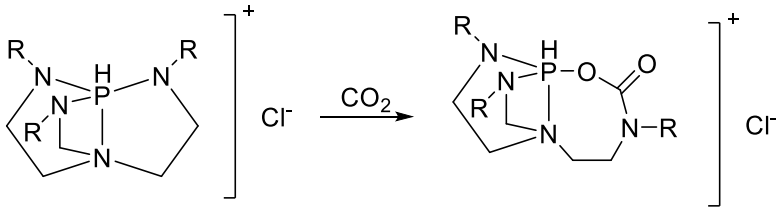
CO_2 binding by phosphorous bases was reported by DIELMANN *et al.* in 2016.[140] They also observed CO_2 splitting with particularly basic phosphines (Scheme 43).[146] Similarly, DUFAUD *et al*. observed the insertion of CO_2 into P-N bonds when they used protonated VERKADE superbases as epoxide-CO_2 coupling catalysts.[147] The metathesis of phospahzenes with CO_2 has also been describe in the literature.[136]



Fontaine *et al.* 2015



Dielmann *et al.* 2017



Dufaud *et al.* 2013

Scheme 43: Insertion of CO_2 into P-N-bonds of organic superbases.[136,146,147]

LIU *et al*. used CO_2 adducts of carbodicarbenes as catalysts for the insertion of CO_2 into epoxides and aziridine in 2018.[148] Over 90% yield could be achieved at 100 °C, 20 bars and 5 mol% catalyst loading for various aromatic and aliphatic epoxides.

3.2 Aim of this chapter

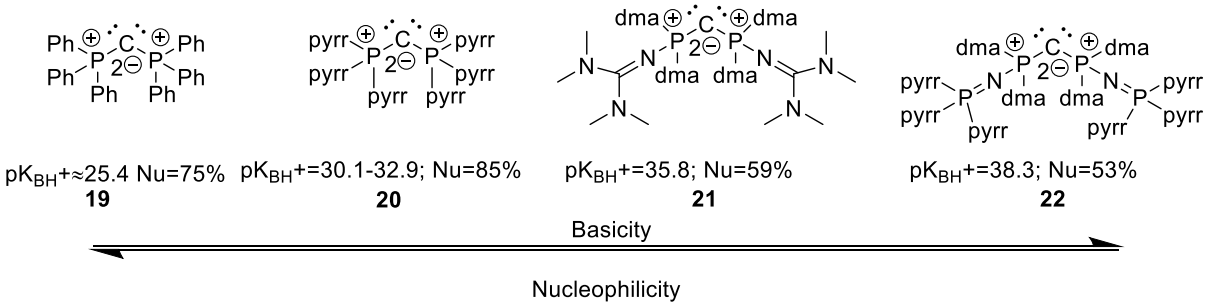
As mentioned in Chapter 1.1.2 organic superbases can be highly effective catalysts for the coupling of CO_2 and epoxides. The vast majority of organic superbase catalysts for this reaction are nitrogen based. To our knowledge, only a few examples exist for carbon or phosphorous superbase catalysts. Since our group has developed a large variety of carbon and phosphorous superbases over the years, we were interested in investigating their capabilities as organocatalysts and CO_2 activators.[129,130,149–162] With their unique and tuneable steric and

electronic properties they represent a class of potential organocatalysts that is well worth exploring.

3.3 Results and discussion

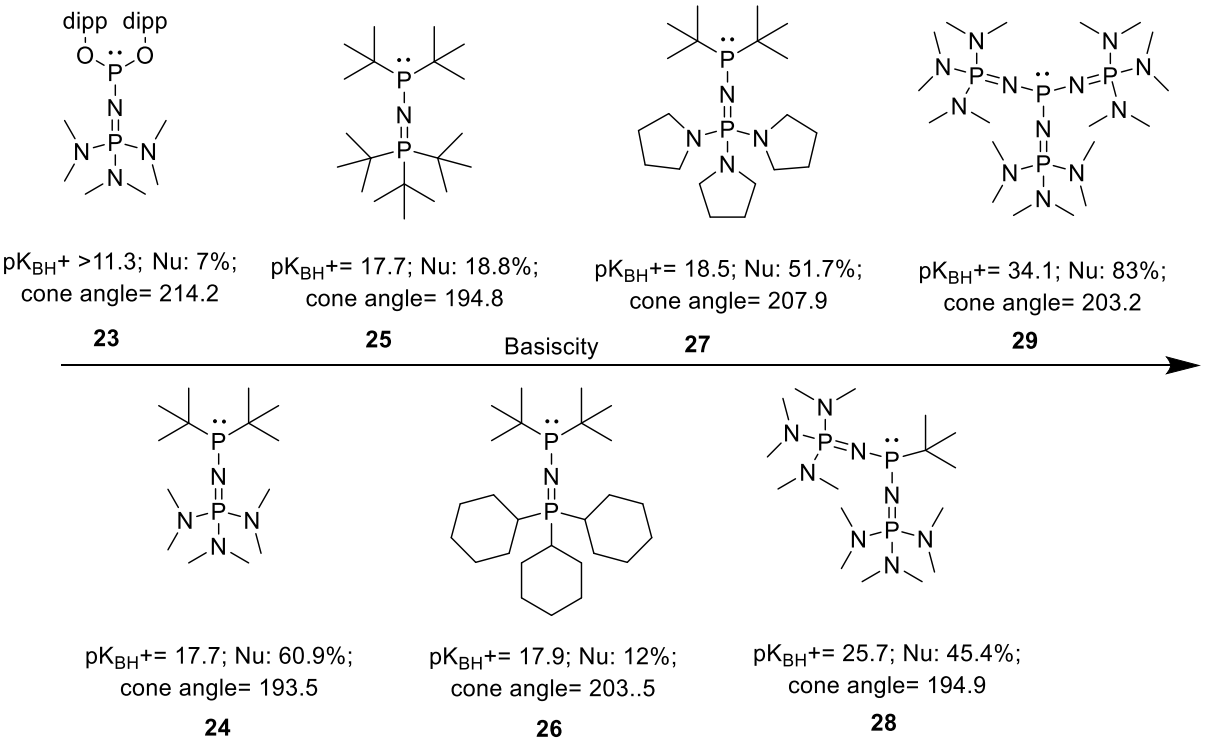
3.3.1 Phosphazenyl phosphines and carbodiphosphoranes as organocatalysts for the carboxylation of epoxides

In this chapter phosphazenyl phosphine (PAP) and carbodiphosphorane (CDP) super bases developed by SEBASTIAN WAGNER[163], IGOR MARTIN[164] and SEBASTIAN ULLRICH[165] were utilized in the coupling of CO_2 and epoxides as part of a group internal cooperation. The compounds as well as data about their properties where provided by IGOR MARTIN for the CDPs[164] and by SEBASTIAN WAGNER for the phosphazenyl phosphines[163] unless noted otherwise. The following bases were investigated:



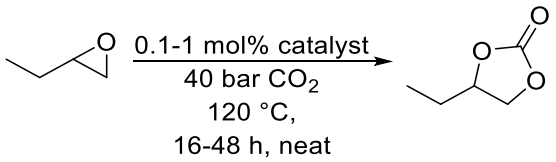
Scheme 44: Investigated CDPs and their basicity (in THF) and their nucleophilicity versus basicity towards ethyl iodide.[164,166,167]

The investigated CDPs are strong bases and their nucleophilic character decreases with increased basicity and steric hinderance of the basicity centre. It should be noted that these CDPs only show nucleophilic behaviour if strong electrophiles like ethyl iodide are used. Only HBr elimination occurs with ethyl bromide.[164]



Scheme 45: Investigated phosphazenyl phosphines and their basicity (in THF) and their nucleophilicity versus basicity towards ethyl iodide.[150]

It has previously been shown that most of these bases reversibly form isolatable CO_2 adducts.[163,164] While the CDP-CO_2 adducts are stable at room temperature for several hours, the mono-PAP CO_2 adducts are only stable at temperatures below room temperature. The P-CO_2 bond becomes more stable with rising basicity. While carboxylation of phosphazenyl phosphines is reversible, the carbodiphosphorane adducts are highly susceptible towards to the presence of traces of moisture, forming the corresponding hydrogen carbonate salt.[163,164,168] Preliminary testing was performed with bases **20, 21, 23, 24-27, 29** and butylene oxide as model substrate. The bases were chosen due to their difference in basicity, nucleophilicity and steric hindrance. The goal was to evaluate the conditions under which these compounds were active carboxylation catalysts (Scheme 46, Table 10).



Scheme 46: Coupling of butylene oxide and CO_2 catalysed by organic superbases.

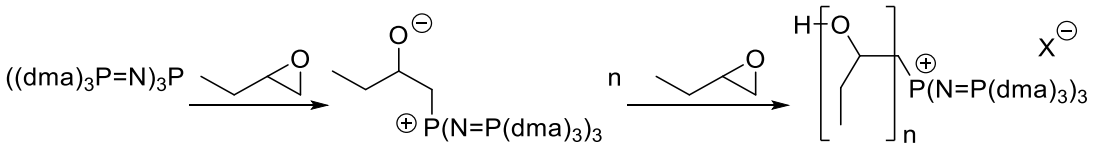
Table 10: Initial screening of organic superbases (Scheme 44 and 45) as catalysts for the carboxylation of butylene oxide.

Entry	Superbase	T [°C]	T [h]	Catalyst load [mol%]	Conversion BO [%]	Selectivity BC [%]	Yield BC [%]
1	**24**	120	16	2	93	>99	93
2	**24**	50	16	2	-	>99	-
3	**20**	120	16	1	56	>99	56
4	**20**	120	48	1	74	>99	74
5	**20**	120	48	0.1	68	>99	68
6	**24**	120	48	0.1	62	>99	62
7	**21**	120	48	0.1	51	>99	51
8	**20·H_2O**	120	48	0.1	86	>99	86
9	**23**	120	48	1	-	>99	-
10	**27**	120	48	1	84	>99	84
11	**25**	120	48	1	45	>99	45
12	**26**	120	48	1	65	>99	65
13	**29·CO_2**	120	48	1	42	>99	42
14	**19**	120	48	0.1	-	>99	-

Conditions: 20 mmol butylene oxide **1**, 40 bar CO_2, yields determined by GC-FID, no oligomers were detected by ^{1}H-NMR-spectroscopy

With exception of the least basic and nucleophilic superbase **23**, all tested bases exhibited catalytic activity. The temperature plays an important role, as no conversion is observed at 50 °C compared to the 93% conversion at 120 °C (Entry 1-2). As CO_2 activation occurs at room temperature and is reversible under mild heating, the required energy input is likely due to the activation barrier of the epoxide ring opening. Interestingly, high conversion could be achieved at low catalyst loadings: Carbon base **20** reaches 68% conversion even at only 0.1 mol% catalyst load compared to 74% at 1 mol% (Entry 4-5). **24** performed similarly well at 0.1 mol% (62%, Entry 6), though 93% yield were achieved with 2 mol% catalyst loading in 1/3 of the time. To check if small quantities of moisture could deactivate the catalyst, especially when used at low concentration, “wet” substrate (not previously dried) was utilized. Surprisingly, the residual water did not deactivate the superbase **20**. Instead, a significant improvement in catalyst performance was observed as the yield increased to 86% (Entry 5 and 8). While the neutral CDPs are sensitive towards hydrolysis induced by formation

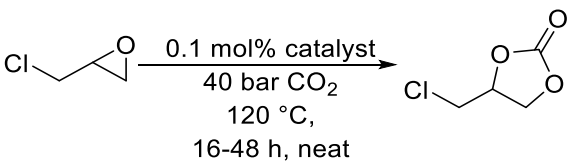
of OH^-, their protonated salts are more stable. The CO_2 adduct might similarly stabilize the base towards hydrolysis. The improved activity can be attributed to the activation of the epoxide *via* hydrogen bonding by water or the protonated CDP. The HCO_3^- salt of the base formed with trace amounts of moisture is likely the actual catalyst in this case, considering their sensitivity towards protonation and the low catalyst load.[169,170] When the highly basic and nucleophilic P-base **29** was used, polymerization of the epoxide was observed immediately after addition of the substrate, before CO_2 is added. It might be nucleophilic enough to attack and open the epoxide ring and initiate the anionic polymerisation (Scheme 47).



Scheme 47: Potential polymerisation pathway for BO with a nucleophilic P base.

Similar phosphazenyl phosphines of the type $P(NP(NR_2)_3)_3$ have been described as efficient catalyst for epoxide polymerisations, suggesting that these classes of P-bases are too reactive.[171] The preformed CO_2-adduct of **29** (**29·CO_2**, Entry 13) on the other hand does not initiate the polymerization of the epoxide. It can be used as catalyst like the other bases and gives butylene carbonate in 42% yield. **29** forms the most stable CO_2 adduct of the investigated phosphazenyl phosphines, which could slow down the final ring closing rate determining step. A similar relation between NHC-CO_2 adducts and their catalytic activity is known.[143] **19** and its CO_2 adduct are insoluble in butylene oxide. Therefore, no conversion was observed (Entry 14).

As some of the catalysts and their CO_2-adducts exhibited limited solubility in butylene oxide, we switched to epichlorohydrin as substrate. **20** was chosen as benchmark catalyst for further investigation of reaction conditions and for comparison with other catalysts (Scheme 48, Table 11). No reaction with the C-Cl bond of epichlorohydrin was observed.



Scheme 48: Coupling of epichlorohydrin and CO_2 catalysed by organic superbases.

Table 11: Screening of organic superbases (Scheme 44-45) for the carboxylation of epichlorohydrin.

Entry	Base	T [°C]	t [h]	Conversion epichlorohydrin [%]	Selectivity carbonate [%]	Yield carbonate [%]	TON
1	**20**	120	20	99	>99	99	990
2[a]	**20**	120	20	86	>99	86	8600[a]
3	**20**	120	3	83	>99	83	880
4	**20**	120	6	96	>99	96	960
5	**20·CO_2**	120	6	92	>99	92	920
6	**20·H_2O**	120	6	96	>99	96	960
7	**19**	120	6	84	>99	84	840
8	**19**	120	6; 20	98[b]	>99	98[b]	1960
9	**26**	120	6	89	>99	89	890
10	**19**	80	6	41	>99	41	410
11	**28**	120	6	94	>99	94	940
12	**22**	120	6	99	>99	99	990
13[c]	**22**	120	6	88	>99	88	880
14	**EMIY**	120	6	91	>99	91	910

Conditions: 23 mmol epichlorohydrin, 0.1 mol% (0.023 mmol) catalyst, neat, 20 bar CO_2; a) 0.01 mol% (0.0023 mmol) catalyst; b) additional 23 mmol epichlorohydrin added after 6 h, total yield after 20 h, c) 5 bar CO_2, yields determined by GC-FID, no oligomers were detected by ^{1}H-NMR-spectroscopy, EMIM = 1-ethyl-3-methylimidazol-2-ylidene

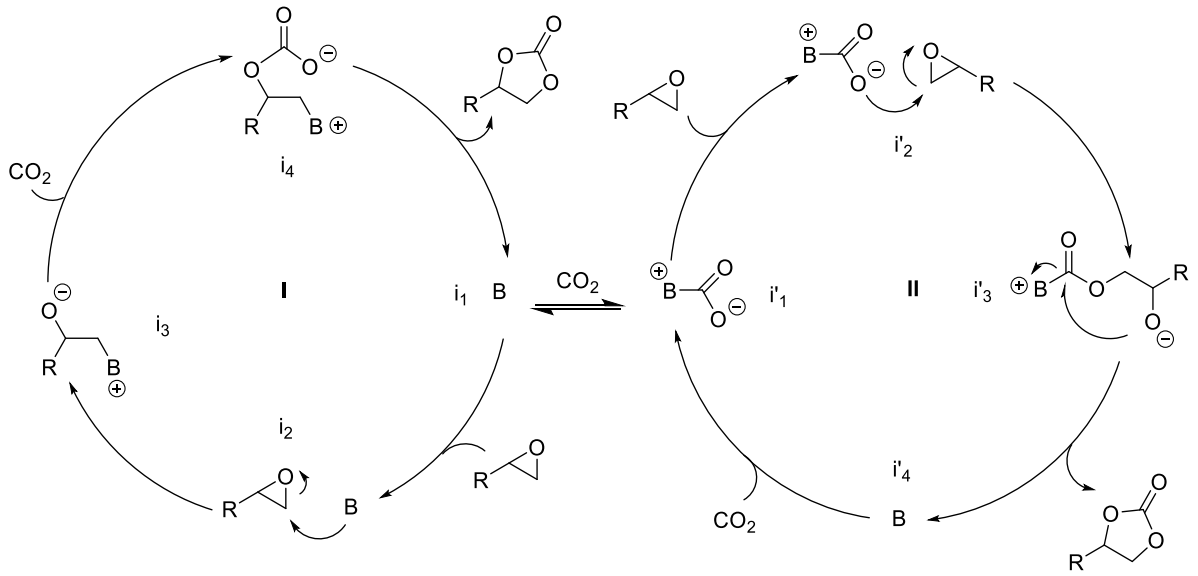
With 0.1 mol% **20** the quantitative conversion of epichlorohydrin was achieved after 20 h. Decreasing the catalyst load to 0.01 mol% still yields 86% carbonate, effectively increasing the TON by a factor of 8.7 (Entry 2). Shortening the reaction times reveals that most of the conversion is done after 3 h with nearly quantitative conversion after 6 h (Entry 3-4). Only 4% difference is observed if the CO_2-adduct **20·CO_2** instead of the free base is used as the catalyst (Entry 5). If the adduct is the catalytically active species, then this indicates that the adduct is formed rapidly under reaction conditions. If the free base is the active species, it means that the exchange between free base and adduct is fast, even in large excess of CO_2. The water adduct **20·H_2O** (prepared from **20** and a small excess of H_2O) is highly active (96% entry 6), underlining that water in low concentrations does not decompose the catalyst. Under non-anhydrous condition the formed HCO_3^- salt is likely the actual catalyst.[169,170] Lowering the temperature has again a drastic impact on the reaction as only 41% conversion is achieved

(Entry 9). The less basic and less nucleophilic **19** showed a slightly poorer performance. No solubility issues were observed with **19** or its CO_2-adduct in epichlorohydrin. Addition of fresh epichlorohydrin (23 mmol) to the reaction mixture after 6 h shows that the catalyst **19** does not decompose during the reaction as near quantitative conversion is observed in after 20 h (Entry 6-7), doubling the TON. Both phosphazenyl phosphines, **26** and **28**, achieved high conversions (Entry 9, 11) with 89% and 94%, respectively. Finally, the highly basic **22** proved to be the most active catalyst, achieving quantitative conversion after 6 h. It performs well even at 5 bar pressure (88%, Entry 13). It is notably less nucleophilic than PAP **29** which should supress polymerisation.

To the best of our knowledge, these carbodiphosphoranes and phosphazenyl phosphines achieve the highest TON reported for the purely organocatalysed carboxylation of epichlorohydrin. NHCs achieve TONs of 200[143], however, when the EMIY was used under the same conditions as the CDPs and phosphazenyl phosphines, it achieved a TON of 910. Carbodicarbenes achieve a TON of 18.[148] The CO_2 adducts of phosphorous mono-ylides (non CDPs) achieve TONs of 18, however this is remarkably achieved at room temperature and under ambivalent CO_2 pressure.[145]

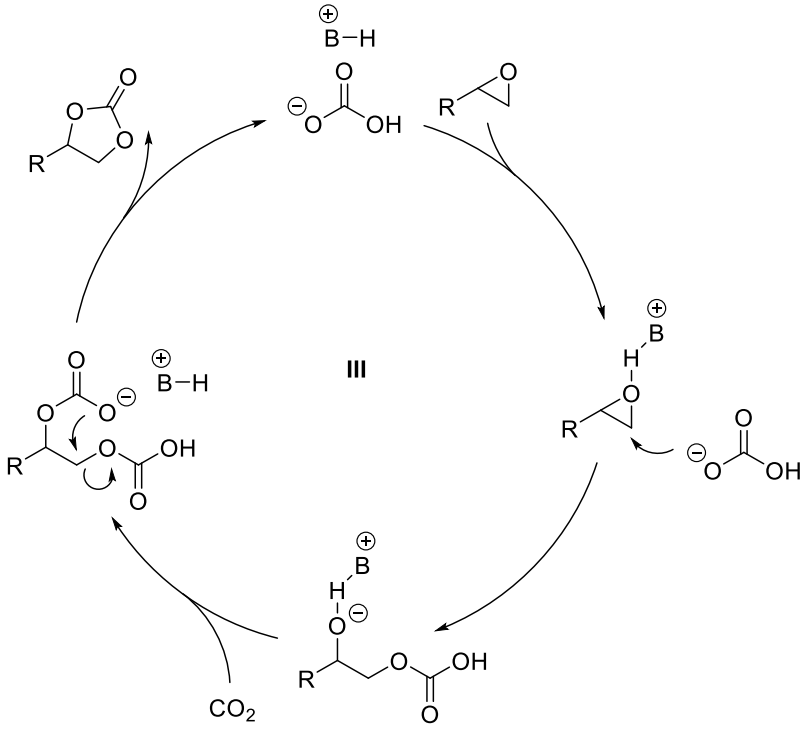
3.3.2 Mechanistical investigations of the epoxide-carboxylation catalysed by phosphazenyl phosphines and carbodiphosphoranes

The exact mechanism is still debated and two general mechanisms are proposed, one that is analogue to the mechanism with other LEWIS bases/nucleophiles (I) and one, where the base-CO_2-adduct is the catalyst (II) (Scheme 49). In mechanism **I** the base acts as nucleophile and attacks the epoxide ring at the sterically less hindered carbon. Intermediate $\mathbf{i_3}$ attacks CO_2 forming $\mathbf{i_4}$. The ring is closed by nucleophilic attack of the carboxylate and the base is regenerated. A theoretical study by SURESH and AJITAH suggest a variation where $\mathbf{i_3}$ is the active catalyst.[172]



Scheme 49: Proposed mechanisms for the base catalysed carboxylation of epoxides.[143,148]

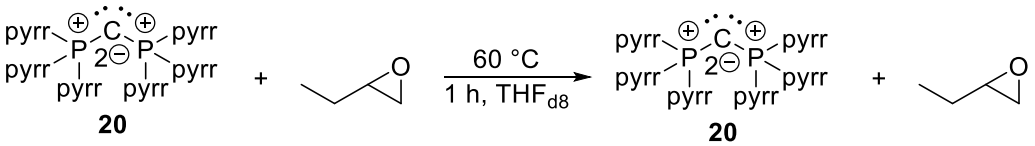
In mechanism **II** CO_2 reacts with the base **B** and forms a zwitterionic carboxylate **i'$_1$**. This carboxylate then opens the epoxide ring *via* nucleophilic attack, typically at the less shielded, more electrophilic epoxide carbon atom. The ring is then closed by internal nucleophilic substitution of base by the alkoxide. The catalytic species is regenerated *via* reaction of the base with CO_2. LU et al. postulated a variation of mechanism **II** where zwitterion **i'$_1$** activates an additional CO_2 which inserts into the epoxide.[145] In presence of moisture the formation of an onium HCO_3^- salt occurs, which is also catalytically active (mechanism III) (Scheme 50).



Scheme 50: Mechanism of the carboxylation of epoxides by HCO_3^- salts.[169]

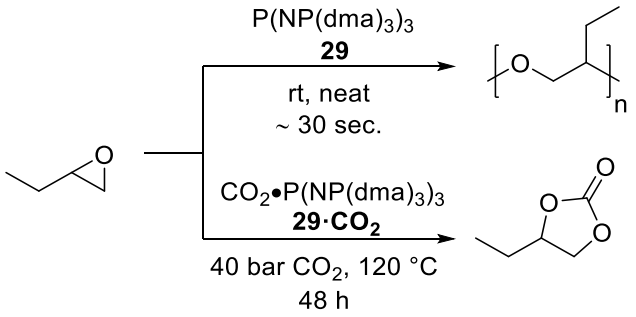
Mechanism III is analogue to the carboxylation mechanism with nucleophilic anions [Chapter 1.1.2]. In this case HCO_3^- acts as the nucleophilic catalyst for the epoxide ring opening and as leaving group in the final step.

The CDPs are rather poor nucleophiles but still highly active: Nucleophilic reactivity of these CDPs was only observed for the strong electrophile ethyl iodide. With ethyl bromide only elimination occurs.[164] No reaction between CDP **20** and butylene oxide was observed in absence of CO_2 (Scheme 51).[164]



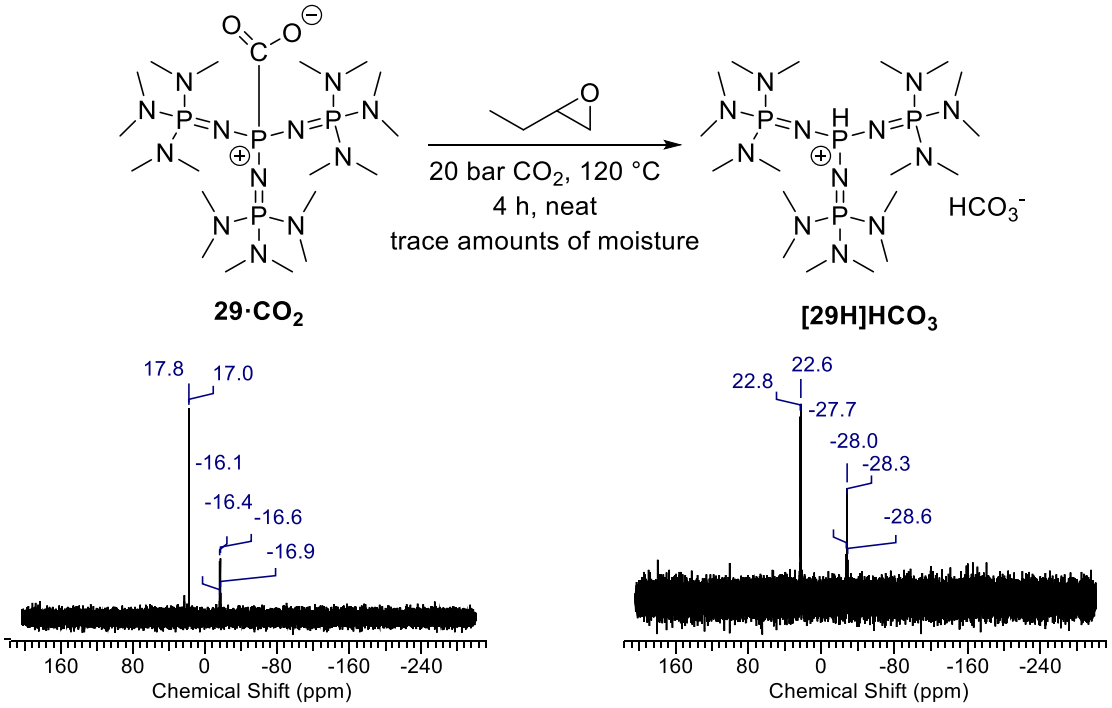
Scheme 51: NMR investigation of the reaction between CDP 20 and butylene oxide.

The ^{31}P-NMR of **20** shows only free base (δ 12.7 ppm) after the reaction. This demonstrates that the free base form of **20** is not able to undergo the ring opening step necessary for catalytic cycle **I**. Additionally, **20** exhibits catalytic activity when used as the CO_2-adduct and after pre-treatment with water (Table 11, entry 5 and 6). Especially in the latter case the presence of free base can be ruled out. The highly basic and nucleophilic phosphazenyl phosphine **29** catalyses the epoxide polymerisation in absence of CO_2 and at room temperature. The CO_2 adduct of **29 (29·CO$_2$)** catalyses the CO_2-insertion without polymerization (Scheme 52).



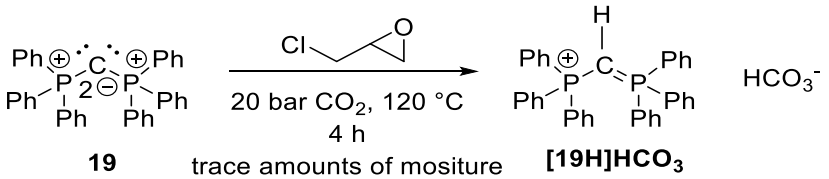
Scheme 52: Reactivity of phosphazenyl phosphine 29 (top) and its CO_2-adduct 29·CO_2 (bottom) towards butylene oxide.

Additionally, **29·CO$_2$** is completely protonated at the end of the reaction (Scheme 53).



Scheme 53: ^{31}P-NMR spectrum of 29·CO_2 before (right) and after (left) its use in the carboxylation of butylene oxide.

The protonated form of CDP **19** (^{31}P-NMR: δ -3.60 ppm for free **19**, δ 21.77 ppm after reaction) was observed after its usage as catalyst for the carboxylation of epichlorohydrin (Scheme 54).



Scheme 54: CDP 19 before (left) and after (right) its use in the carboxylation of epichlorohydrin.

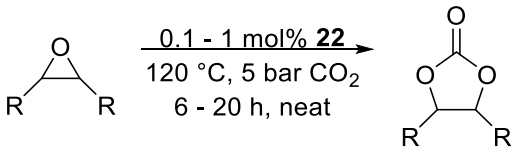
Since **19** remains active after one catalytic run, hydrogen carbonate [**19H]HCO$_3$** must be involved in the catalytic cycle. Either as resting state or as active catalyst itself. Due to the high basicity of CDPs it is highly unlikely that the free base is formed through deprotonation. Therefore, [**19H]HCO$_3$** is likely the active catalyst. The CO_2-adducts form rapidly at atmospheric pressure and are likely the dominant species at elevated pressure and in absence of moisture.

Due to the low catalyst loadings only trace amount of free base, if any, would be present. Most of the catalyst will form adducts with CO_2 or CO_2/H_2O. Due to the sensitivity of the epoxide moiety, the selection of drying agents is limited for epoxides. CaH_2 is commonly used in the literature.[143] Being a mild desiccant, it is possible that traces of moisture are still present in the epoxide.[173] Additionally, the presence of free CO_2 is known to inhibit the decarboxylation

of the similar NHC-CO_2 adducts.[143] Furthermore, CDP **20** showed high catalytic activity even in presence of water. Therefore, mechanism **III** (Scheme 50) is most likely the correct catalytic mechanism.[169] In case of the HCO_3^- salts, more basic and sterically hindered onium cations lead to more 'naked' anions.[174,175] These are more nucleophilic, which would increase their catalytic performance.

3.3.3 Substrate scope of the carbodiphosphorane catalysed carboxylation

As the CDPs have proven themselves as highly active catalysts in the carboxylation of epichlorohydrin, we investigated their activity with other epoxides (Scheme 55, Table 12).



Scheme 55: Coupling of various epoxides with CO_2 catalysed by 22.

Table 12: Carboxylation of various epoxides catalysed by CDP 22.

Entry	Base	Substrate	Catalyst load [mol%]	t [h]	Yield carbonate [%]
1	**22**	Cyclohexene oxide	0.1	6	18
2	**22**	Cyclohexene oxide	1	6	47
3	**22**	Cyclohexene oxide	1	20	75
4	**22**	Hexene oxide	0.1	6	34
5	**22**	Hexene oxide	1	6	56
6	**22**	Butylene oxide	0.1	6	15*
7	**22**	Butylene oxide	0.5	6	31*
8	**22·CO_2**	Glycidol	0.1	6	nd*
9	**22**	Epichlorohydrin	0.1	6	96%

Conditions: 23 mmol substrate, 120 °C, 5 bar CO_2, yield determined by GC-FID or ^{1}H-NMR. *Significant amounts of oligomers were detected *via* NMR.

Being an internal epoxide cyclohexene oxide is much less reactive. Expectedly, conversion under standard conditions is low with 18%. Increasing the catalyst load to 1 mol% gives only 47% and extending the reaction time to 20 h gives the carbonate with 75% yield. 1,2-epoxy hexane also reacts more sluggish. As hexene oxide is rather non-polar, the solubility of the CDP-CO_2 adduct might be an issue. With butylene oxide **1** polymerization to the polyether becomes a relevant side reaction again. **22** is more basic than the other catalysts

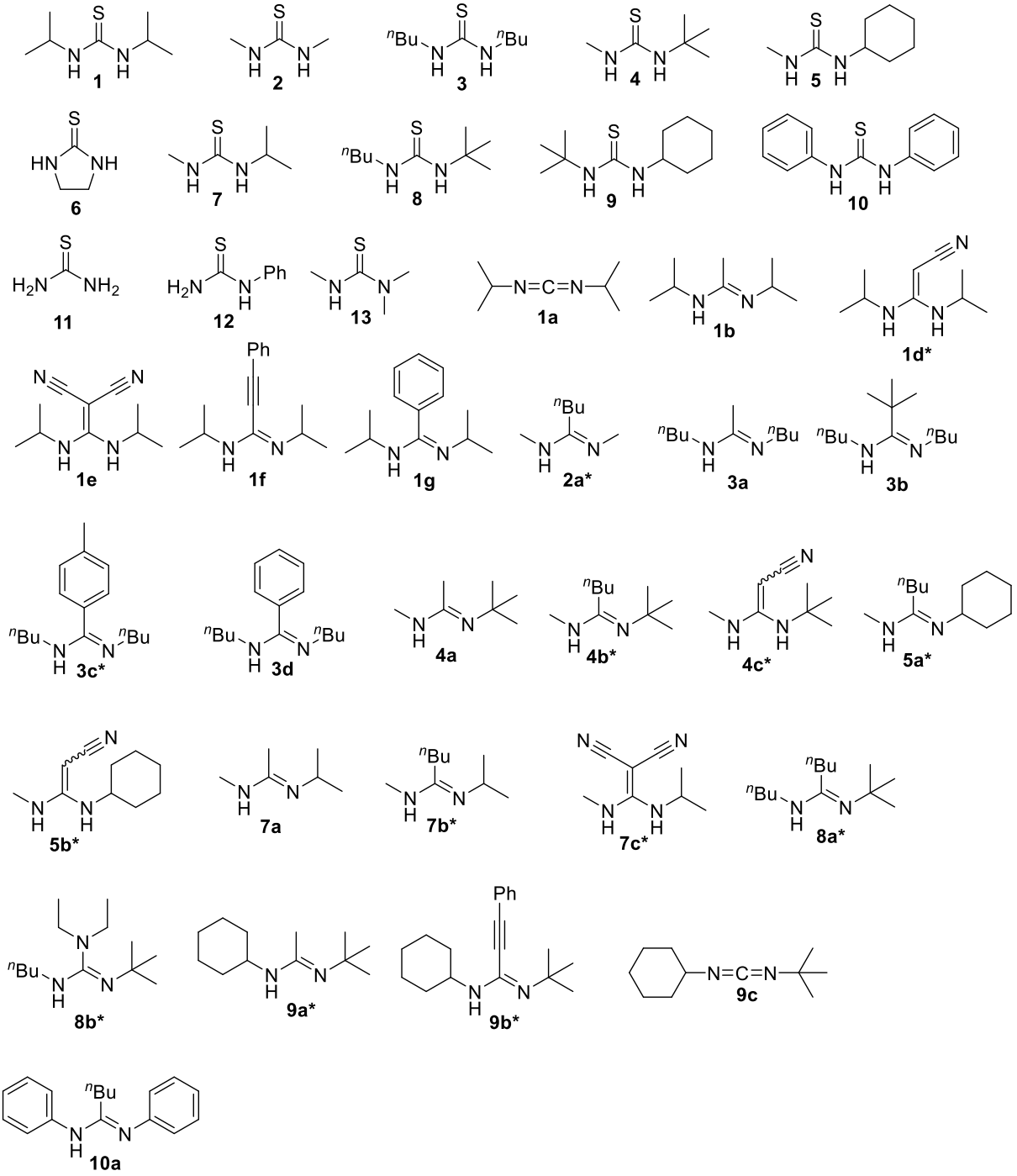
which were previously used with butylene oxide **1** and could have a similar effect as **29.** Glycidol always gives an unspecified mixture of poly-and oligomers. It is especially prone to polymerization, due to its acidic hydroxyl moiety. Even masking the base catalyst as CO_2-adduct did not resolve this issue.

In this chapter it was demonstrated that phosphazenyl phosphine and carbodiphosphorane superbases are highly effective organocatalysts for the carboxylation of epichlorohydrin. With just 0.1 mol% catalyst load near quantitative yields of the corresponding cyclic carbonate were obtained. Additionally, these organocatalysts are tolerant towards moisture and do not decompose during the reaction. It was also shown that the superbases likely act as precursors to a catalytically active onium bicarbonate species formed *in situ* from the base, CO_2 and traces of moisture.

Part II:

Carbodiimides and amidines from thioureas

List of compounds [No SciFinder entry exists for compounds marked with a *]



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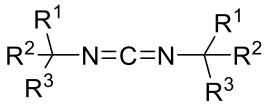
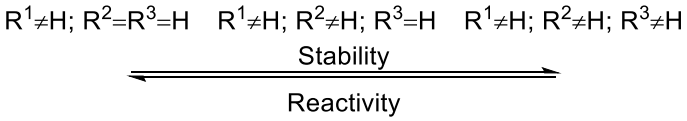
4 Theoretical background

4.1 Carbodiimides: properties, applications and synthesis

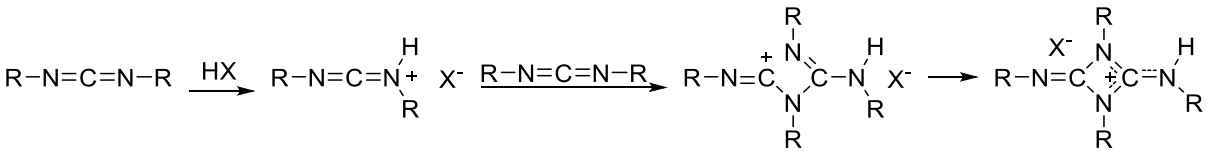
Carbodiimides (CDIs) are bisimino derivatives of the C_1-building block CO_2 with the structure R-N=C=N-R (Scheme 56). Despite their C=N bonds CDIs are not classified as typical bases, they can be protonated by acids. They have two main centres of reactivity: the electrophilic central carbon atom and the nucleophilic nitrogen atoms.[176–179] The central carbon in carbodiimides is significantly less electrophilic[180] than that of other heteroallenes like CO_2 and isocyanates as demonstrated by OFIAL and MAYR.[181] In their work to establish a quantitative electrophilicity scale, they showed that diphenyl carbodiimide is several orders of magnitude less electrophilic than CO_2 and dicyclohexyl carbodiimide did not even react with carbon nucleophiles (e.g. carbanions of nitriles, malonesters and β-keto esters) in absence of a catalyst. The reactivity and especially the stability of CDIs depends on the character of the *N*-substituents.[182–184]





Scheme 56: Aliphatic carbodiimide structure and stability.

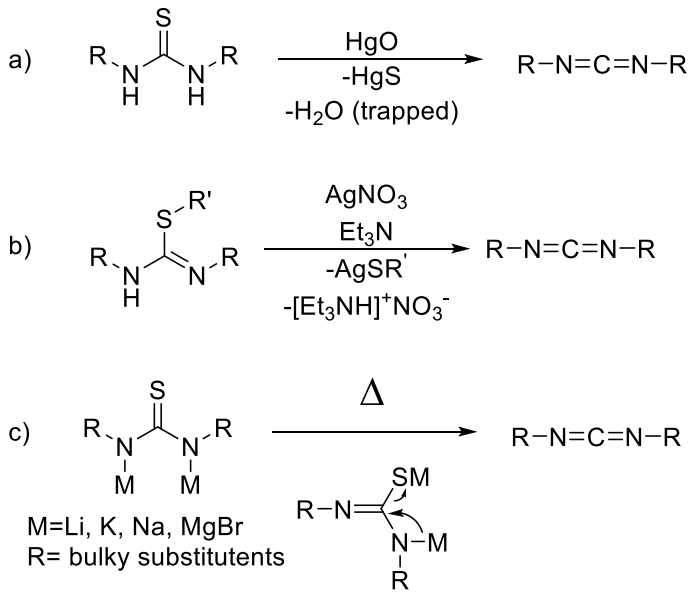
The stability of dialkylcarbodiimides greatly increases in the order primary < secondary < tertiary (Scheme 56),[183] while the length of the alkyl chain has a much smaller effect.[177] Dimethyl carbodiimide polymerizes at temperatures below 0 °C and is difficult to isolate[182]. Dicyclohexyl carbodiimide (DCC) and diisopropyl carbodiimide (DIC) are commercially available and widely used as reagent in organic synthesis as water traps or coupling agents.[185,186] Unsaturated substituents have a negative impact on the CDIs stability[177] and aryl substituted carbodiimides vary greatly in their stability.[183] Diaryl carbodiimides with electron poor substituents are less stable than their electron rich counterparts.[177,187] Unstable carbodiimides rapidly undergo side reactions like dimerization or polymerisation (Scheme 57)[180] and unsymmetric carbodiimides can also undergo metathesis reactions at elevated temperatures.[188,189]



Scheme 57: Dimerization of carbodiimides catalysed by water-free acid.[180]

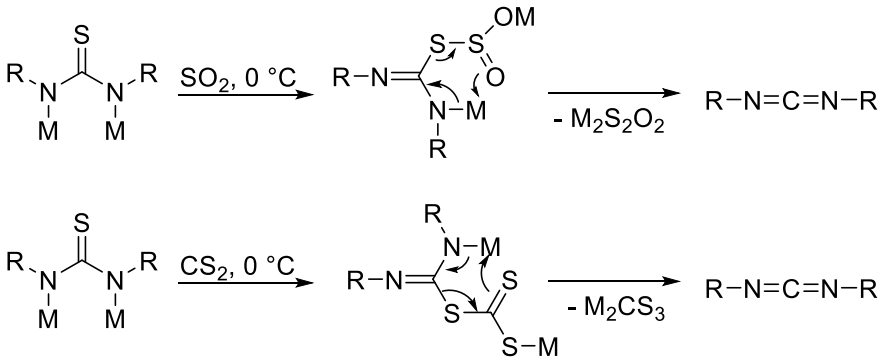
These side reactions can occur in presence or absence of other chemicals and are often observed after distillation attempts or simply after prolonged storage.[183]

Despite being known for over a century there is, so far, no general synthesis for all types of carbodiimides.[179] Simple carbodiimides (alkyl or aryl substituted CDIs without additional functional groups) are usually prepared *via* dehydrodesulfurisation of thioureas, by dehydration of ureas or by metathesis of isocyanates. Dehydrodesulfurisation is commonly achieved by three different approaches: with a thiophilic metal sulphur acceptor[190–192], oxidative[193,194] or by thermal decomposition.[195–197] WEITH *et al.* reported the use of HgO as dehydrodesulfurisation agent, a method that was developed in 1873, which is, despite the toxicity of HgO, still in use today (Scheme 58a).[198] Other metal oxides like PbO,[199] ZnO and salts of Ag and Cu have also been used,[177,179,200] but none are as effective as HgO.[176–178,184] Dehydration agents are common additives to these reactions in order to remove the water formed as by-product, preventing the formation of urea.[177] The addition of small quantities of elemental sulphur has been reported to catalyse the reaction and supress the formation of by-products.[201] Iso-thioureas can be desulfurized *via* a metallic *S*-acceptor like Ag^{+}[202] (Scheme 58b) or by thermal decomposition (Scheme 58c).[203] The thermal decomposition of di-metalated thioureas to carbodiimides is also known. Here, thioureas are deprotonated twice by strong metal bases like ^{n}BuLi or GRIGNARD reagents. These generate carbodiimides and metal sulfide when heated under reduced pressure at 170 °C to 200 °C (Scheme 58c).[195,197]



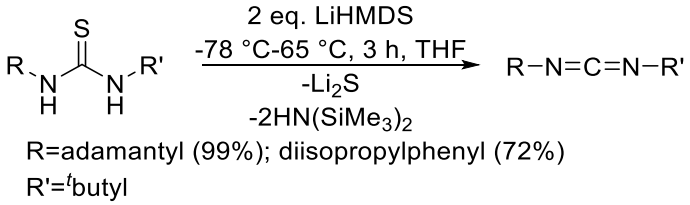
Scheme 58: Synthesis of carbodiimides *via* thermal decomposition of di-metalated thioureas.

By addition of SO_2 or CS_2 the reaction proceeds under much milder conditions (Scheme 59).[195,197]



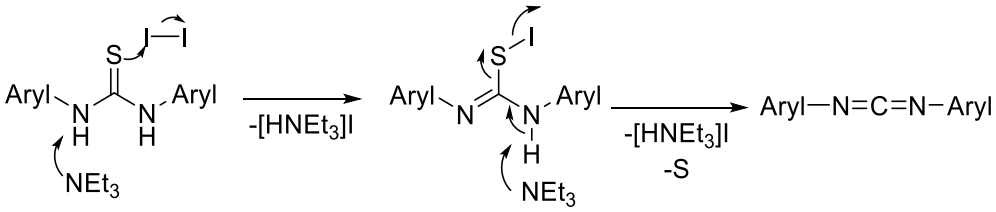
Scheme 59: Synthesis of carbodiimides by reaction of di-metalated thioureas with SO_2 (top) and CS_2 (bottom).

Thioureas with bulky substituents such as cyclohexyl or ^{t}butyl can be converted with 67-87% yield, but thioureas with less demanding groups give lower yields or don't react at all. SCHLACK and KEIL used sodium bases like $NaNH_2$, NaO^tBu and NaH to prepare several stable and symmetrical carbodiimides from their corresponding thioureas under reflux conditions.[204] This method was fairly effective with yields ranging from 45-75%. It is limited to carbodiimides with secondary or tertiary substituents like cyclohexyl and ^{t}butyl. DRIESS *et al.* prepared *N*-diisopropylphenyl-*N*-^{t}butyl carbodiimide and *N*-adamantyl-*N*-^{t}butyl carbodiimide from their corresponding thioureas under mild conditions and in good yields (72-99%) with Li(HMDS) as the sole reagent (Scheme 60).[196]



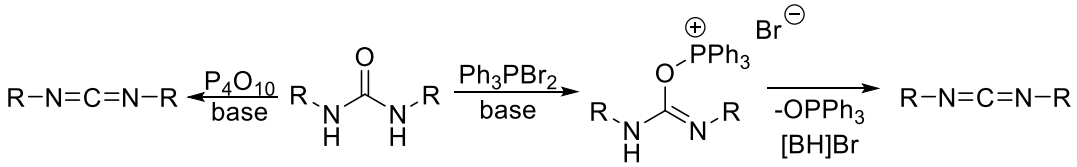
Scheme 60: Synthesis of carbodiimides as reported by DRIESS *et al.*

Another method used is the oxidative desulfurization. Alkaline solutions of $NaClO_4$ transform thioureas to their carbodiimides in good yields under phase transfer conditions.[205] Iodine has been successfully used in presence of base like triethylamine. Carbodiimides can be prepared from diaryl and aryl alkyl thioureas with sulphur and triethylammonium iodide as by-products (Scheme 61).[184,193]



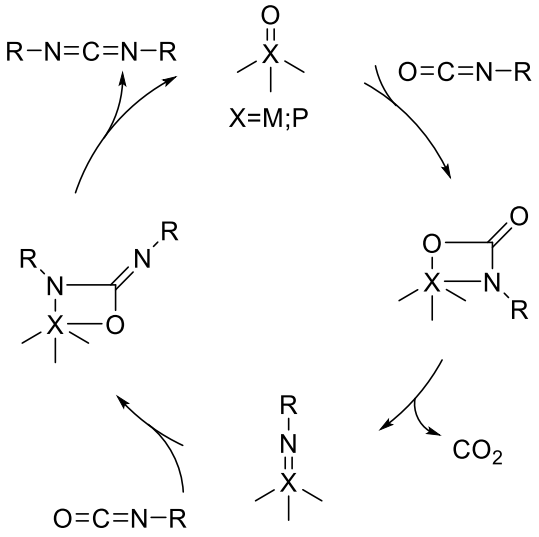
Scheme 61: Oxidative desulfurisation of diaryl-thioureas with I_2 as oxidant.

However, dialkyl carbodiimides were not accessible this way. Many more methods following one of these principles have been utilized in cyclodesulfurisation reactions, where carbodiimides are likely intermediates.[200] In 2018 YANG *et al.* used $(Boc)_2O$ as dehydrodesulfurisation agent with 20 mol% DMAP as catalyst. Diaryl thioureas were transformed to the corresponding carbodiimides in good yields under mild conditions.[206] *N*-Boc substituted thioureas where obtained as side-products and no carbodiimides where obtained when aryl-alkyl or dialkyl thioureas where used. For dehydration of ureas, strong dehydration agents like P_4O_{10}, thionyl chloride or phosgene are also used (Scheme 62).[207]



Scheme 62: Example for the preparation of carbodiimides by dehydration of ureas.

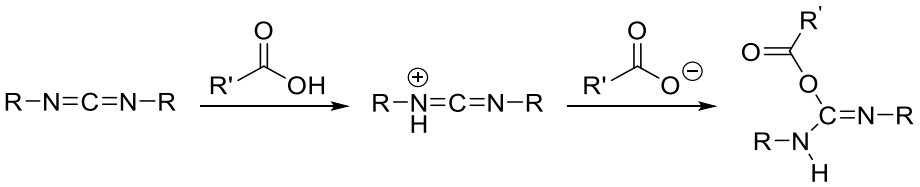
N,N-disubstituted carbodiimides have been prepared catalytically or non-catalytically *via* isocyanates metathesis under elimination of CO_2 (Scheme 63).



Scheme 63: Metathesis of isocyanates to CDIs catalysed by metals or phosphine oxides.[208–210]

Phosphorous compounds like phosphine oxides are among the most active catalysts.[211] Various metal catalysts have also been reported.[208–210,212] The first isocyanate forms an imide with the metal or phosphor oxide catalyst as intermediate *via* a 4-membered intermediate and CO_2 is eliminated as by-product. This imide then reacts with a second isocyanate under [2+2] addition via a similar 4-membered intermediate. The carbodiimide is liberated and the catalyst is regenerated.

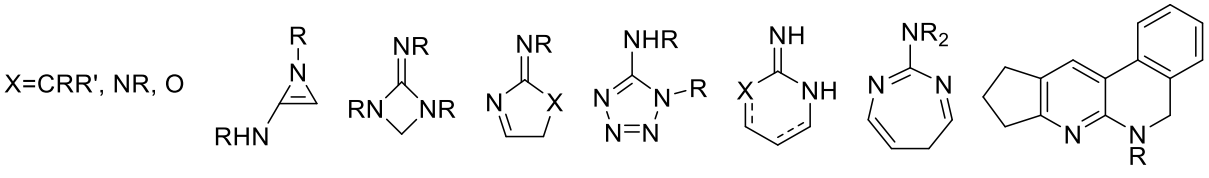
Simple carbodiimides like DIC and DCC are widely used as coupling agents in peptide synthesis[185] or in the STEGLICH-Esterfication (Scheme 64).[213]



Scheme 64: Formation of an O-acyl urea by a CDI and a carboxylic acid during STEGLICH-Esterfication.

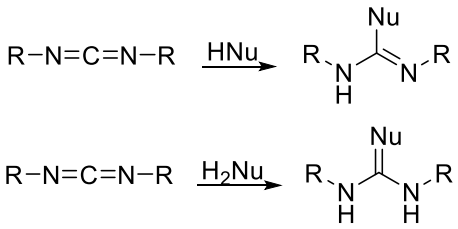
The formation of a highly reactive O-acyl urea as depicted in Scheme 64 is the first step of these reactions. The carbodiimide is activated by protonation prior to nucleophilic attack by the carboxylate.

Additionally, CDIs are valuable building blocks for various heterocycles (Scheme 65).[214]



Scheme 65: Selected examples for heterocycles prepared from carbodiimides.[214]

4-Membered heterocycles are accessible by [2+2] cycloaddition of unsaturated compounds like alkynes, ketenes and *iso*-cyanates with carbodiimides.[215–217] 5-membered heterocycles are accessible by reaction of carbodiimides and aldehydes[218], alcohols[219], acid chlorides[220] and carboxylic acids[221], esters[222] and epoxides.[223] Tetrazoles are formed by addition of N_3^- to carbodiimides.[224] Many more syntheses for larger heterocycles starting from CDIs have been described in the literature.[214] Additionally, carbodiimides undergo addition reactions with several nucleophilic compounds and weak acids such as H_2O, H_2S[225] and HCN (Scheme 66).[176,179] Stable aliphatic carbodiimides like DCC usually require harsher reaction conditions or a catalyst to undergo these addition reactions.[179]

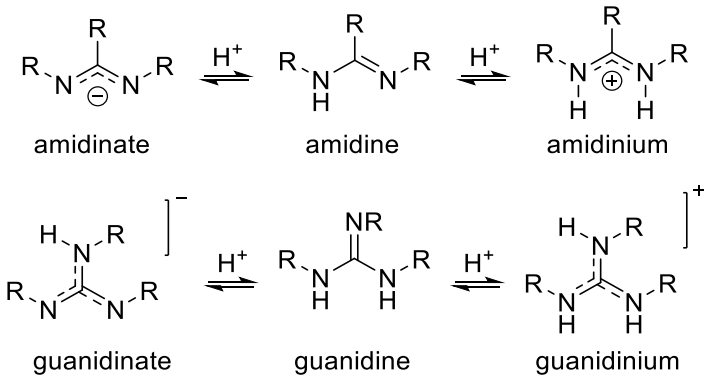


Scheme 66: General reaction of carbodiimides and nucleophiles.

Diaryl carbodiimides form acyl ureas with carboxylic acids whereas dialkyl carbodiimides give the acid anhydride and urea.[226] With carbon nucleophiles amidine derivatives are obtainable, amines and phosphines yield the corresponding guanidine derivatives and hydrazines give triazoles.[227]

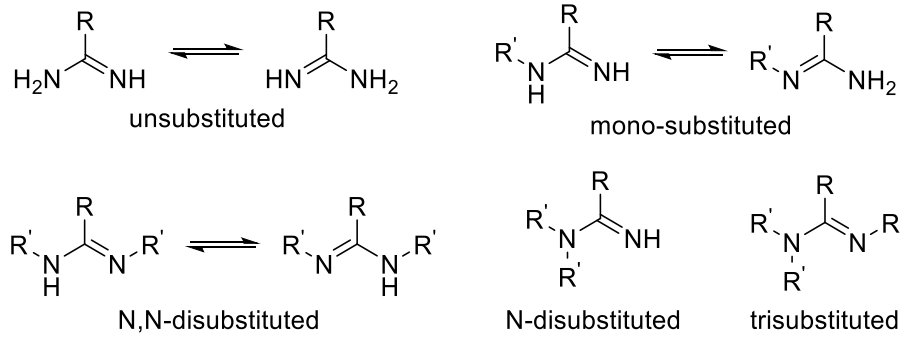
4.2 Amidines, guanidines and related derivatives: properties, applications and synthesis

An important class of compounds which can be derived from carbodiimides are amidines and guanidines (Scheme 67).



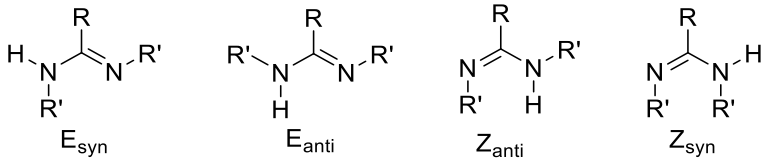
Scheme 67: Generic structure of amidines and guanidines and their salts.[228]

Amidines and guanidines are stronger organic bases than amines, due to the delocalization of the positive charge in the amidinium or guanidinium cation. Their anions are similarly stabilised and are called amidinates and guanidinates. The basicity depends on the degree of substitution on the *N* atoms as well as the type of substituents.[229–231] Based on their substituents, amidines can be divided into different categories (Scheme 68).



Scheme 68: Amidines classified by their degree of substitution and their tautomerisation.[231]

Since linear amidines can be formally described as the imino-amino derivatives of carboxylic acids, their name is often derived from that acid.[231] For example, amidines with R=H are known as formamidines, amidines with R=Me are known as acetamidines and with R=Ph as benzamidines. Unsubstituted, mono-substituted and *N,N*-disubstituted amidines exhibit tautomerism. If the difference in electronic properties of the substituents is large enough, a specific tautomer might be preferred. *N,N*-disubstituted amidines posess additional isomers due to *C-N*-rotation of the different tautomers (Scheme 69).

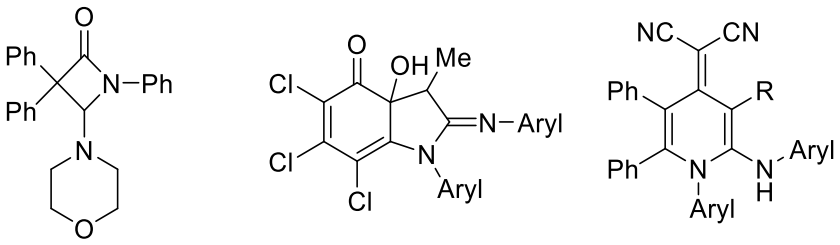


Scheme 69: Isomeric forms of *N,N*-disubstituted amidines.[228,232]

These isomers usually exist in a dynamic equilibrium in solution, but distinct isomers can be preferred in the solid state or upon complexation. For example, amidines which have been reported to exist in different isomeric states in solution can form isomerically pure complexes.[232] Aggregation *via* hydrogen bonds can also occur.[233] Temperature, the solvent used and the nature of the substituents all impact the structural configuration.[232,233] The barrier of rotation of the C-N bond for sterically non-demanding substituents R' is usually low enough to occur at room temperature. Rotation around the C=N bond does usually not occur at room temperature, but prototrophic tautomerisation is fast for amidines and enhanced by their ability to form dimeric structures in solution.[228,233–235] The literature and the examples

shown in this chapter, therefore show generic structures of amidines without indication of the various isomers.

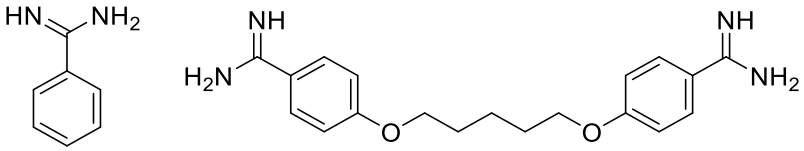
Like carbodiimides, amidines are valuable building blocks for various nitrogen containing heterocycles (Scheme 70). The centres of reactivity are in most cases the two *N*-atoms.[236]



Kugajevsky *et al*. 1966 Döpp *et al*. 2003

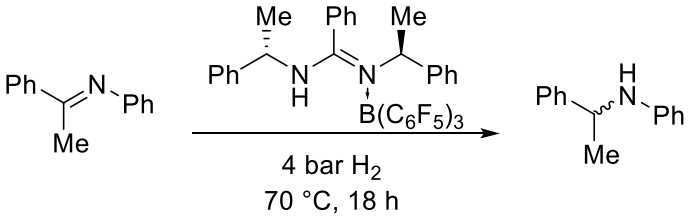
Scheme 70: Exemplary heterocycles prepared from *N,N*-disubstituted amidines.[237–239]

Aryl amidines are known for their biological activity (Scheme 71). They have been used as Trypsin inhibitors and are a relevant class of antiprotozoal agents.[240–243]



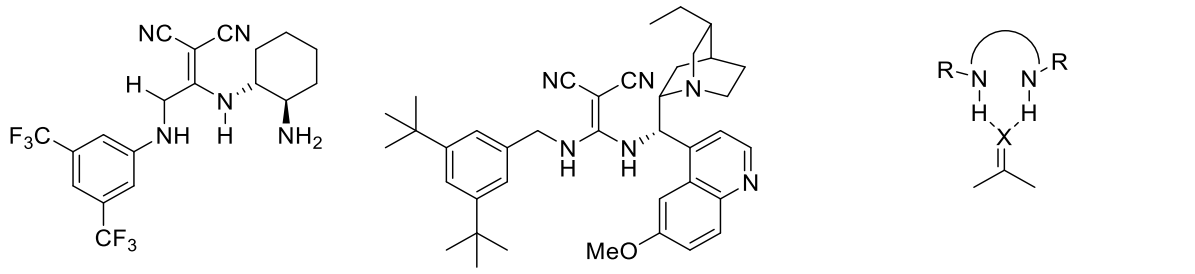
Scheme 71: Trypsin inhibitor benzamidine (left) and antiprotozoal agent pentamidine (right).

DBU and other cyclic amidines find widespread application as organic catalysts.[244] Few reports for the use of acyclic amidine organocatalysts exist, though chiral acyclic amidines have been used in catalysis (Scheme 72).[244–246]



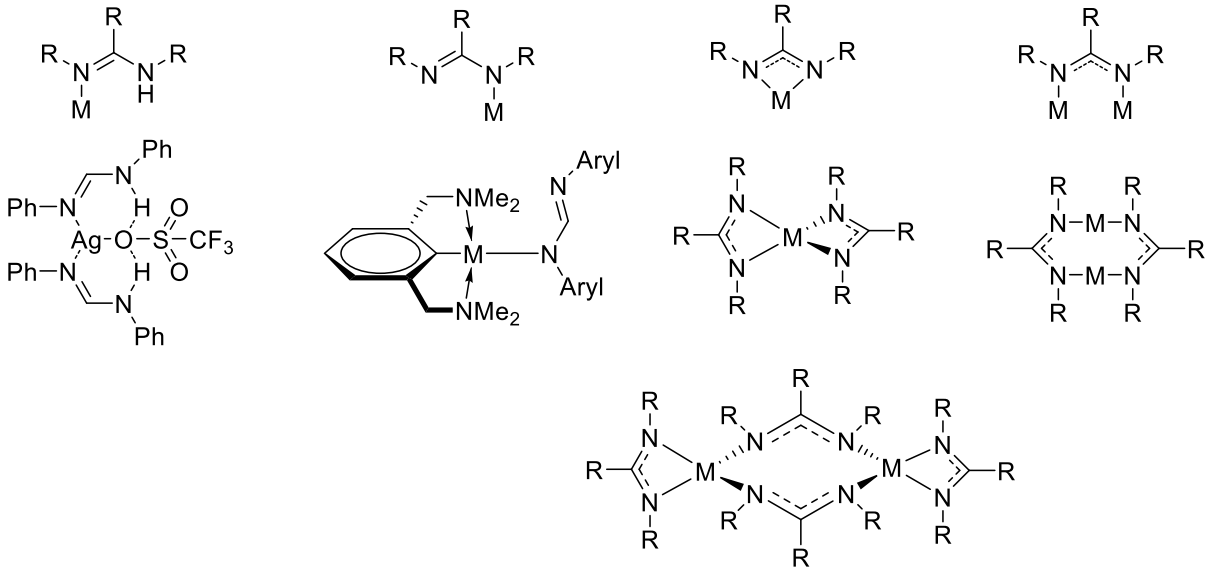
Scheme 72: Frustrated LEWIS pair-amidine catalysts for hydrogenation.[245]

Over the past decade MIURA *et. al* have introduced 2-bis(amino)methylene nitriles as organocatalysts for several asymmetric reactions (Scheme 73).[247–249] Analogue to thioureas and squaramides, these compounds are hydrogen bonding catalysts.



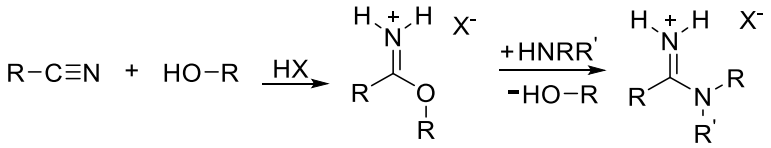
Scheme 73: Chiral 2-bis(amino)methylene nitrile catalysts and mechanism of activation.[247–249]

The N-C=N moiety of *N,N*-disubstituted amidines and amidinates enables a rich coordination chemistry and multiple bonding modes have been described[228,250] They can act as mono- and bidentate ligands[250] and can bind *via* the C=N imide function[251,252] or as amide ligands.[253] Amidines with *N*-aryl groups can also bind *via* the aryl ring[232] and neutral amidine ligands can exhibit additional hydrogen bonding.[254] The preferred mode of binding depends on the *N*-substituents of the amidine and the metal it binds to (Scheme 74).[228,232,250]



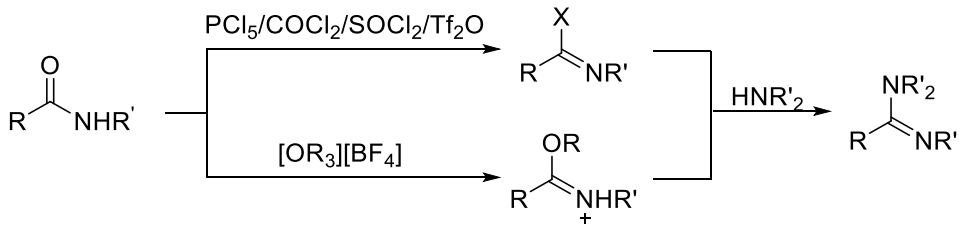
Scheme 74: Binding modes for amidines and amidinates and exemplary complexes.[253,254]

Amidinato-complexes of low molecular weight amidines like *N,N*-diisopropyl acetamidine are volatile enough to be used as precursors in chemical vapor deposition (CVD) processes.[250] Amidines have been known for well over a century. Therefore, several synthetic methods for their preparation have been described.[229,231,235,236] This chapter will focus on the most important methods, in particular those relevant to the research presented in this work. Unsubstituted, mono-substituted and *N*-disubstituted amidines are accessible from nitriles. First introduced by PINNER in 1877, the PINNER-Synthesis is one of the most well-known routes to amidines (Scheme 75).[255]



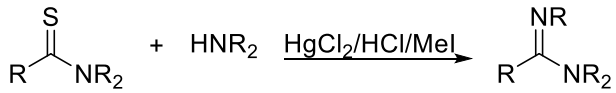
Scheme 75: Preparation of an amidinium salt *via* PINNER-Synthesis

Here, a nitril is protonated by a strong acid such as HCl gas and the generated cation is attacked by an alcohol, commonly ethanol. The resulting imidic ester, also known as PINNER salt, is a versatile intermediate for several compound classes. With ammonia, primary or secondary amines as reagent, amidinium salts are obtained. The reaction is performed under anhydrous conditions since the PINNER salt is sensitive towards hydrolysis. With an excess of amine *N,N*-disubstituted amidines can also be obtained.[231,256] Alternatively, the nitril is converted to the corresponding amidine by reaction with an amine in presence of a catalyst. These catalysts include acids and LEWIS acids like $AlCl_3$[257], CuCl[258] and La^{3+} salts.[259] Electron poor nitriles undergo the transformation without catalyst.[231,235,258,260] Aryl nitriles are converted to amidines with alkali metal amides or amines deprotonated *in situ* by strong bases like ^{n}BuLi.[261] Amides are another class of building blocks used in the synthesis of amidines. Mono substituted amides react with MEERWEIN salts[256] or halogenation agents such as PCl_5[262] to substituted equivalents of PINNER salts or imidoyl chlorides, respectively. These are subsequently converted with amines to the corresponding amidines (Scheme 76). The latter method is also applicable to disubstituted amides.[229–231,235,236]



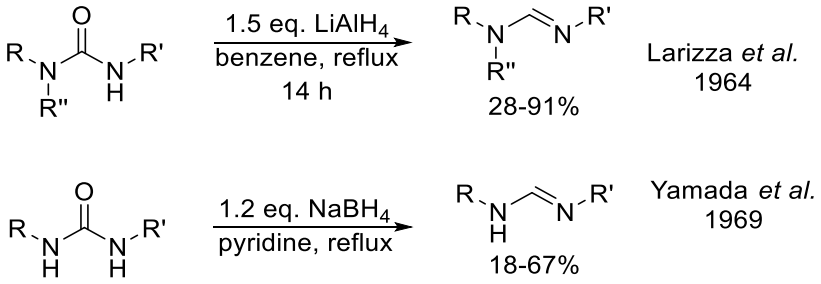
Scheme 76: General synthesis of amidines from amides.[235,256,262,263]

Multiple syntheses based on the condensation of ammonia, amines or their ammonium salts with thioamides are known (Scheme 77). The reaction can be enhanced by adding a desulfurization agent like Ag[264] or Hg salts.[265] *S*-Alkylated thioamides can be used as well.[266] All types of amidine are accessible *via* this method.[229,231,235]



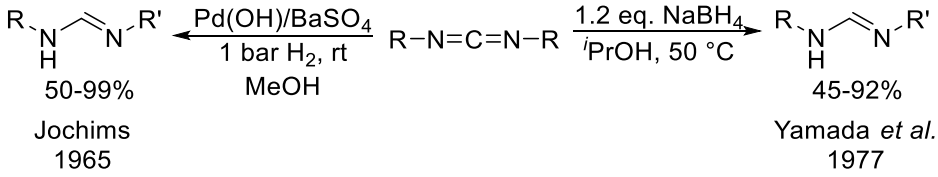
Scheme 77: General synthesis of amidines from thioamides.[231,265,266]

Formamidines are also accessible by the reduction of ureas, thioureas and carbodiimides (Scheme 78-79).



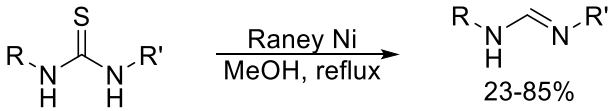
Scheme 78: Reductive transformation of ureas to formamidines by $LiAlH_4$[267] and $NaBH_4$.[268]

Formation of amine side-products *via* C-N cleavage is observed if $LiAlH_4$ is used as reductant. Dialkyl and diaryl carbodiimides have been reduced to their corresponding formamidines by $NaBH_4$[269] or by catalytic hydrogenation[270] (Scheme 79).



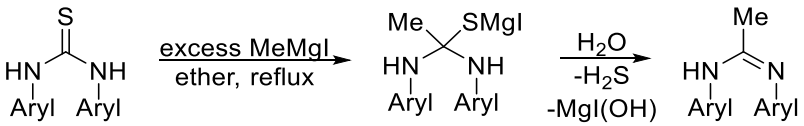
Scheme 79: Catalytic (right) and non-catalytic reductive transformation of CDIs to formamidines.

With Raney-nickel, thioureas have been reduced to formamidines in presence of methanol (Scheme 80).[271]



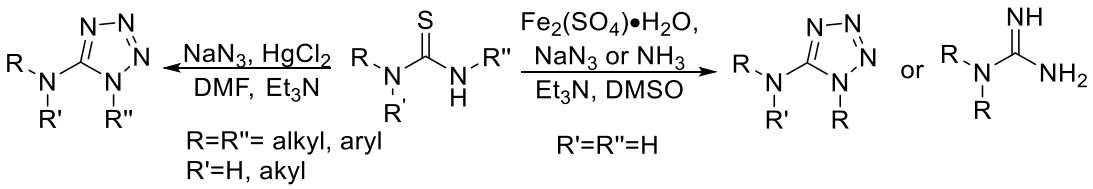
Scheme 80: Reductive transformation of thioureas to formamidines by Raney-Ni.[271]

The synthesis of *N,N*-diaryl acetamidines from thioureas and MeMgI was reported by KOSHKIN in 1958 (Scheme 81).[272]



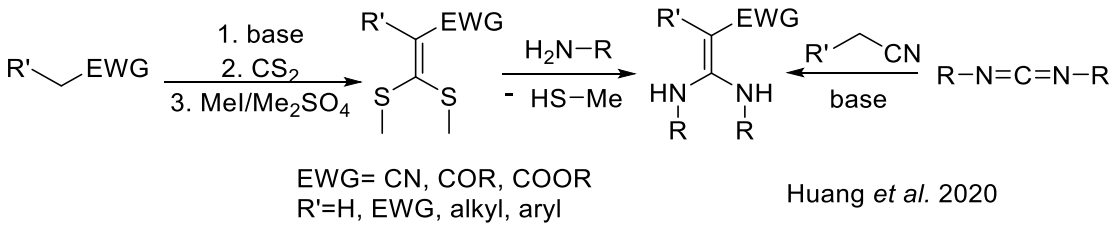
Scheme 81: Synthesis of *N,N*-diaryl acetamidines from thioureas as postulated by KOSHKIN.

Tetrazoles and guanidines have been prepared from thioureas in presence of *S*-acceptors like Hg^{2+} or Fe^{2+} and bases (Scheme 82).[273,274]



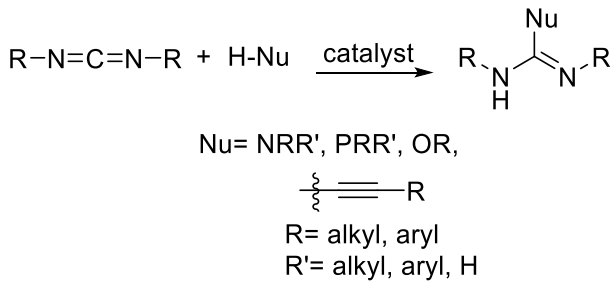
Scheme 82: Synthesis of tetrazoles and guanidines from thioureas.

Guanidines have also been prepared from thioureas and amines in presence of other *S*-acceptors like $HgCl_2$,[275,276] HgO[277] and $CuSO_4$.[278] More complex guanidines have been prepared from amines and thioureas with commercially available carbodiimides as dehydrodesulfurisation agents.[279,280] A variety of amidines and related compounds can be prepared from carbodiimides [see Scheme 66, Chapter 4.1]. Grignard reagents and Li-organyles add to carbodiimides and form the corresponding amidinates.[281] Nitriles react with carbodiimides in the presence of strong bases to 2-bis(amino)methylene nitrile compounds sometimes also called ketene aminales (Scheme 83).[282,283]



Scheme 83: General synthesis of 2-bis(amino)methylene compounds.

These can also be obtained by reaction of carbanions with electron withdrawing substituents with CS_2 followed by MeI or Me_2SO_4. The obtained dithioethers are then converted with amines into the corresponding 2-bis(amino)methylene compounds (Scheme 83).[284,285] Amines,[286,287] alcohols,[288] terminal alkynes[289] and phosphines[290,291] add to the central *C* atom of carbodiimides to from guanidines, iso-ureas, amidines and phosphaguanidines (Scheme 84).



Scheme 84: Catalytic addition of compounds with active hydrogen to carbodiimides.[227]

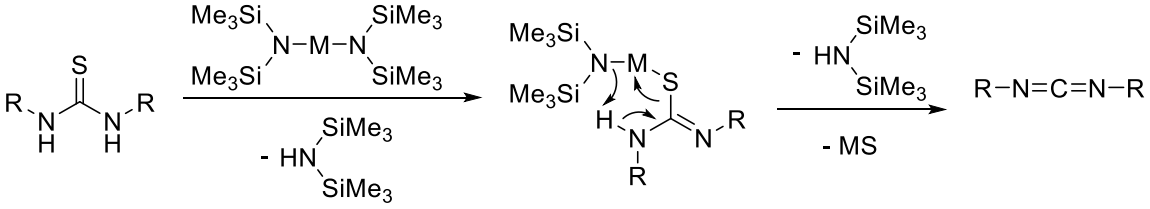
These reactions are catalysed by rare earth metal complexes, like La and Y, or bases such as LiHMDS.[227,288,289,291,292]

5 Results and discussion

5.1 Preparation of carbodiimides from thioureas

5.1.1 Aim of this chapter

As previously established, there is no general applicable synthetic method for carbodiimides (CDI). Especially the synthesis of primary alkyl substituted carbodiimides remains a challenge. Often toxic and highly aggressive reagents as well as harsh conditions are required. Therefore, a mild synthesis with less toxic reagents is highly desirable. The goal of this chapter was to find a 'greener' synthesis for CDIs. If it might be performed under mild conditions, it would allow the synthesis of thermally unstable CDIs. The dehydrodesulfurisation of thioureas with thiophilic metal complexes of a strong non-nucleophilic base was chosen as starting point. In particular, HMDS complexes of the type $M(HMDS)_2$, where M is a metal that forms very stable sulfides of the type MS and the hexamethyldisilazane anion ($HMDS^-$) acts as base, should be suitable reagents. They incorporate an *S*-acceptor and the base in the correct stoichiometry and are soluble in most organic solvents (Scheme 85).

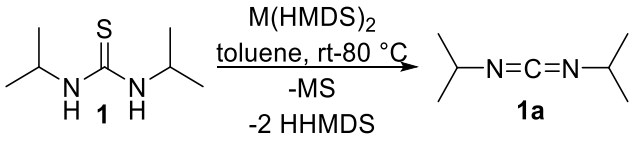


Scheme 85: Proposed dehydrodesulfurisation of thioureas with $M(HMDS)_2$ complexes.

This proposed reaction path might be followed in the known transformation of thioureas with bulky substituents with Li-HMDS.[196] This method would allow the reaction to occur under homogenous conditions, compared to the heterogenous dehydrodesulfurisation with other metal salts of oxides which are reported in the literature. Additionally, the by-products formed are not reactive towards the CDI. The formation of side-products should therefore be avoided.

5.1.2 Results and discussion

Diisopropyl thiourea has been chosen as model substrate as the product diisopropyl carbodiimide (DIC) is commercially available and relatively stable, which allows for easier analytics. $Pb(HMDS)_2$, $Sn(HMDS)_2$, $Zn(HMDS)_2$, $Fe(HMDS)_2$ and K(HMDS) have been investigated (Scheme 86, Table 13).



Scheme 86: Synthesis of DIC from thiourea 1 and different M(HMDS)$_2$ complexes.

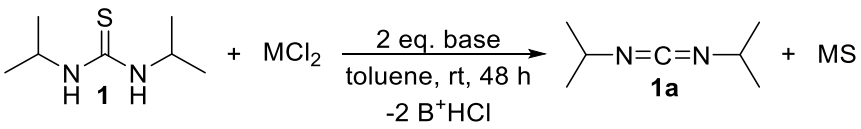
Table 13: Screening of different metal HMDS complexes for the dehydrodesulfurisation of 1.

Entry	M(HMDS)$_2$	Yield [%]	D_S(M) [kJ/mol][293]	$\Delta U_{lattice}$ (MS) [kJ/mol][294,295]
1	Sn(HMDS)$_2$	80	467	-3201
2	Pb(HMDS)$_2$	78	398	-3161
3	Fe(HMDS)$_2$	57	329	-3506
4	Zn(HMDS)$_2$	21	225	-3674
5	K(HMDS)	0	-	-1979

1.eq. diisopropyl thiourea, 1 eq. M(HMDS)$_2$ or 2 eq. K(HMDS), 20 h rt than 3 h 80 °C, toluene, D_S(M) = bond dissociation enthalpy of the metal sulfide MS; $U_{lattice}$ = lattice energy of the metal sulfide MS.

With exception of K(HMDS) all reagents desulfurize thiourea **1** to DIC **1a**. The performance roughly correlates with the M-S bond dissociation enthalpy (D_S(M)) which can be used as a rough measure for the MS lattice energy of the resulting metal sulfide MS.[293] Sn^{2+} and Pb^{2+} HMDS complexes give the highest yields and form the thermodynamically most stable MS bonds. The difference between yields is small despite a rather large difference in D_S(M) and $\Delta U_{lattice}$. Fe^{2+} still gives the carbodiimide in 57% yield. Zn^{2+} was the least effective dehydrodesulfurisation agent (with exception of K^+) despite having the highest lattice energy. There may be other factors that affect the reaction, such as the stability of the M(HMDS)$_2$ complex and its ability do deprotonate thioureas.

Since M(HMDS)$_2$ complexes are rather expensive and air sensitive, more convenient alternatives were investigated. Here, simple metal chlorides MCl_2 and base were used in a one-pot reaction (Scheme 87). The effect of the basicity of the employed base was also investigated.



Scheme 87: Synthesis of DIC from thiourea 1 with different metal salts and bases.

Sn^{2+}, $Fe^{2+}$and Zn^{2+} were tested with different metal organic and amine bases of different basicity. The results are listed in Table 14.

Table 14: Screening of different metal chlorides and bases for the synthesis of DIC from thiourea 1.

Entry	Metal	Base ($pK_{BH}+$)[296–298]	D_S(M) [kJ/mol][293]	$\Delta U_{lattice}$ (MS) [kJ/mol][294,295]	Yield [%]
1	Sn^{2+}	KHMDS (30)	467	-3201	64
2	Sn^{2+}	KO^{t}Bu (32.2)	467	-3201	89
3	Sn^{2+}	DBU (13.9)	467	-3201	53
4	Sn^{2+}	Et_3N (9.0)	467	-3201	46
5	Zn^{2+}	KHMDS (30)	225	-3674	27
6	Zn^{2+}	KO^{t}Bu (32.2)	225	-3674	70
7	Zn^{2+}	DBU (13.9)	225	-3674	8
8	Zn^{2+}	Et_3N (9.0)	225	-3674	35
9	Fe^{2+}	KHMDS (30)	329	-3506	47
10	Fe^{2+}	KO^{t}Bu (32.2)	329	-3506	71
11	Fe^{2+}	DBU (13.9)	329	-3506	17
12	Fe^{2+}	Et_3N (9.0)	329	-3506	40
13	Fe^{2+}	OAc^- (12.3)	329	-3506	trace
14	Cu^+	KO^{t}Bu (32.2)	n.a.	-2865	46
15	Cu^{2+}	KO^{t}Bu (32.2)	275	-3795	trace
16	Li^+	^{n}Bu$^-$ (50)	313	-2472	-
17	Ca^{2+}	KO^{t}Bu (32.2)	335	-2966	-

Conditions: 1 eq. diisopropyl thiourea, 2 eq. base, 1 eq. MCl_2, rt, 48 h, toluene (THF in case of KO^{t}Bu); a) basicity in DMSO

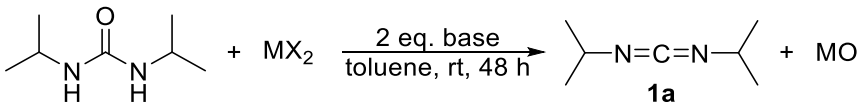
Table 14 indicates the “strength” of the MS bond is indeed not the only driving force. While Sn^{2+} still gives the highest yield (Entry 1-4), Zn^{2+} and Fe^{2+} can reach up to 71% yield under the best conditions (Entry 6 and 10). Ca^{2+} and Cu^{2+} which have a M-S bond dissociation enthalpy comparable to Fe^{2+} and Zn^{2+} respectively are not suitable dehydrodesulfurisation agents under the chosen conditions (Entry 15 and 17). A correlation between the lattice energy of the formed sulfide and the yield of carbodiimide was not observed. Instead, the basicity has significant impact on the performance. KO^{t}Bu (pK_{BH+} = 32.2) was the most effective in all cases, outperforming K(HMDS) (pK_{BH+} = 30) and the $M(HMDS)_2$ complexes in all cases. As the

dehydrodesulfurisation involves deprotonation of the thiourea, a stronger base should be able to accelerate the reaction, especially the abstraction of the second proton, which should be less acidic than the first one. Acetate was the weakest base employed in form of $Fe(OAc)_2$ and gave only trace amounts of carbodiimide. The difference in performance between the MCl_2 - 2 KHMDS system and the $M(HMDS)_2$ system can be explained by the difference in solubility: with $M(HMDS)_2$ a homogenous system is formed, while MCl_2 is mostly suspended in the reaction mixture. As such $M(HMDS)_2$ should be more reactive. Zn^{2+} is the exception to this trend as the $ZnCl_2$ – 2 KHMDS system performs slightly better (27% vs. 21% yield). Triethylamine (Et_3N, $pK_{BH}+ = 9.0$) is another curiosity. Despite possessing a lower basicity than DBU ($pK_{BH}+ = 13.9$), it is superior in combination with Zn^{2+} and Fe^{2+} (Entry 7-8 and 11-12). Indicated by a change in appearance from a brownish suspension to a pinkish solution, Et_3N solubilises the metal salts, allowing the reaction to proceed under homogeneous conditions, resulting in an improved performance. Additionally, in case of $ZnCl_2$ and DBU the formation of a separate colourless phase is observed in presence of the thiourea (Entry 7). This suggests that some sort of stable ionic liquid is formed rather than the carbodiimide. No DIC was obtained with Cu^{2+}, however Cu^{+} gave the carbodiimide in 46% yield. With these results it can be said that the reactions performance depends on: the strength of the base used, the thiophilicity of the metal (for which there is no clear scale or definition) and the solubility of the metal salt or metal complex. No positive effect for increasing the reaction temperature or the amount of base has been observed. However, longer reaction times give the best yields.

During attempts to increase the scope of the reaction to other thioureas it became obvious that this method suffers from similar limitations as other literature known methods. Unstable carbodiimides e.g. primary alkyl substituted ones were only obtained in trace amounts with excessive formation of several unidentified by products. Diaryl thioureas also underwent significant side reactions. While the reaction is performed under mild conditions, the conditions during work-up are harsher. The metal sulphide particles formed as by-product have a small particle size under anhydrous and anaerobic conditions which made filtration not feasible. Therefore, distillation of the crude product is required, which is problematic for thermally unstable carbodiimides or diaryl carbodiimides. Similar boiling points of the CDI and protonated base (eg. ^{t}BuOH, HMDS) can further complicate the distillation process. Aqueous work-up leads to coagulation of the metal sulphide particle allowing for an easier removal but also leads to hydrolysis of the more sensitive carbodiimides. Other coagulation agents were

tested but were proven ineffective. However, as the dehydrodesulfurisation reaction seemed to be successful in most cases, evident by the formation of metal sulphide and by detection of trace amounts of carbodiimides, this approach might be applicable to *in situ* trapping and functionalisation of these carbodiimides. This is explored in greater detail in Chapter 5.2.

As the preparation of stable carbodiimides by dehydrodesulfurisation by thiophilic metal precursor and a base seemed feasible, it was investigated if this approach might be applied to ureas as well. Fe^{2+}, Fe^{3+}, Zn^{2+}, Sn^{2+}, Mn^{2+}, Ca^{2+} and La^{3+}, Ti^{4+} were tested (Scheme 88, Table 15).



Scheme 88: Attempts to prepare DIC 1a from diisopropyl urea.

Table 15: Screening of different metal salts for the synthesis of DIC from diisopropyl urea.

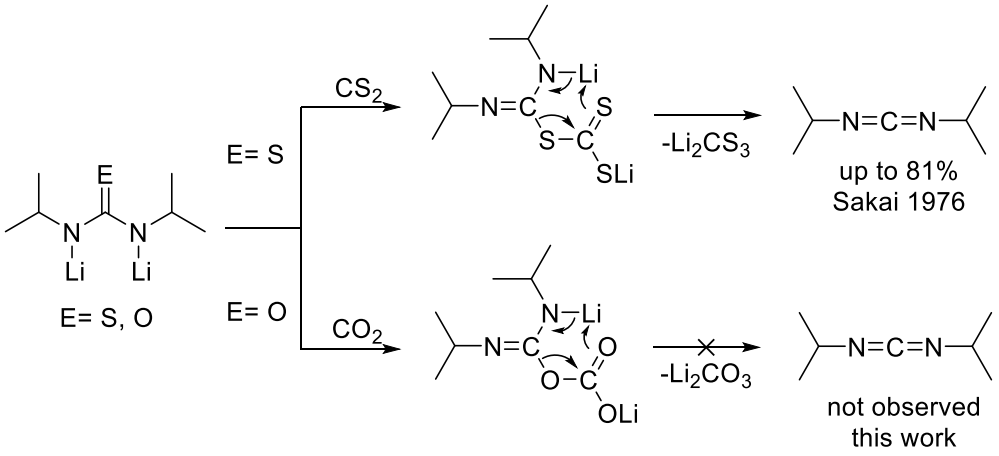
Entry	Metal	Base	$D_O(M)$[293] [kJ/mol]	$\Delta U_{lattice}$[294,295,299] [kJ/mol]	Yield [%]
1	$FeCl_2$	KO^{t}Bu	407	-3865	-
2	$FeCl_3$	KO^{t}Bu	n.a.	-14774	-
3	$Zn(HMDS)_2$	$HMDS^-$	250	-39971	-
4	$Mn(HMDS)_2$	$HMDS^-$	362	-3745	-
5	$Sn(HMDS)_2$	$HMDS^-$	528	-3652	traces
6	Ti(^{i}PrO)$_4$	^{i}PrO$^-$	667	-12054	-
7	$TiCl_4$	KHMDS	667	-12054	-
8	$La(HMDS)_3$	$HMDS^-$	798	-12687	-
9	$CaCl_2$	KO^{t}Bu	383	-3401	-

Conditions: 1 eq. diisopropyl urea, 1 eq. metal salt, 2 eq. base, THF, rt, 24 h.

While deprotonation of the urea takes place, no formation of metal oxides is observed and the substrate was recovered after work up. It seems that the C=O bond of the urea is too strong and the formation of M-O is not a sufficiently high enough driving force for these transformations.

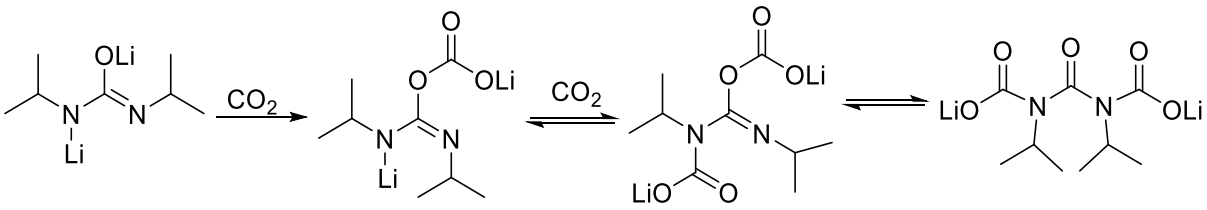
Several potential 'greener' alternative dehydration or dehydrodesulfurisation agents were briefly investigated. SAKAI *et al*. reported that the dehydrodesulfurisation of bulky dimetalated thioureas were greatly enhanced by addition of CS_2 (Scheme 89).[195,197] In this case the sulphide is removed as Li_2CS_3 instead of Li_2S. CO_2 was therefore investigated as additive to the

dehydration and dehydrodesulfurisation of thioureas and ureas. The formation of a lithium carbonate might be a better driving force the formation of metal oxide.



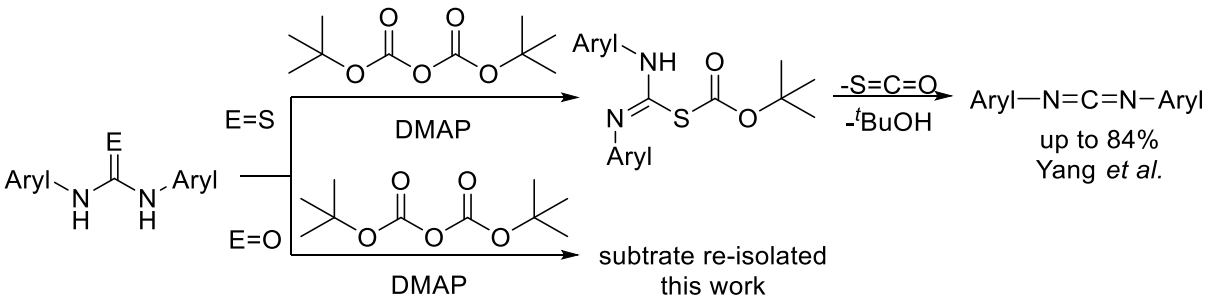
Scheme 89: Synthesis by SAKAI (top) and transfer attempt to the oxygen analogues (bottom).[195]

The formation of carbodiimides *via* this method was not observed. With ureas different CO_2 adducts seem to have formed. Shortly after addition of the base a white precipitate is formed, likely the dilithiated urea. Upon introduction of CO_2 to the reaction, the colourless precipitate dissolved and a slightly yellow, clear solution was formed. After about 10 minutes at 15 bar CO_2 another precipitate formed. This one was far less stable and upon degassing or heating above 50 °C under 15 bar of CO_2 the precipitate dissolved or decomposed again. This suggests that the dilithiated urea and CO_2 form two adducts. One stable under ambient conditions and one only present at elevated CO_2 pressures (Scheme 90). Isolation of the first adduct was also not possible as it decomposed when the solvent was removed. Decomposition likely occurs *via* liberation of CO_2 while heating or under reduced pressure.



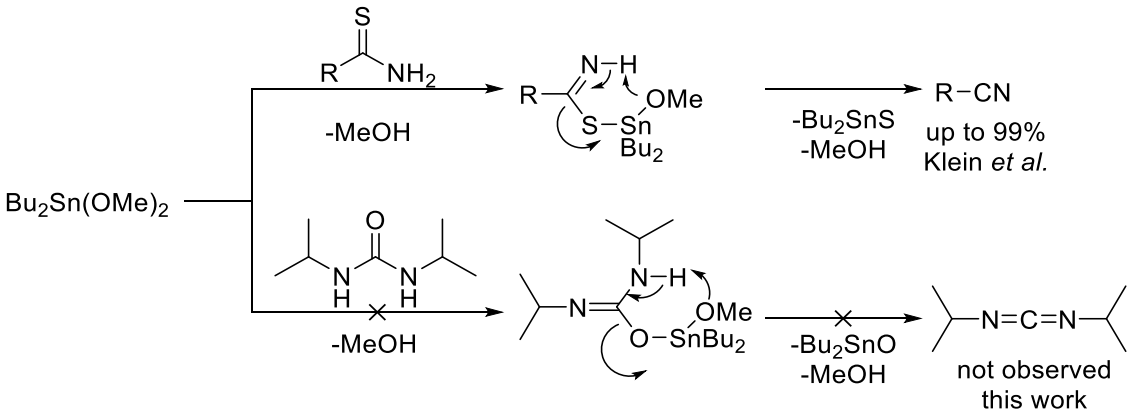
Scheme 90: Proposed reaction between dilithiated *N,N*-diisopropyl urea and excess CO_2.

YANG *et al*. reported the use of di-^{t}butyl dicarbonate (Boc_2O) as dehydrodesulfurisation agent for diaryl thioureas.[206] With 4-dimethylamino pyridine (DMAP) as catalyst good yields of CDIs were obtained with ^{t}BuOH and COS as by-products. They did not report if this system could be used for the dehydration of ureas as the formation of CO_2 could be a good driving force (Scheme 91).



Scheme 91: Carbodiimide synthesis by YANG (top) and transfer attempt (bottom).[206]

Unfortunately, no reaction took place if diaryl urea was used instead of a diaryl thiourea. Substituting Boc_2O by cheaper dimethyl carbonate was also not effective for the dehydrodesulfurisation of thioureas. $Bu_2Sn(OMe)_2$ has been reported as an effective dehydrodesulfurisation agent.[300] Additionally, $Bu_2Sn(OMe)_2$ has been used as a catalyst in the synthesis of dimethyl carbonate from CO_2 and methanol[301] and in the preparation of carbamates.[302] In the latter two cases $Bu_2Sn(OMe)_2$ acts as a dehydration agent. It can be regenerated by reaction with simple acetals or alcohols.[303] It was therefore investigated as a potential reagent in the synthesis of CDIs from urea (Scheme 92).



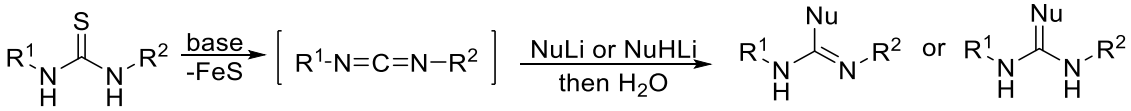
Scheme 92: Dehydrodesulfurisation of thioamides by $Bu_2Sn(OMe)_2$ (top) and attempt of dehydration of diisopropyl urea (bottom).

Unfortunately, no reaction was observed. Similar to the attempt of utilizing oxophilic $M(HMDS)_2$ (Table 15), such as $Mn(HMDS)_2$, as dehydration agents, the formation of a metal oxygen bond is not a sufficient driving force.

5.2 One pot synthesis of amidines and other derivatives from thioureas

5.2.1 Aim of this chapter

While the developed dehydrodesulfurisation of thioureas to carbodiimides worked well for the stable and volatile DIC, other carbodiimides could not be isolated, as they decomposed or polymerized during work up. Since carbodiimides are often used as building blocks for other compounds like amidines and guanidines [see Chapter 4.2], the *in situ* functionalisation of these proposed unstable carbodiimide intermediates was studied instead. This way, instead of the sensitive CDIs, more stable derivatives are isolated. A common derivatisation is the reaction of a carbodiimide with a nucleophile.[227,281,282,288] Carbanions and amine nucleophiles would lead to the important class of amidines and guanidines, respectively (Scheme 93).

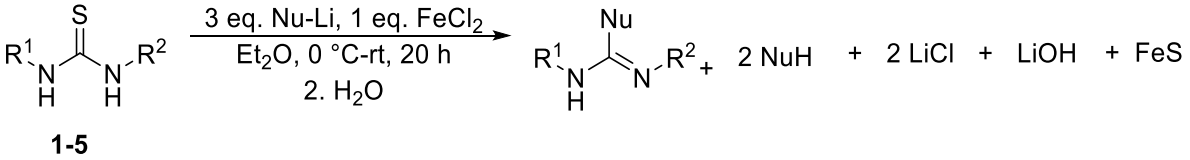


Scheme 93: General reaction scheme for the preparation of derivatives from thioureas *via in situ* formed carbodiimides.

Since the commercial availability of carbodiimides is limited and certain carbodiimides are synthetically challenging to access, a synthetic procedure to amidines and similar compounds from thioureas, that are easy to prepare and handle, would be highly desirable. This work especially aims to provide access to the compounds where R^1 and R^3 are different primary, secondary or tertiary alkyl substituents. R^1 and R^3 are inherited from the parent thiourea. Simple commercially available lithium organyls are particularly interesting as they not only give access to a variety of amidines but can also act as the base required in the dehydrodesulfurisation step. With organolithium reagents as nucleophiles, the Li-amidinate is formed which, upon hydrolysis, gives the amidine. This would allow for an easy method of backbone modification of *N,N*-disubstituted amidines. As previously discussed, these isomers exist in a tautomeric equilibrium in solution. This is observed as a slight broadening of some signals in ^{1}H-NMR spectroscopy. Additionally, isolation of the isomerically pure amidines is not possible. Any determination of the isomers and their ratios to each other would only be accurate for specific conditions. Therefore, all amidine structures depicted in this chapter include their tautomers and stereoisomers in equilibrium.

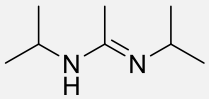
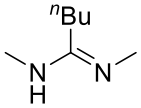
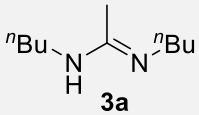
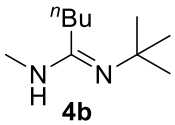
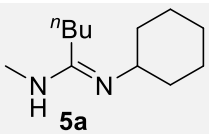
5.2.2 Preparation of *N,N*-disubstituted amidines from thioureas, $FeCl_2$ and alkyl-lithium reagents

The investigation started with MeLi and ^{n}BuLi as the bases and nucleophiles and $FeCl_2$ as a cheap and benign sulphur acceptor. Symmetrically and unsymmetrically substituted thioureas **1**-**5** were chosen as substrates. The carbodiimide intermediates which would presumably be formed are of varying stability: dimethyl carbodiimide as the most unstable[182], di^{n}butyl carbodiimide[176] as fairly stable and diisopropyl carbodiimide as fully stable representatives of this substance class under ambient conditions (Scheme 94, Table 16).[182,183]



Scheme 94: Preparation of amidines from thioureas with $FeCl_2$ as *S*-acceptor.

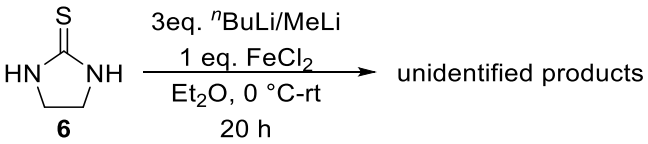
Table 16: Preparation of amidines from thioureas with $FeCl_2$ as *S*-acceptor.

Entry	R^1	R^2	Nu	Amidine	Yield [%]
1	^{i}Pr	^{i}Pr	Me	 **1b**	68
2	Me	Me	^{n}Bu	 **2a**	69
3	^{n}Bu	^{n}Bu	Me	 **3a**	58
4	Me	^{t}Bu	^{n}Bu	 **4b**	55
5	Me	cHex	^{n}Bu	 **5a**	50

Conditions: 1g thiourea **1-6**, 1 eq. $FeCl_2$, 3 eq. MeLi or ^{n}Bu-Li, 50 mL diethyl ether, 0 °C-rt, 20 h, isolated yields

The *in situ* functionalisation was successful for all non-cyclic thioureas and the desired *N,N*-disubstituted amidines were obtained in satisfying yields (>50%). The stability of the presumable intermediate carbodiimide plays no discernible role, amidine **2a**, formally derived

from the highly unstable dimethyl carbodiimide, is just as accessible as amidine **1b** derived from the stable DIC. Unsymmetrically substituted amidines like **4b** and **5a** are also accessible by this method. Only a mixture of unidentified products was obtained when cyclic thiourea **6** was used (Scheme 95).

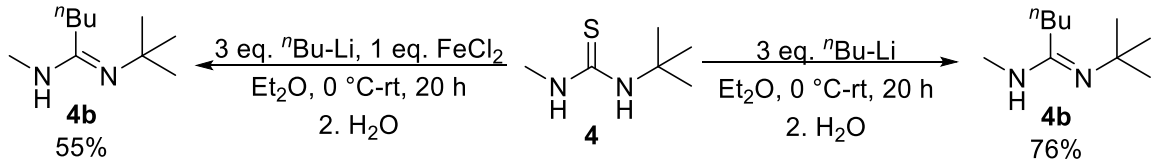


Scheme 95: Attempt to prepare an amidine from cyclic thiourea 6.

The work-up is simple, after quenching with 2M NaOH, the mixture separates into an upper ether phase and lower aqueous phase. The finely suspended FeS particles coagulate in presence of water and sink to the bottom, resulting in a mostly iron-free product phase. Additionally, many thioureas are poorly soluble in diethyl ether while the corresponding amidines are fully soluble. As a result, the amidines are obtained relatively pure without further purification, though small impurities remain. Other solvents like THF and DME lead to significant formation of side-products, partially through reactions between the solvent and ^{n}BuLi. Amidines are more stable then carbodiimides, their stability towards hydrolysis depends on the substituents R^1 and R^2.[231] While amidines with bulky *N*-substituents do not hydrolyse under ambient conditions, small quantities of amide where detected in the crude product after aqueous work up for amidines with R^1 and/or R^2 = Me. Fortunately, hydrolysis for **2a**, **4b** and **5a** is slow under the present conditions, so that this method remains feasible. The amidines are thermally stable enough to be further purified by distillation or sublimation.

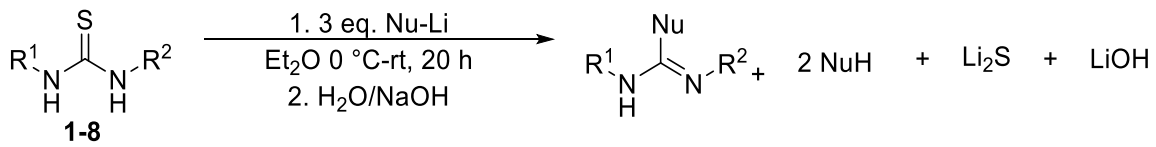
5.2.3 Preparation of *N,N*-disubstituted amidines from thioureas and lithium organyls without additional *S*-acceptor

There have been a handful of reports about the dehydrodesulfurisation of bulky thioureas with non-thiophilic metal organic bases over the last 90 years [see Chapter 4.1], mainly for the preparation of carbodiimides. A particularly interesting method was reported by KOSHKIN in 1934 and 1958.[272,304] Diphenyl thiourea reacts with sodium malonate to the corresponding amidine.[304] Aryl thioureas react with methyl magnesium iodide under reflux conditions to aryl acetamidines.[272] To the best of our knowledge, these are the only known examples for the synthesis of alkyl amidines directly from thioureas and no mention of this method was found after 1975. With these reports in mind, the necessity for a thiophilic *S*-acceptor was investigated. Thiourea **4** which was previously reacted with 3 eq. ^{n}BuLi in presence of $FeCl_2$ was now reacted with 3 eq. ^{n}BuLi in absence of $FeCl_2$ (Scheme 96).



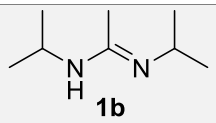
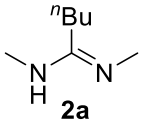
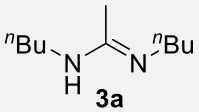
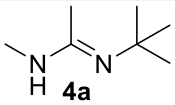
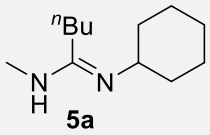
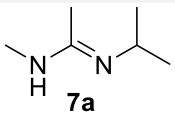
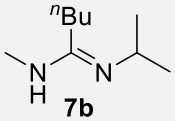
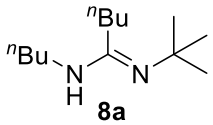
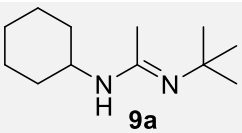
Scheme 96: Preparation of amidines from thioureas in absence of an additional *S*-acceptor.

Delightfully, the reaction proceeded smoothly under mild conditions and amidine **4b** was obtained in 76% yield. With it's Me substituent, thiourea **4** is not very bulky, suggesting that this method may not suffer from the same limitations as the literature known dehydrodesulfurisation reactions with metal organic bases.[195] Seven additional thioureas with varying substituents were used with this method to determine its general applicability (Scheme 97). Indeed, all thioureas could be converted into the corresponding amidine in absence of any additional *S*-acceptor. Symmetrically or unsymmetrically substituted thioureas as well as primary, secondary or tertiary alkyl substituted thioureas are suitable substrates for this reaction (Table 17).



Scheme 97: Preparation of amidines from thioureas without additional *S*-acceptor.

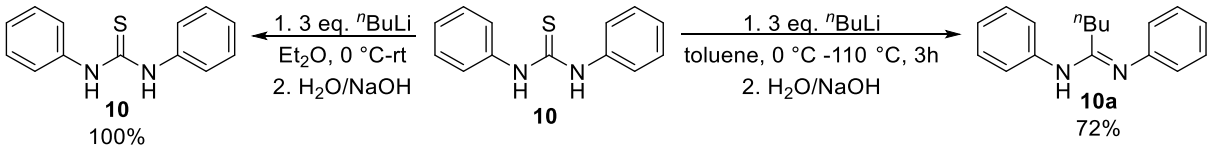
Table 17: Preparation of amidines from thioureas without additional *S*-acceptor.

Entry	R^1	R^2	Nu	Amidine	Yield [%]
1	^{i}Pr	^{i}Pr	Me	 **1b**	55
2	Me	Me	^{n}Bu	 **2a**	63
3	^{n}Bu	^{n}Bu	Me	 **3a**	58
4	Me	^{t}Bu	Me	 **4a**	64
5	Me	cHex	^{n}Bu	 **5a**	75
6	Me	^{i}Pr	Me	 **7a**	43
7	Me	^{i}Pr	^{n}Bu	 **7b**	82
8	^{n}Bu	^{t}Bu	^{n}Bu	 **8a**	99
9	cHex	^{t}Bu	^{n}Bu	 **9a**	89

Conditions: 1g thiourea **1-6**, 3 eq. MeLi or ^{n}BuLi, 50 mL diethyl ether, 0 °C-rt, 20 h, isolated yields

With ^{n}BuLi higher yields of amidine are achieved compared to the corresponding amidine obtained with MeLi. Amidine **4b** obtained from thiourea **4** and ^{n}BuLi with 76% whereas **4a** was only obtained with 64% yield with MeLi as nucleophile. The yield of **7b** is almost double that of **7a** and in case of thiourea **5** no amidine was obtained with MeLi as base and nucleophile and the substrate was reisolated at the end of the reaction. With ^{n}BuLi the corresponding

amidine **5a** was obtained in 75% yield. The acetamidines **1b, 3a, 4a, 7a** and **9a** are also more sensitive towards hydrolysis relative to their butyl counterpart. Especially in case of **7a** the amide hydrolysis product (Me-CO-NHMe) is always observed as a side product. The cyclic thiourea **6** and *N,N*-diphenyl thiourea **10** did not react under these conditions. Only deprotonation occurred and the substrate was recovered after aqueous work up. Since KOSHKIN's synthesis of *N,N*-diaryl acetamidines was performed at elevated temperatures, the experiment was repeated under reflux conditions. (Scheme 98).[272]

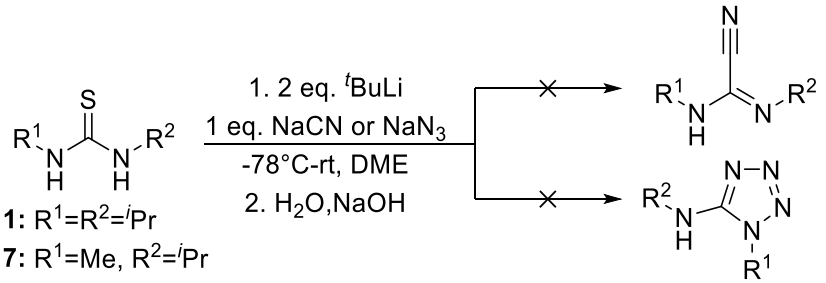


Scheme 98: Preparation of *N,N*-diphenylpentanamidine.

The diaryl amidine **10a** was obtained in 72% yield. This suggests, that diaryl thioureas are far less reactive in this reaction. Isolation of the Li-amidinates was attempted as well, but they were contaminated by large quantities of Li_2S in all cases. A potential reason for this is the complexation of Li_2S by the Li-amidinates. The fact in some cases no precipitation of Li_2S was observed even though an amidine was obtained after aqueous work-up supports this hypothesis.

5.2.4 Preparation of amidines, guanidines and other derivatives with *in situ* generated nucleophiles.

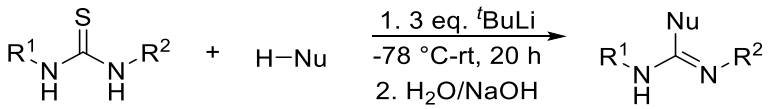
Having established a synthetic pathway for *N,N*-disubstituted alkyl amidines, focus was put on more complex derivatives. If other nucleophiles than alkyl-Li could be successfully employed a slew of different compound classes could become accessible by this method. Cyanide and azide are known to add to carbodiimides to form cyanoamidines[305] and tetrazoles[306] respectively. NaCN and NaN_3 were reacted with thiourea **1** and **7** and ^{t}BuLi as a less nucleophilic base (Scheme 99).



Scheme 99: Attempts to prepare cyanoamidines and tetrazoles from thioureas.

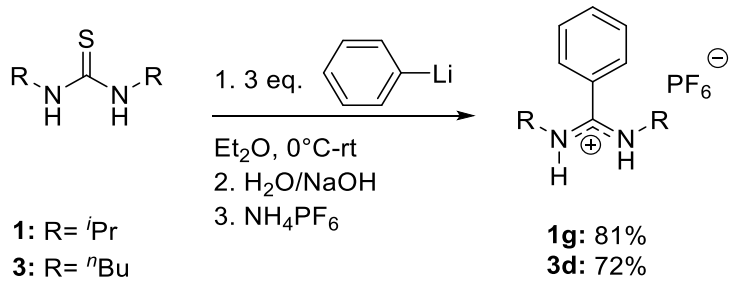
However, no product formation was observed and thiourea **1** and **7** were recovered after work-up. While it may be possible that CN^- and N_3^- are not nucleophilic enough to add to a carbodiimide intermediate under present conditions, it appears that no carbodiimide intermediate was formed in the first place [See Chapter 5.2.5 for a more detailed discussion] since the thioureas were recovered and no carbodiimide was detected.

Another class of nucleophiles are carbanions prepared *in situ* from CH acids. These are known to readily undergo addition reactions with carbodiimides.[282] These are especially interesting as they may be formed *in situ* by slight modification of the synthesis of alkyl amidines discussed previously (Scheme 100).



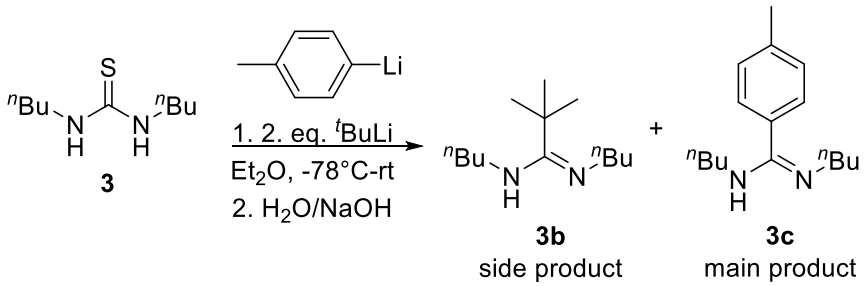
Scheme 100: General reaction scheme for the preparation of amidines and related compounds from thioureas and *in situ* prepared carbon nucleophiles.

When benzyl potassium (BnK) or sodium cyclopentadienyl (NaCp) were used as the base and nucleophile, analogue to MeLi or ^{n}BuLi, no product was formed. The reaction of thiourea **1** with cyclopentadiene or diphenylmethane and 3 eq. of ^{t}BuLi also resulted in the re-isolation of the thiourea. Carbenes prepared *in situ* from CHX_3 (X = Cl, Br, I) and the base, result in a mixture of unidentified products. Since amidines with an aryl backbone are an important class of biologically active compounds[240,241,307], their synthesis was briefly investigated. PhLi and 4-bromotoluene were chosen as model substrates (Scheme 101 and 102).



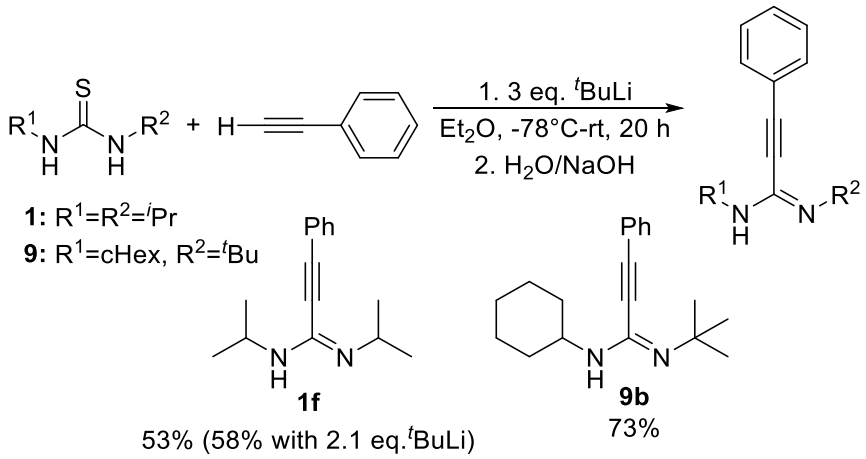
Scheme 101: Preparation of *N,N*-disubstituted benzamidines.

With PhLi, *N,N*-diisopropyl benzamidine and *N,N*-di-^{n}butyl benzamidine are obtained as PF_6 salt in 81% and 72% yield, respectively. Two amidines were obtained when the carbanion generated from 4-bromotoluene was used with 2 eq. of ^{t}BuLi as sacrificial base.



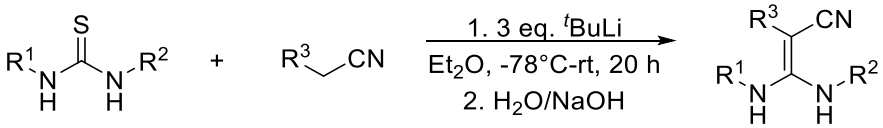
Scheme 102:Preparation of a *N,N*-disubstituted arylamidine with a substituted aryl.

The desired aryl amidine **3c** is the main product and **3b** is formed as side product. It seems that under certain conditions even ^{t}BuLi can act as a nucleophile for this reaction. Some carbanions generated from C-H acidic compounds also react with thioureas to the corresponding derivative. Phenylacetylene reacts with thiourea **1** and **9** and ^{t}BuLi to the corresponding phenyl propiolamidines (Scheme 103).



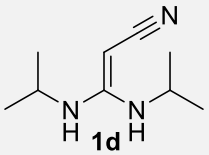
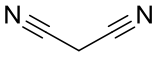
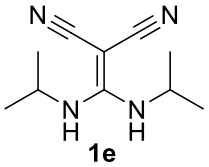
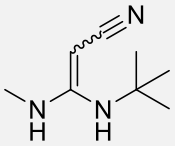
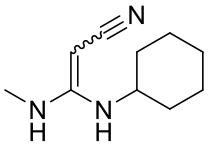
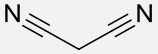
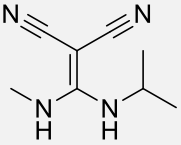
Scheme 103: Preparation of phenyl propiolamidines from thioureas and phenylacetylene.

In case of thiourea **1** the reaction with phenylacetylene even proceeds with just 2.1 eq. of ^{t}BuLi. This suggests that resulting amidinate is capable of deprotonating phenylacetylene to generate the required nucleophile. Nitriles also react with thioureas, although they do not yield amidines but 2-bis(amino)methylene nitriles (Scheme 104, Table 18).[282]



Scheme 104: Preparation of 2-bis(amino)methylene nitriles from thioureas.

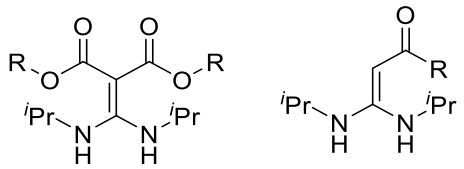
Table 18: Preparation of 2-bis(amino)methylene nitriles from thioureas.

Entry	R^1	R^2	R^3CH_2CN	Product	Yield [%]
1	^{i}Pr	^{i}Pr	MeCN	 **1d**	55
2	^{i}Pr	^{i}Pr		 **1e**	67
3	Me	^{t}Bu	MeCN	 **4c**	n.d. impure
4	Me	cHex	MeCN	 **5b**	n.d. impure
5	Me	^{i}Pr		 **7c**	24

Conditions: 1g thiourea, 1 eq. nitrile, 3 eq. ^{t}BuLi, diethyl ether 50 mL, -78 °C – rt, 20 h, isolated yields.

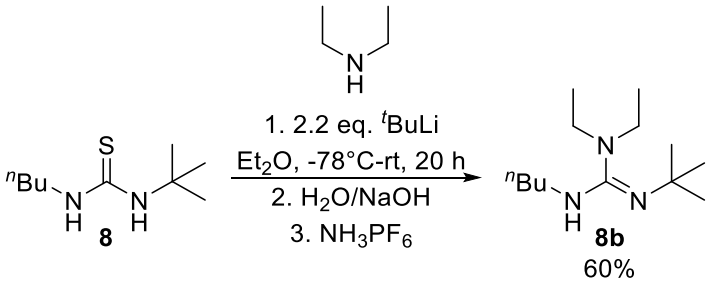
The carbanion generated *in situ* from malonodinitrile reacts with thiourea **1** and **7** to the 2-bis(amino)methylene malonodinitriles **1e** and **7c**. Acetonitrile also reacts with thioureas **1**, **4** and **5**. The reaction is not stereoselective, so that two different isomers are obtained if unsymmetrically substituted thioureas are used. The symmetrically substituted **1d** and **1e** can be purified by simple crystallisation, but not the unsymmetrically substituted **4c** and **5b**. Attempts to distil these products lead to the formation of several unidentified products. Purification by column chromatography was only successful for **7c** and parts of the product have been lost, possible due to the relative hydrolytic sensitivity of Me substituted 2-bis(amino)methylene nitrile compounds towards hydrolysis. For similar reasons the isolation of pure **4c** and **5b** and the separation of the isomers *via* column chromatography over AlO_x and silica was not successful. However, the presence of these products could be confirmed by mass spectrometry. If nitromethane is used as the C-H acid instead of

acetonitrile, only trace amounts of the desired product is detected by mass spectrometry alongside several unidentified side products. C-H acidic compounds capable of forming enolates are similarly unsuitable substrates under the present synthetic protocol (Scheme 105).



Scheme 105: Literature known products of the addition of CH-acids to carbodiimides.[181,308]

Another important substance class that can be prepared from carbodiimides are guanidines and phosphaguanidines[227,291] While the reaction of diphenyl phosphine with thiourea **7** was not successful, diethyl amine reacts with thiourea **8** and 2.2 eq. ^{t}BuLi to guanidine **8b** (Scheme 106).

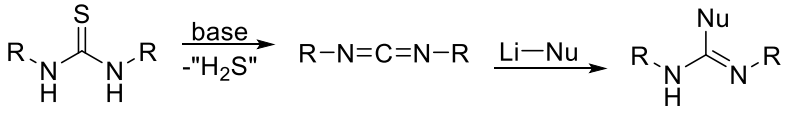


Scheme 106: Preparation of guanidine 8d from thiourea 8.

8b is isolated in good yield and purity with NH_4PF_6 as its guanidinium salt.

5.2.5 Mechanistic investigation of the reaction of thioureas with strong nucleophiles in absence of a thiophilic *S*-acceptor

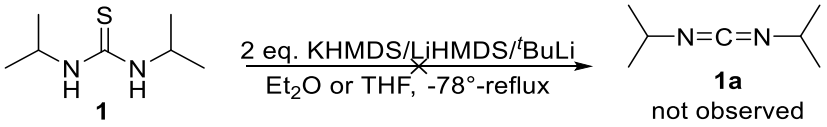
One hypothesis about the mechanism involves the formation of intermediate carbodiimides *via* dehydrodesulfurisation (Scheme 107).



Scheme 107: Expected mechanism of the formation of amidines from thioureas.

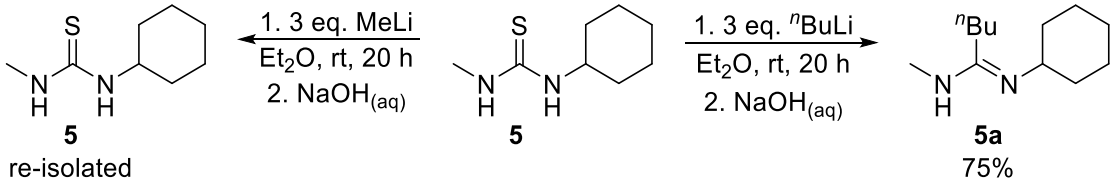
Certain observations made during the investigation of this reaction call this hypothesis into question. First and foremost, the dehydrodesulfurisation of thioureas to carbodiimides by a metal organic base in absence of a *S*-acceptor is limited to thioureas with sterically demanding

substituents.[195–197] In this work, diisopropyl thiourea **1** was reacted with 2 eq. of several non-nucleophilic metal organic bases under different conditions and only trace amounts of **1a**, if any, were observed (Scheme 108).



Scheme 108: Attempts to prepare carbodiimide 1a from thiourea 1 in absence of an additional *S*-acceptor.

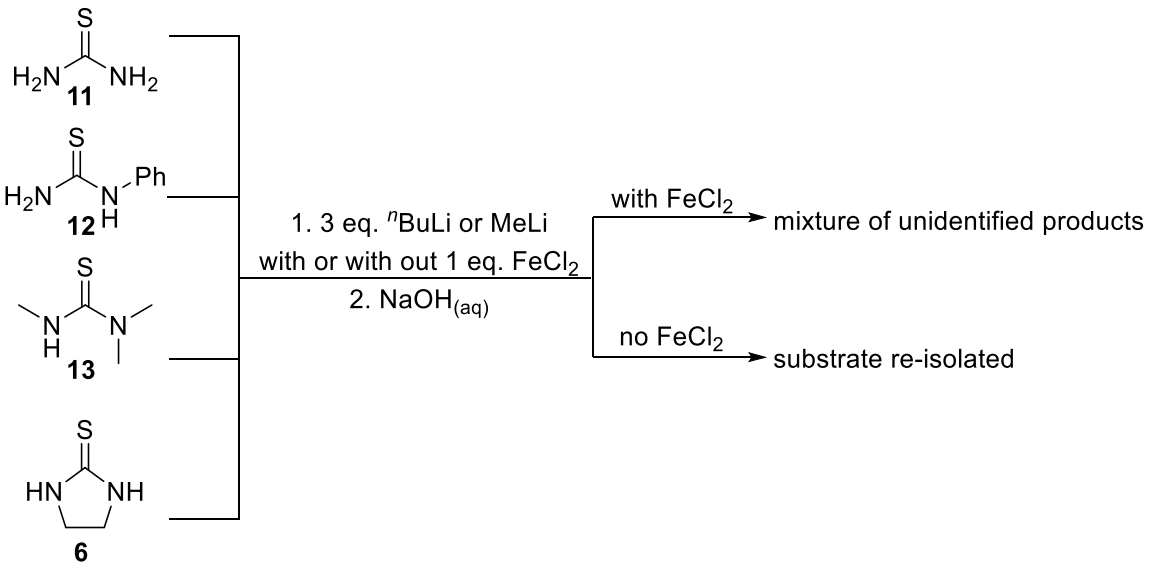
Thioureas with less bulky substituents should be less prone to undergo this reaction. The type of nucleophile generally seems to affect the outcome of the reaction: **5** reacts with ^{n}BuLi to amidine **5a** but is reisolated when MeLi is used instead (Scheme 109).



Scheme 109: Reactivity of 5 towards ^{n}BuLi and MeLi.

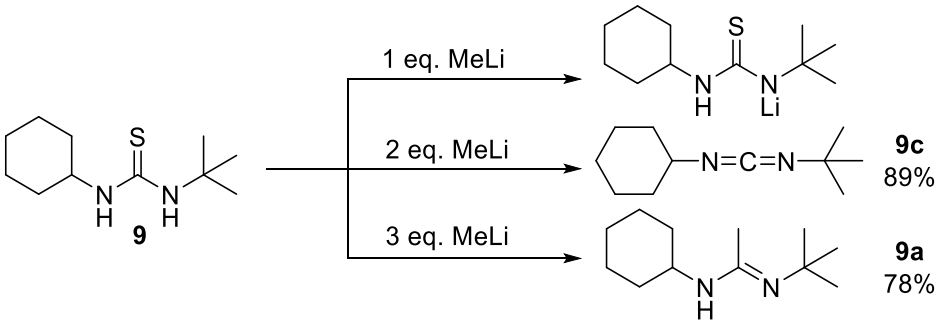
Furthermore, some nucleophiles known to undergo addition reactions with carbodiimides like malonic esters[181] and azides[200] did not yield the corresponding derivative under the present reaction conditions.

On the other hand, some observations support the carbodiimide intermediate hypothesis. Tri substituted, mono substituted and unsubstituted thioureas, which are unable to form carbodiimides, did not react (Scheme 110).



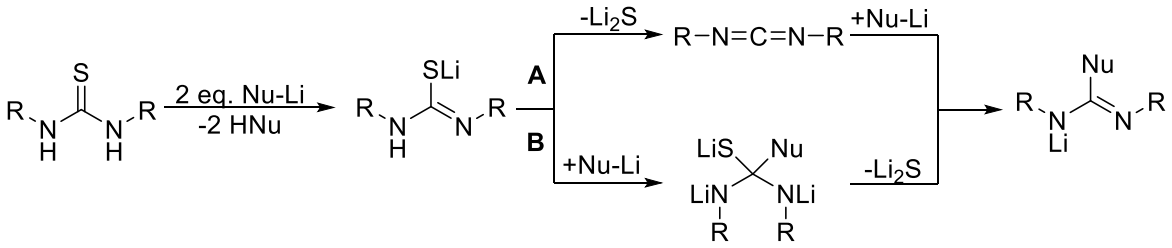
Scheme 110: Reaction of unsubstituted, mono-and trisubstituted thiourea with ^{n}BuLi or MeLi.

The cyclic thiourea **6** showed a similar reactivity. Additionally, for the bulky thiourea **9**, the formation of carbodiimide was observed (Scheme 111).



Scheme 111: Reaction of thiourea 9 with different equivalents of MeLi.

With 1 eq. MeLi only deprotonation occurs and the thiourea is recovered. Wit 2 eq. MeLi carbodiimide **9c** is obtained in 89% yield. With 3 eq., acetamidine **9a** is obtained with 78% yield. Based on these observations, one may conclude that two different mechanistic pathways exist (Scheme 112).



Scheme 112: Proposed mechanism for the formation of amidines from thioureas without additional *S*-acceptor.

Both pathways require the double deprotonation of the thiourea, as no product was ever observed with just 1 eq. of MeLi. For the dilithiated thiourea, there are now two possible reaction paths. **Path A** involves the elimination of Li_2S and the formation of a carbodiimide. The carbodiimide is then subsequently attacked by the nucleophile to form the amidinate. Following **Path B**, the dilithiated thiourea is attacked by the nucleophile and Li_2S is either simultaneously eliminated or a quaternary transition state is formed which subsequently eliminates Li_2S. In both cases the amidinate is obtained. The path, **A** or **B**, the reaction follows seems to depend on the nature of the thiourea. Bulky ones like **9** which form rather stable carbodiimides follow **Path A**. Thioureas with sterically less demanding substituents follow **Path B**. The nature of the nucleophile likely plays a larger role in **Path B**, since the reaction can't proceed if the nucleophile is unable to attack the dilithiated thiourea. As a result, poorer nucleophiles might not react with less bulky thioureas but might be suitable for thioureas that follow **Path A**.

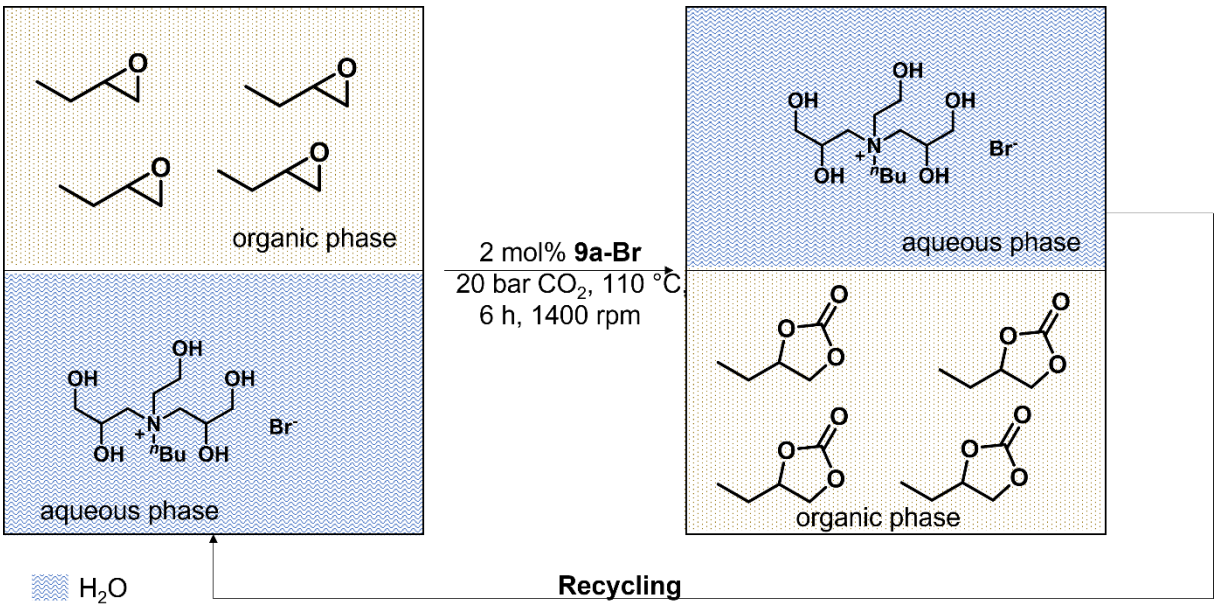
6 Summary

This dissertation deals in part I with the synthesis of cyclic organic carbonates from the most sustainable C_1-building block: CO_2. Part II deals with the synthesis of amidines from carbodiimides, the diimino derivatives of CO_2, or from thioureas as more accessible substrates, respectively.

Part I

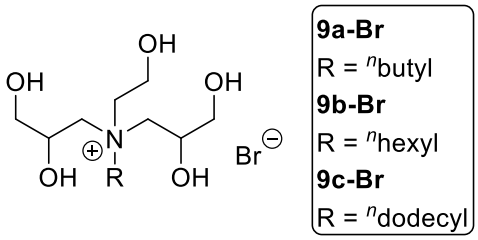
Aqueous two-phase synthesis of cyclic carbonates from CO_2 and epoxides

The focus of this chapter was on the development of a multiple phase catalysis for the preparation of organic carbonates with water as sustainable solvent (Scheme 113).



Scheme 113: Two phase synthesis of butylene carbonate with catalyst 9a-Br.

The aim was to utilise the miscibility gap between water and most cyclic organic carbonates for an energy efficient catalyst recycling. Additionally, water acts as co-catalyst *via* hydrogen bonding to the epoxide. The developed water-soluble organocatalysts **9a-Br** demonstrated a high productivity for the carboxylation of propylene oxide (94% yield, 95% selectivity) and butylene oxide (95% yield, 97% selectivity). Through modification of the catalyst into surfactants (Scheme 114) highly hydrophobic epoxide could be used as substrates as well.

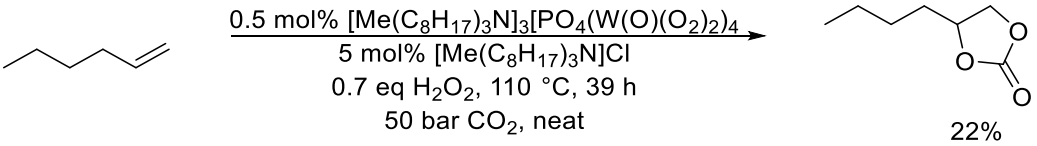


Scheme 114: Water-soluble catalyst 9a-Br and its surfactant analogues.

The catalyst could be recycled multiple times through simple phase separation, though a slow decline in productivity was observed. However, it was demonstrated that the catalyst **9a-Br** can be regenerated *in situ* by addition of small quantities of aqueous HBr after each run. This is explained by replacing the bromide lost through the formation of bromohydrin as trace product.

Synthesis of cyclic carbonates from olefines and H_2O_2

1,2-hexane carbonate was obtained in 22% yield from olefines, CO_2 and H_2O_2 under solvent free conditions (Scheme 115).

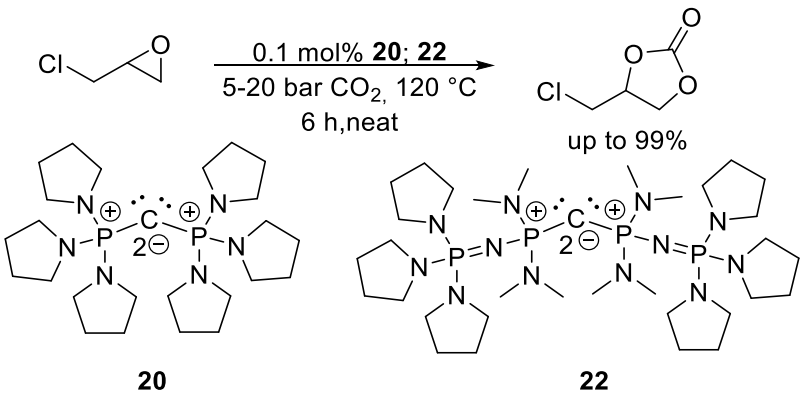


Scheme 115: One-pot synthesis of 1,2-hexane carbonate from 1-hexene.

Towards oxidation by H_2O_2 stable, but less nucleophilic anions NO_3^- and Cl^- were used as nucleophilic carboxylation catalysts instead of oxidation sensitive bromide and iodide. Unfortunately, decomposition of the quaternary ammonium cation of the ionic catalysts inhibited the implementation of an efficient orthogonal tandem catalysis as one pot synthesis. Additionally, both reaction steps favour different temperatures.

Organic superbases as catalysts for the coupling of CO_2 and epoxides

In this chapter carbodiphosphorane and phosphazenyl phosphine superbases have been used as organocatalysts for the carboxylation of epoxides for the first time. The C- and P-bases, provided by IGOR MARTIN and SEBASTIAN WAGNER, were highly active organocatalysts. Epichlorohydrin conversion >80% with yields up to 99% at full selectivity were achieved with just 0.01-0.1 mol% and TONs up to 8600 (Scheme 116).



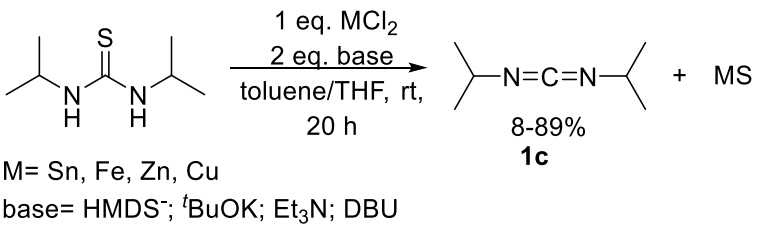
Scheme 116: Coupling of CO_2 and epichlorohydrin with carbodiphosphorane superbases as catalyst.

The catalysts were also robust and remained active after 8 h reaction time and in presence of moisture. The free C-and P-base as well as the corresponding CO_2- or water-adduct can be used as precursor. Additionally, it was shown that a too strong nucleophilic character of the superbase catalysts leads to the undesired polymerisation of the epoxide. Investigation of the reaction mechanism revealed that, regardless of if the free base or the CO_2-adduct is employed, the onium bicarbonate of the superbase is present at the end of the reaction. This suggests that the reaction proceeds *via* an onium bicarbonate formed *in situ* from the superbase, CO_2 and traces of moisture as catalytically active species.

Part II

Preparation of carbodiimides from thioureas

Diisopropyl carbodiimide was prepared from diisopropyl thiourea *via* dehydrodesulfurisation with strong bases and thiophilic metal cations as sulfur acceptors (Scheme 117).

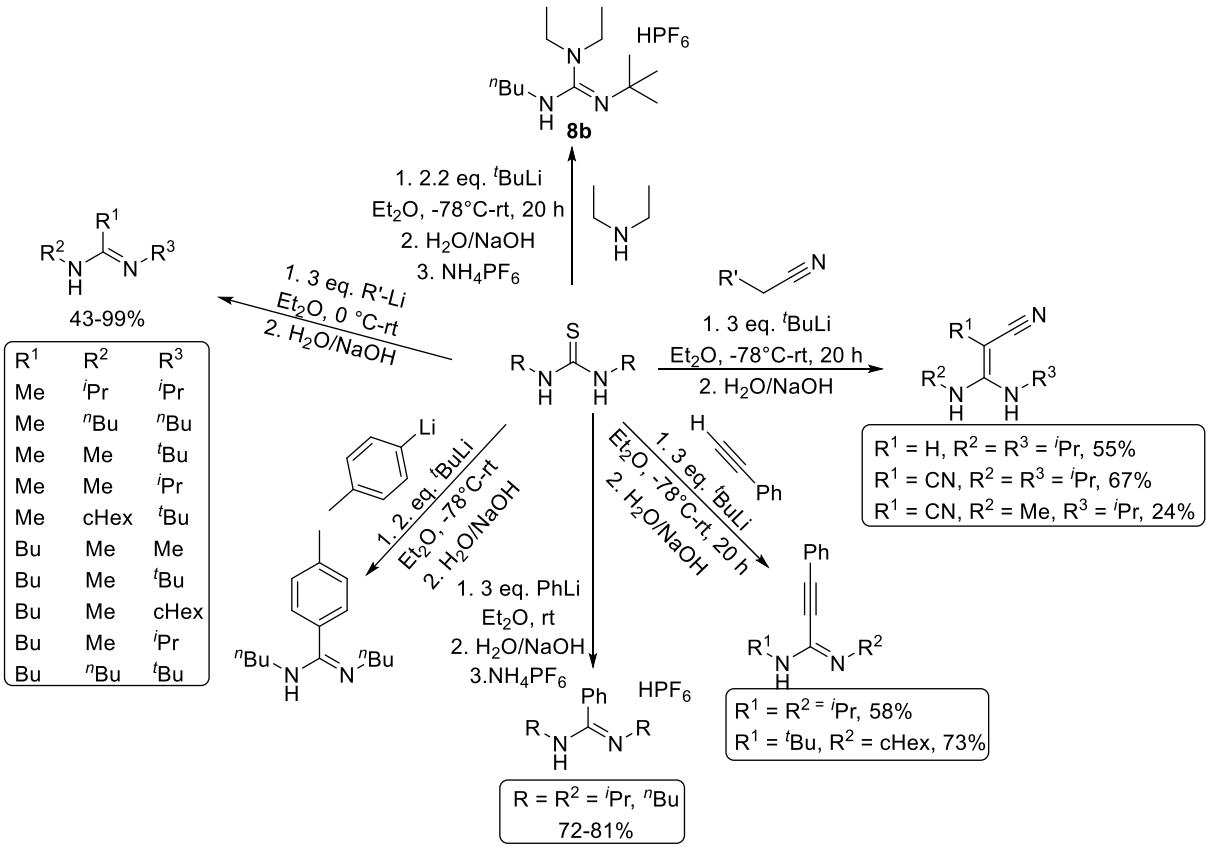


Scheme 117: Dehydrodesulfurisation of diisopropyl thiourea to diisopropyl carbodiimide.

The thiophilicity of the metal and the strength of the base impact the yield of the reaction. However, the concept could not be transferred to a wider selection of thioureas or ureas. The isolation of unstable primary alkyl substituted carbodiimides was not feasible.

One-pot synthesis of amidines from thioureas

In 2-position alkyl, aryl or alkinyl substituted amidines were prepared from dialkyl and diaryl thioureas with MeLi, ^{n}BuLi, PhC≡CLi or PhLi. The desulfurisation does not require an additional sulfur acceptor next to the lithium cation itself. Through simple modification of the synthetic protocol, the method was extended to the synthesis of an unsymmetrical guanidine and a selection of 2-bis(amino)methylene nitriles (Scheme 118).



Scheme 118: Synthesis of amidines and related compounds from thioureas.

The required nucleophiles were prepared *in situ* by the same lithium base used for the deprotonation of the thiourea. This enables one pot conditions for these reactions. The isolation of carbodiimide intermediates is not necessary. This method allows the synthesis of several valuable compound classes from a single cheap, stable and accessible thiourea as starting material without the need for toxic metals.

7 Zusammenfassung

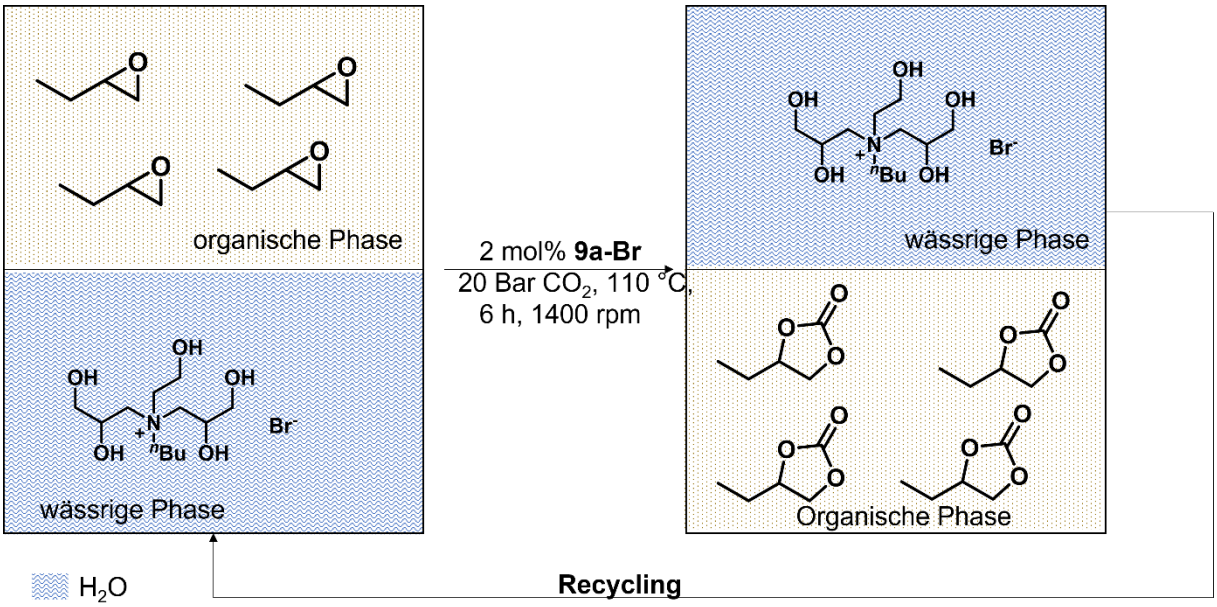
Diese Dissertation befasst sich in Teil I mit der Synthese zyklischer organischer Carbonate aus dem nachhaltigsten aller C_1-Bausteine: CO_2. Teil II handelt von der Synthese von Amidinen aus

Carbodiimiden, den Diiminoderivaten des CO_2, beziehungsweise aus Thioharnstoffen als leichter zugänglichen Edukten.

Teil I

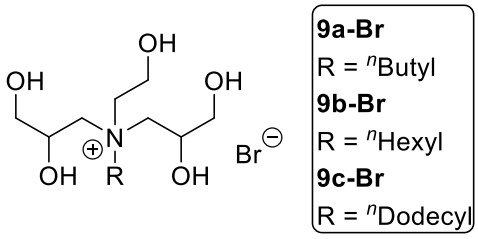
Wässrige Zweiphasensynthese zyklischer organischer Carbonate ausgehend von CO_2 und Epoxiden

Der Fokus dieses Kapitels lag auf der Entwicklung einer Mehrphasenkatalyse zur Darstellung organischer Carbonate mit Wasser als nachhaltigem Lösungsmittel (Schema 119).



Schema 119: Zweiphasensystem von Butylencarbonat und Recycling des wasserlösliche Katalysators 9a-Br.

Ziel war es, die Mischungslücke zwischen Wasser und den meisten zyklischen organischen Carbonaten für ein besonders energieeffizientes Katalysatorrecycling auszunutzen. Außerdem wirkt Wasser durch die Ausbildung von Wasserstoffbrückenbindungen mit dem Epoxid als Co-Katalysator für die Reaktion. Der zu diesem Zweck entwickelte Katalysator **9a-Br** zeigte eine hohe Produktivität für die Carboxylierung von Propylenoxid (94% Ausbeute, 95% Selektivität) und Butylenoxid (95% Ausbeute, 97% Selektivität). Des Weiteren konnte durch die Modifikation des Katalysators in tensidische Moleküle (Schema 120) auch hochgradig hydrophobe Epoxide erfolgreich als Substrat verwendet werden.

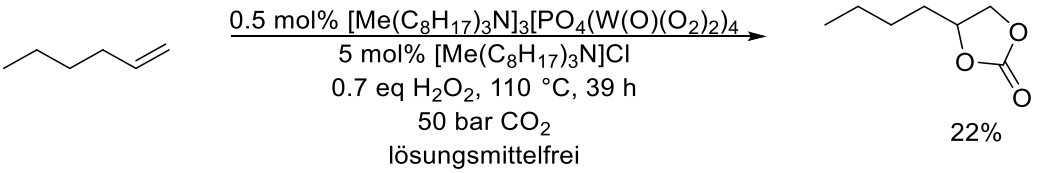


Schema 120: Wasserlöslicher Katalysator 9a-Br und seine tensidischen Analoga.

Der Katalysator konnte mehrfach durch Phasentrennung zyklisiert werden, auch wenn eine langsame Abnahme der Produktivität beobachtet wurde. Es konnte jedoch gezeigt werden das der Katalysator **9a-Br** *in situ* durch Zugabe einer kleinen, nicht-stöchiometrischen, Menge wässriger HBr nach jedem Lauf regeneriert werden kann. Erklärt wird dies durch den Ausgleich an Bromidverlusten des in Spuren gebildeten Nebenprodukts eines Bromhydrins.

Synthese zyklischer organischer Carbonate aus Olefinen, CO_2 und H_2O_2

1,2-Hexencarbonat wurde in 22% Ausbeute aus 1-Hexen, CO_2 und wässriger H_2O_2 unter lösungsmittelfreien Bedingungen dargestellt (Schema 121).



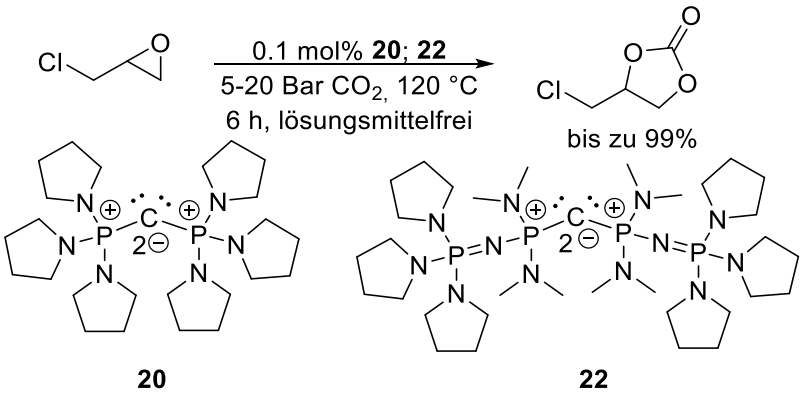
Schema 121: Eintopfsynthese von 1,2-Hexencarbonat aus 1-Hexen.

Anstelle des oxidationsempfindlichen Bromids oder Iodids wurden die gegenüber Oxidation durch H_2O_2 stabilen, aber weniger nucleophilen Anionen NO_3^- und Cl^- als nucleophile Katalysatoren für den Carboxylierungsschritt der Eintopfreaktion verwendet. Die unvorteilhafte Zersetzung des quaternären Ammonium-Kations der Katalysatoren ist weiterhin ein Problem und verhinderte eine effiziente orthogonale Tandemkatalyse als Eintopfreaktion. Beide Teilschritte bevorzugen zudem ein unterschiedliches Temperaturregime.

Organische Superbasen als Katalysatoren für die Carboxylierung von Epoxiden

In diesem Kapitel wurden Carbodiphosphorane und Phosphazenylphosphine erstmalig als Organokatalysatoren für die Carboxylierung von Epoxiden verwendet. Diese von IGOR MARTIN und SEBASTIAN WAGNER bereitgestellten C- und P-Superbasen erwiesen sich in dieser Kooperation als hoch aktive Katalysatoren. Epichlorhydrin Umsätze von >80% mit Ausbeuten

bis zu 99% bei einer Selektivität >99% wurden unter Verwendung von nur 0.01-0.1 mol% Katalysator mit einer Produktivität bis zu TON = 8600 erzielt (Schema 122).



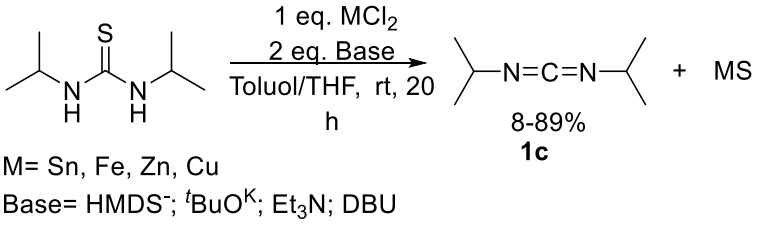
Schema 122: Carboxylierung von Epichlorhydrin durch Carbodiphosphoran-Superbasen.

Die Katalysatoren erwiesen sich außerdem als robust und behielten ihre katalytische Aktivität nach mehr als 8 h Reaktionszeit und in Gegenwart von Feuchtigkeit. Sowohl die freie C- oder P-Base als auch das entsprechende CO_2- oder Wasseraddukt können als Präkatalysatoren verwendet werden. Des Weiteren wurde beobachtet, dass eine zu starke Basizität bzw. Nukleophilie zu einer unerwünschten Polymerisation einiger Epoxide führt. Untersuchungen zum Reaktionsmechanismus zeigten, dass unabhängig davon, ob die freie Base oder ihr CO_2-Addukt verwendet wurde, die Superbase am Ende als Onium-Bicarbonat vorliegt. Dies deutet darauf hin, dass die Reaktion mit einem aus der Base, CO_2 und Spuren von Wasser *in situ* gebildeten nukleophilen Bicarbonat-Anion als katalytisch aktive Spezies verläuft.

Teil II

Synthese von Carbodiimiden aus Thioharnstoffen

Diisopropylcarbodiimid wurde durch Dehydrodesufurierung von Diisopropylthioharnstoff in Gegenwart starker Basen und thiophiler Metallkationen als Schwefelakzeptor hergestellt (Schema 123).

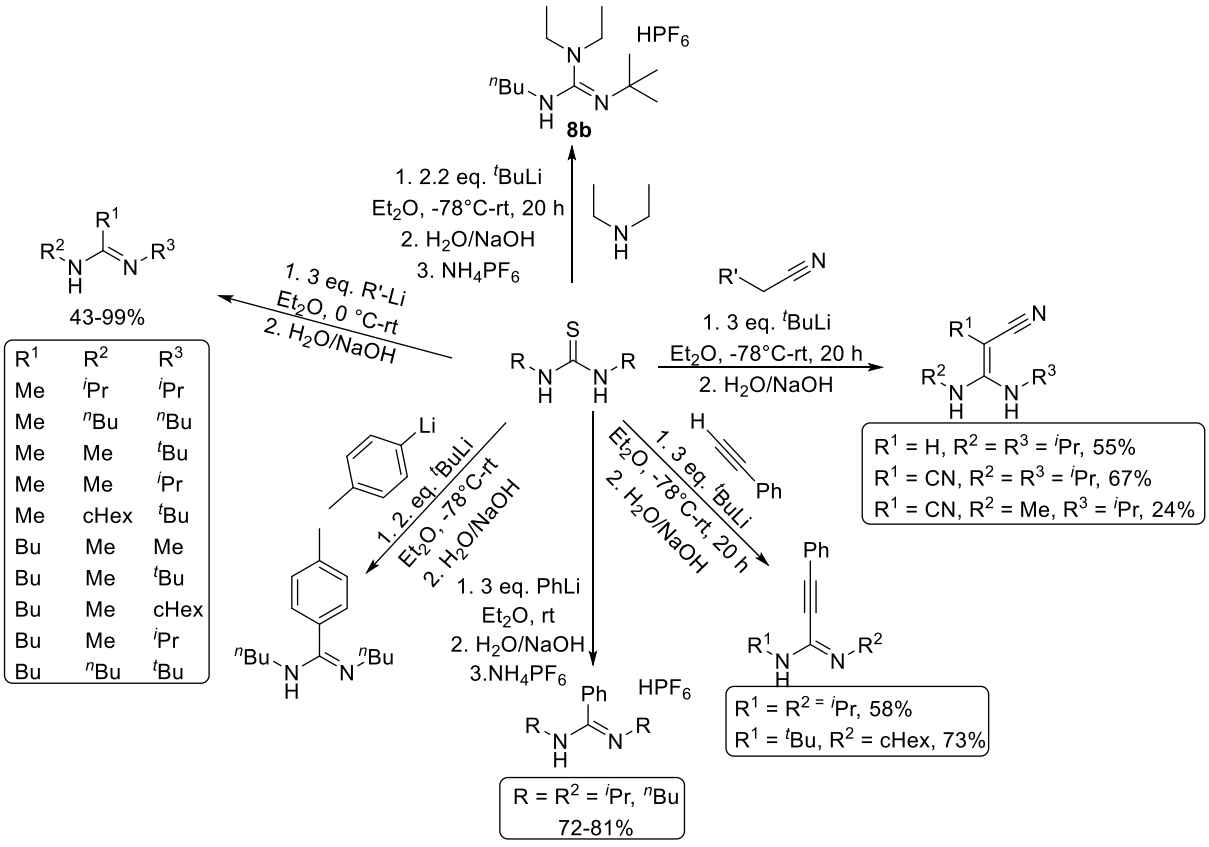


Schema 123: Dehydrodesulfurierung von Diisopropylthioharnstoff zu Diisopropylcarbodiimid.

Sowohl die Thiophilie des Metalls als auch die Stärke der Base beeinflussen die Ausbeute der Reaktion. Das Konzept war jedoch nicht auf eine größere Bandbreite an Thioharnstoffen übertragbar. Die Isolierung instabiler, flüchtiger Carbodiimide mit primären Alkylgruppen erwies sich als nicht praktikabel. Auch ließ sich die Reaktion nicht auf Harnstoffe übertragen.

Eintopfsynthese von Amidinen aus Thioharnstoffen

In 2-Position Alkyl-, Aryl- und Alkinyl-substituierte Amidine wurden aus *N,N*-alkyl-und aryl substituierten Thioharnstoffen und MeLi, ^{n}BuLi, PhC≡CLi oder PhLi hergestellt. Die Entschwefelung benötigt keinen zusätzlichen Schwefelakzeptor außer das Lithium-Kation selbst. Durch einfache Modifikationen der Durchführung konnte die Methode auf die Synthese eines unsymmetrischen Guanidines und verschiedener 2-Bis(amino)methylennitrile erweitert werden (Schema 124).



Schema 124: Synthese verschiedener Amidine und verwandter Stoffklassen aus Thioharnstoffen.

Die entsprechenden Nucleophile können *in situ* durch die zur Deprotonierung des Thioharnstoffs verwendeten organolithium Base hergestellt werden. Dadurch kann die Reaktion als Eintopfsynthese durchgeführt werden. Die aufwendige Isolierung eines

Carbodiimides als Zwischenstufe entfällt. Diese Methode ermöglicht die Synthese verschiedener wertvoller Verbindungsklassen ausgehend von einem einzigen günstigen, stabilen und leicht zugänglichen Thioharnstoff ohne die Verwendung giftiger Metalle.

Experimental Part I

8 Experimental Part 1

General

All reactions involving moisture or air sensitive substances were carried out under argon atmosphere using standard Schlenk technique or in a nitrogen filled glove box. Reactions involving air stable compounds or aqueous conditions were performed under ambient conditions. Solvents were purified and if necessary dried following common literature procedures.[309] Deionized water was used. All reagents and substrates were used as provided with the exception of butylene oxide, cyclohexene oxide, 1,2-epoxy hexene, glycidol and epichlorohydrin which have been dried and purified according to literature[143,309] when they were used in the superbase catalysed carboxylation. NMR solvents were purchased from Eurisotope and Sigma Aldrich and used without further purification. NMR spectra were measured with an AV II 300 MHz or AV III HD 500 MHz spectrometer. Chemical shift δ is given in ppm relative to $CDCl_3$, D_2O, DMSO-d_6 residual proton signals. The abbreviations for multiplicity are: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), sext. (sextet), sept. (septet), m (multiplet), and br (broad). NMR spectra were analysed with ACD/Labs. HR-ESI mass spectra were acquired with a LTQ-FT Ultra mass spectrometer (Thermo Fischer Scientific). The resolution was set to 100.000. HR-EI mass spectra were acquired with a AccuTOF GCv 4G (JEOL) Time of Flight (TOF) mass spectrometer. An internal or external standard was used for drift time correction. GC analysis was performed with an Agilant 7820A GC system equipped with an FID and HP-5 column (30m x 0.32 mm x 0.25 µm) and an automatic sampler. GC chromatogram signals were assigned and calibrated with prepared or purchased authentic compounds. Chromatograms were analysed with OpenLAB CDS. The calculations were performed with Excel. The necessary calibration factors have been determined by external calibration. The calibration curves are listed below. Double injections were performed for calibrations. Most catalytic reactions were performed in duplicate to ensure reproducibility. If the discrepancy between two replicates was larger than 5% an additional experiment was conducted. Weigh ins were performed with a precision scale (d = 0.0001g).

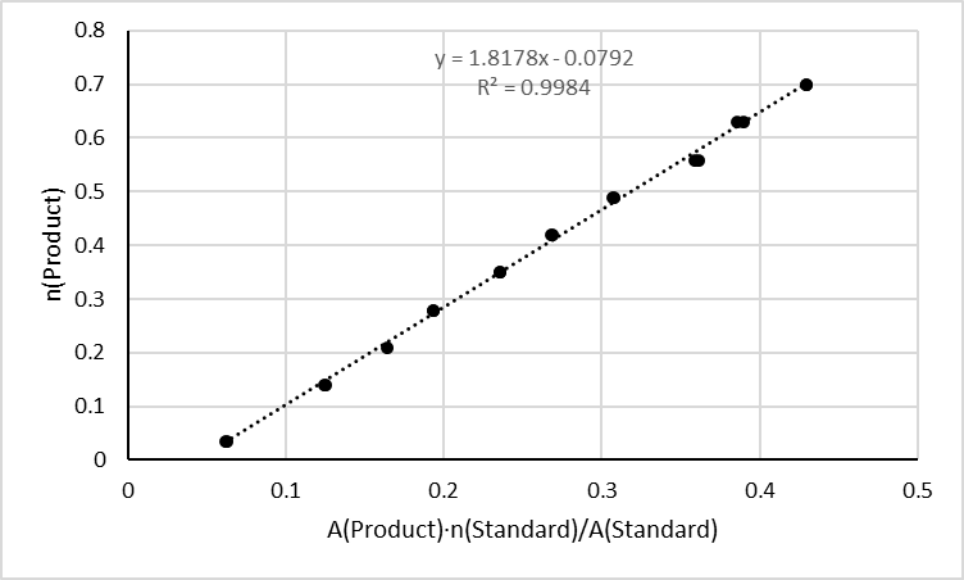


Figure 10: GC-calibration curve for butylene oxide 1.

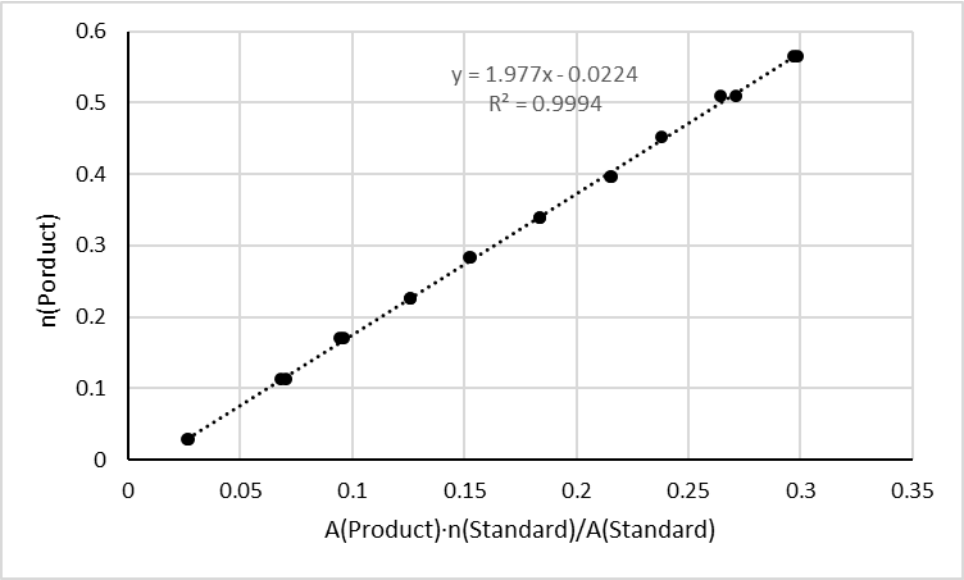


Figure 11: GC-calibration curve for butylene diol 2.

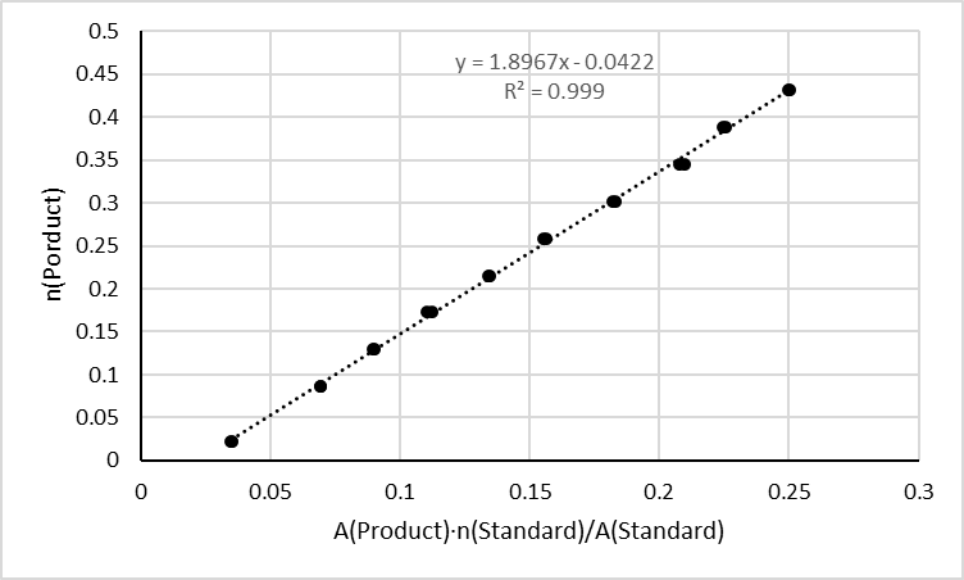


Figure 12: GC-calibration curve for butylene carbonate 3.

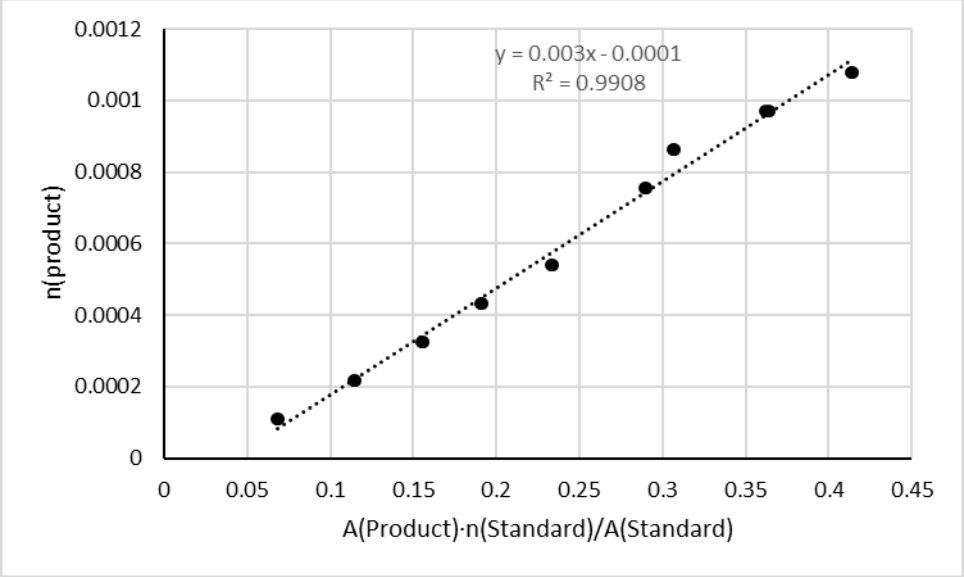


Figure 13: GC-calibration curve for epichlorohydrin.

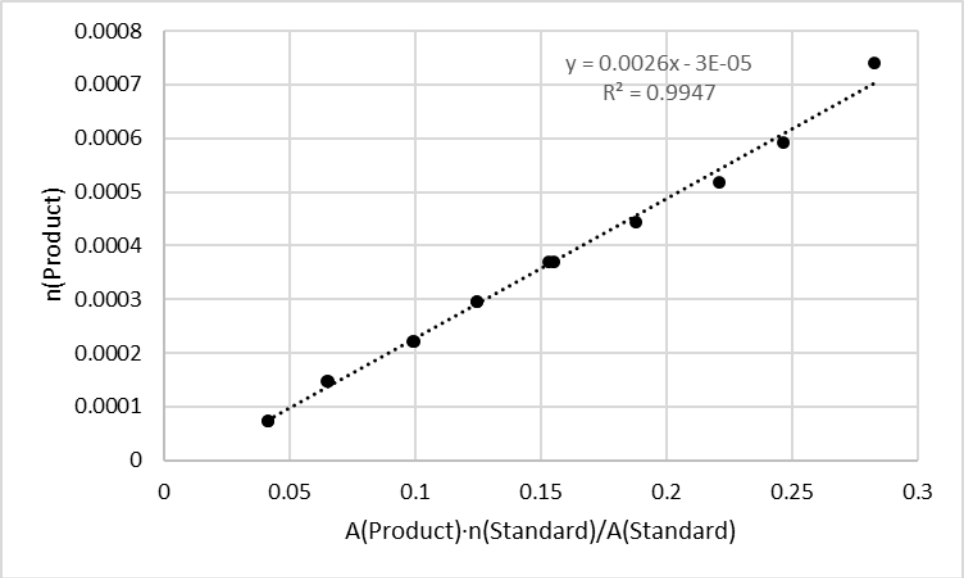


Figure 14: GC-calibration curve for epichlorohydrin carbonate.

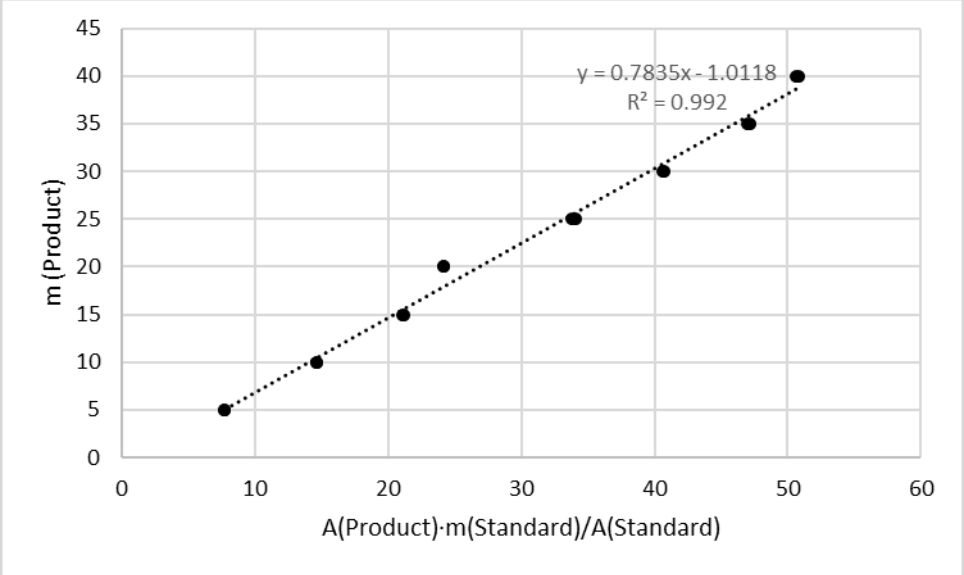


Figure 15: GC-calibration curve for 1,2-hexane oxide.

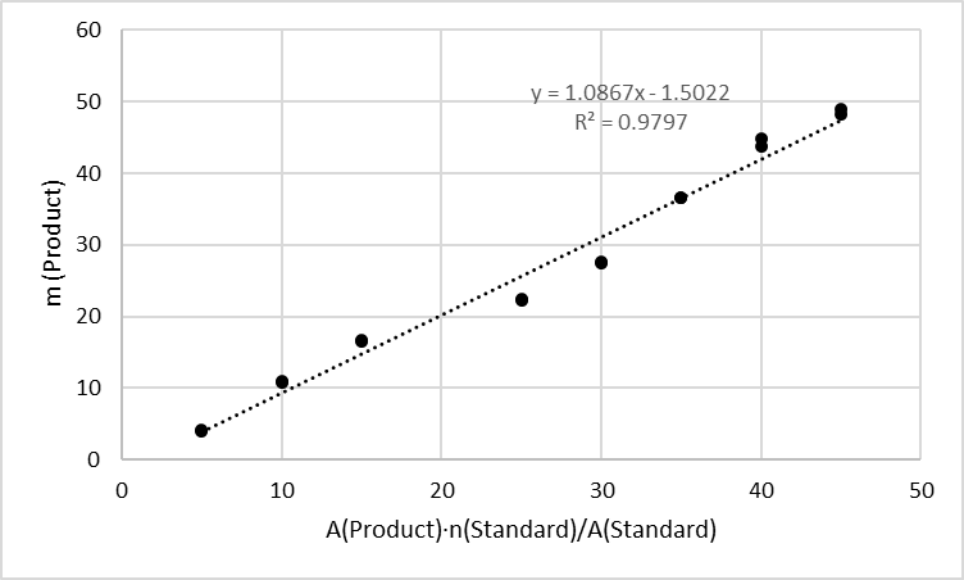


Figure 16: GC-calibration curve for 1,2-hexane carbonate.

The percentual yield was calculated using the following equation:

$$n_{\%} = \frac{r_f \times A_{Product}}{\sum(r_{f_i} \times A_i)} \quad (1)$$

$n_{\%}$ is the percentual amount of analyte. $A_{Product}$ and A_i are the Chromatograms peak area for the analyte and all other substances respectively. r_f is the calibration factor determined *via* calibration.

In the case of epoxidation and tandem reactions, hydrogen peroxide was the limiting factor. In this case yields were determined by the following equations:

$$m_{Product} = \frac{m_{Standard} \times \frac{A_{Product}}{A_{Standard}} - b}{r_f} \quad (2)$$

and

$$yield = \frac{m_{product}}{m_{max}} \times 100 \quad (3)$$

The TON is determined by the following equation:

$$TON = \frac{n_{Product}}{n_{catalyst}} \quad (4)$$

For reactions requiring elevated pressure stainless steel autoclaves and glass autoclaves have been used (Fig. 17).

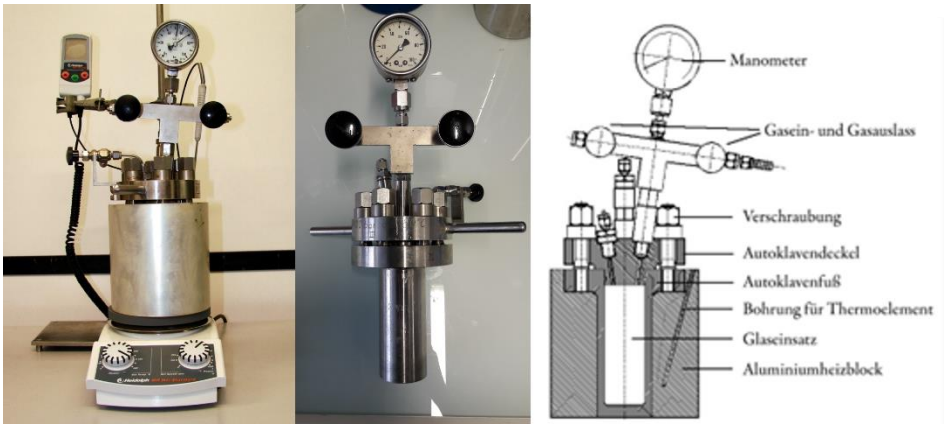


Figure 17: Stainless steel autoclave used for pressure reactions.[310]

General procedure for coupling of epoxides and CO_2 with water-soluble catalysts in an aqueous-organic biphasic system:

To 2.5 mL (2 g, 27.7 mmol) butylene oxide **1** in an 80 mL stainless steel autoclave with stirring cross, a solution of 2 mol% (0.55 mmol) catalyst in 2 mL deionized H_2O was added. The autoclave was sealed and pressurised with the desired amount of CO_2 at room temperature and subsequently placed in a preheated heating block equipped with a magnetic stirrer. After the desired reaction time has passed the autoclave was cooled down in an ice bath and then slowly degassed. The reaction mixture was removed from the autoclave and the phases were allowed to separate (5-30 min). GC samples were prepared by charging a GC vial with 25 mg phenyl bromide as standard, 50 mg of the sample and 1 mL of ethyl acetate or chloroform. The conversion of epoxides and the yields of cyclic carbonates and 1,2-diols have been determined by nominated area comparison. For recycling experiments, the phases were separated and the aqueous phase was added to the epoxide instead of fresh catalyst solution.

General procedure for the epoxidation of olefins with H_2O_2

A Schlenk flask was charged with olefine, the desired amount of catalyst and, if necessary, solvent. The solution was heated to the desired temperature and a 35%wt aqueous solution of H_2O_2 was added. After the desired amount of time has passed, the reaction was allowed to cool down and the phase were allowed to separate. A catalytic amount of MnO_2 was added to destroy remaining H_2O_2. GC samples were prepared by charging a GC vial with 25 mg phenyl bromide as standard, 50 mg of the sample and 1 mL of ethyl acetate or chloroform for

reactions without solvent. For epoxidations in presence of solvent 1 mL of the reaction solution was taken and charged into a GC vial with 25 mg phenyl bromide as standard.

General procedure for the one pot synthesis of cyclic carbonates from olefins

Hex-1-ene **18**, 0.48 mol of epoxidation catalyst, 5 mol% of nucleophilic catalyst and H_2O_2 (35 %wt) were added to a stainless-steel autoclave equipped with a Teflon inlet. The autoclave was pressurized with CO_2 at room temperature and placed in a preheated heating block equipped with a magnetic stir bar. After the desired reaction time has passed the autoclave was cooled down in an ice bath and then slowly degassed. The reaction mixture was removed from the autoclave and the phases were allowed to separate (5-30 min). A catalytic amount of MnO_2 was added to destroy remaining H_2O_2 and a sample of the organic phase was taken and analysed *via* GC. GC samples were prepared as described in the previous procedure.

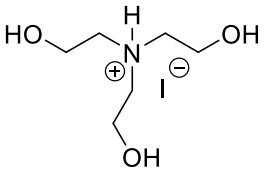
General procedure for the coupling of epoxides and CO_2 with organic superbases as catalysts

In a glove box, the desired amount of superbase catalyst was charged in a Schlenk tube and dissolved in epichlorohydrin. This solution was then transferred *via* syringe to a stainless-steel autoclave which has previously been dried under vacuum, filled with argon and is equipped with a Teflon inlet. The autoclave was then pressurised with CO_2 and placed in a preheated heating block equipped with a magnetic stirrer. After the desired reaction time has passed, the autoclave was cooled down in an ice bath and slowly degassed. GC samples were prepared by charging a GC vial with 25 mg phenyl bromide as standard, 50 mg of the sample and 1 mL of ethyl acetate or chloroform. The conversion of epoxides and the yields of cyclic carbonates and 1,2-diols have been determined by nominated area comparison.

The corresponding CO_2 superbase adducts were prepared by dissolving the free base in dry pentane and introducing a CO_2 atmosphere to the Schlenk tube equipped with an over pressure valve. The solutions are stirred for 30 min during which a white precipitate formed. The solvent was removed under reduced pressure. The obtained white precipitate was dissolved in epichlorohydrin and then transferred to the autoclave following procedure.

Preparation of water-soluble catalysts:

5 [CAS 7601-53-8]



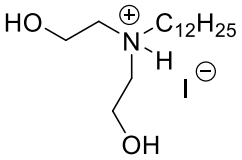
5

5 was prepared by adding 1 eq. of HI (57% in water) to a solution of triethanolamine (1 g, 6.7 mmol) in acetonitrile. After 30 min of stirring the precipitating salt is filtered of, and the crude product is recrystalized from ethanol (1.8 g, 6.5 mmol, 97%)

Reacting Triethanolamine with various alkyl iodides yielded **5** instead of the alkylated quaternary salt.

^{1}H-NMR: 300 MHz; D_2O; δ (ppm) = 3.51 (t, 6H), 3.98 (t, 6H)

6 [CAS 1541-67-9] (free base)

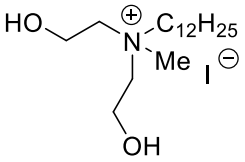


6

Diethanolamine (1 g, 9.6 mmol, 1 eq.) and acetonitrile (10 mL) was charged into an ice cooled flask. 1-Idododecane (3.2 mL, 13 mmol, 1.4 eq) was added dropwise. The mixture was allowed to reach room temperature and stirred over night at 50 °C. The mixture was the cooled in a fridge to -17 °C and after 20 h, the precipitating solid was filtered of, washed with pentane and dried in vacuum to give **6** (2.11 g, 6.27 mmol, 55 %) as white solid. The NMR-spectrum is in agreement with the literature (literature values for the free base).[311]

^{1}H-NMR: 300 MHz, D_2O; δ (ppm) = 3.91-3.90 (m, 4H), 3.40-3.37 (m, 4H), 3.27 (m, 2H), 1.74 (m, 2H), 1.34 (s, 4H), 1.25 (s, 14H), 0.83-0.81 (m, 3H)

7 [CAS 55653-50-4]

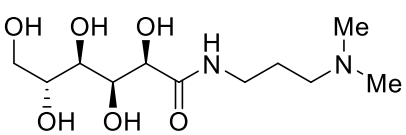


7

Methyl diethanolamine (1 g, 8.4 mmol, 1 eq.) was dissolved in 50 mL acetonitrile. 1-Idododecane (2.48 g, 8.4 mmol, 1 eq) was added dropwise and the mixture was refluxed for 24 h. **7** precipitated from the solution as white solid. The yield after filtration in drying under vacuum was 2 g (61%). The NMR-spectrum is in agreement with the literature.[312]

^{1}H-NMR: 300 MHz, D_2O; δ (ppm) = 4.07 (t, 4H), 3.65 (t, 4H), 3.54 (m, 2H), 3.25 (s, 3H), 1.82 (m, 2H), 1.40-1.30 (m, 18H), 0.88 (t, 3H)

***N,N*-(3-(Dimethylamino)propyl)-d-gluconamide** [CAS 51812-79-4]



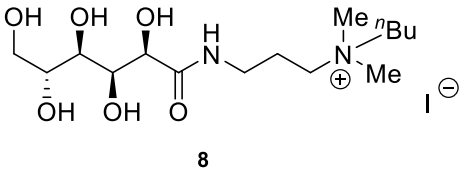
N,N-(3-(Dimethylamino)propyl)-d-gluconamide was prepared according to modified method reported by Ferreira.[92] To a solution of D-1,5-glucnolatcon (1.74 g, 9.8

mmol) in DMF *N,N*-Dimethylpropane-1,3-diamine (1 g, 9.8 mmol) was added. The mixture was stirred for 20 h at room temperature. The solvent was removed under reduced pressure and the residue was washed with ethanol/ether (1:1) to yield *N,N*-(3-(Dimethylamino)propyl)-d-gluconamide as yellow oil in 77 % yield. The NMR-spectra are in agreement with the literature.[92]

^{1}H-NMR: 300 MHz; D_2O; δ (ppm) = 1.71 (m, 2H), 2.19 (s, 6H), 2.39 (m, 2H), 3.22 (m, 2H), 3.58-3.79 (m, 4H), 4.03 (m, 1H), 4.25 (m, 1H)

^{13}C-NMR: 75 MHz; D_2O; δ (ppm) = 174.2, 73.4, 72.3, 70.4, 62.7, 55.8, 43.8, 38.5, 37.2, 26.0

8 [CAS 2448400-80-2]



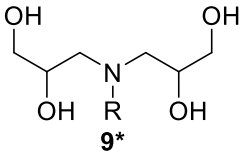
8

N,N-(3-(Dimethylamino)propyl)-d-gluconamide (2.12, 7.56 mmol) was dissolved in ethanol and 1.39 g of 1-Iodobutane (1.39 g, 0.85 mL, 1 eq) was added. The mixture was heated 60 °C for 24 h. After that the solvent was removed in vacuum and crude product (yellow oil) was washed with acetonitrile to give **8** as highly viscous light-yellow oil (2.3 g, 6.8 mmol, 89%). The NMR-spectra are in agreement with the literature.[313]

^{1}H-NMR: 300 MHz, D_2O; δ (ppm) = 1.00-1.04 (t, 3H), 1.41-1.49 (sext, 2H), 1.80 (m, 2H), 2.10 (m, 2H), 3.14 (s, 6H), 3.41 (m, 6H), 3.74-3.89 (m, 4H), 4.15 (d, 1H), 4.41 (d, 1H)

^{13}C-NMR: 75 MHz, (D_2O); δ (ppm) = 174 (C-6), 73.5, 72.3, 71.3, 70.5 (C-5, C-4, C-3, C-2), 66.7 (C-11) 64.4 (C-1), 62.8 (C-9), 51.1 (Me), 36.1 (C-7), 24.1 (C-12), 22.5 (C-8), 19.3 (C-13), 13.3 (C-14)

9a-c



9*

9a was prepared following a modified method described in DE2730302A1.[93] 2 eq. of glycidol (10.15 g, 137 mmol) where slowly added to solution of 1 eq. *n*-butyl amine (5 g, 68 mmol) (*n*-hexyl amine for **9b** and *n*-dodecyl amine for **9c**) in toluene (100 mL) under Ar-atmosphere. The mixture was heated to reflux for 18 h. When the reaction is cooling down, **9a** separates as colourless, viscous, and very hygroscopic liquid (white, waxy solid for **9c**). The solvent is decanted off and the crude product is washed with toluene and dried in vacuum. **9a** is NMR pure and in quantitative yields (15 g, 68 mmol). It can be stored under dry atmosphere for several months without any change.

9a (R = butyl):

^{1}H-NMR: 300 MHz; D_2O, δ (ppm) 0.83-0.88 (t, 3H), 1.26 (sext, 2H), 1.42 (q, 2H), 2.56 (m, 6H), 3.46-3.50 (m, 2H), 3.55-3.60 (m, 3H), 3.82 (m, 2H)

^{13}C-NMR: 75 MHz, D_2O, δ (ppm) = 69.2 (C-6), 64.5 (C-7), 56.9 (C-5), 54.7 (C-4), 27.7 (C-3); 20.1 (C-2), 13.3 (C-1)

9b (R = hexyl):

^{1}H-NMR: 300 MHz; DMSO-d_6, δ (ppm) 0.86 (t, 3H), 1.24-1.37 (m, 8H), 2.30 (m, 6H), 3.32-3.51 (m, 6H), 4.39-4.47 (m, 4H)

^{13}C-NMR: 75 MHz; DMSO-d_6, δ (ppm) 69.2, 64.5, 58.7, 58.3, 55.35, 31.2, 26.5, 22.1, 13.9

HRMS: ESI calc. for $C_{12}H_{28}NO_4$ ([M+H$^+$]) 250.2013, found 250.2014

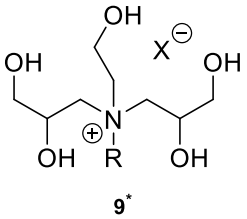
9c (R = dodecyl):

^{1}H-NMR: 300 MHz, DMSO-d_6 δ (ppm) 1.01 (t, 3H), 1.40-1.53 (m, 20H), 2.46-2.66 (m, 6H), 3.48-3.66 (m, 6H), 4.39 (br, 4H)

^{13}C-NMR: 75 MHz, DMSO-d_6 δ (ppm) 69.4, 69.3, 64.6, 64.5, 58.7, 58.3, 55.3, 31.3, 29.0, 28.7, 26.8, 26.5, 22.1, 13.9

HRMS: ESI calc. for $C_{18}H_{39}NO_4$ ([M+H$^+$]) 334.2952, found 334.2948

9a-Cl, 9a-Br, 9a-I, 9b-Br, 9c-Br



9*

9a-Cl, **9a-Br**
9a-I
R= n-Butyl
9b-Br
R= n-Hexyl
9c-Br
R= n-Dodecyl

9a (15 g, 68 mmol) was added to Schlenk flask under Ar atmosphere. Due to its high viscosity heating it to 50 °C and the use of a syringe needle with large diameter is recommended. Dry toluene (150 mL) and 2-bromoethanol (8,7 g, 80 mmol) (2-iodoethanol or 2-chloroethanol for X= I, Cl) were added and then refluxed for 24 h. Formed **9a-Br** separates during refluxing as colourless, highly viscous, and hygroscopic ionic liquid. **9a-I** has a distinct amber colour. After decanting of the solvent and drying in vacuum **9a-X** is in near quantitative yields (23.5 g, 68 mmol). If necessary, **9a-X** can be purified by dissolving in hot acetonitrile followed by decanting of the solvent after cooling. **9a-Br** can be stored under dry atmosphere for several months, while **9a-I** visibly darkens from amber to a dark red brown.

9a-Br

^{1}H-NMR: 300 MHz; D_2O; δ (ppm) = 0.92-0.96 (t, 3H), 1.38 (m, 2H), 1.71 (m, 2H), 3.06 (m, 2H), 3.58 (m, 12H), 4.02 (m, 2H), 4.27 (m, 2H)

HRMS: ESI+, calc for $C_{12}H_{28}NO_5$ $[M]^+$ 266.1962, found 266.1972; ESI-calcd for Br $[M]^-$ 78.9189; 80.9168 found 78.9189; 80.9168

9b-Br

^{1}H-NMR: 300 MHz; DMSO-d_6; δ ppm = 0.79 (t, 3H), 1.18 (m, 6H), 1.35 (m, 2H), 3.24-3.39 (m, br, 7H), 3.50 (m, 3H), 4.66 (m, br, 4H)

^{13}C-NMR: 75 MHz; DMSO-$_{d6}$; δ (ppm) = 70.5, 68.85, 68.87, 64.5, 63.1, 61.6, 58.3, 57.9, 55.1, 35.7, 31.2, 26.3, 22.0, 13.9

HRMS: ESI+, calc. for $C_{14}H_{32}N_1O_5$ $[M^+]$ 294.2275, found 294.2279

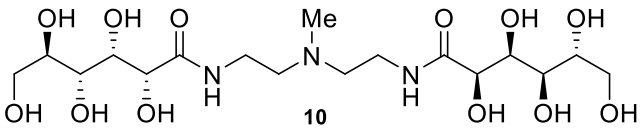
9c-Br

^{1}H-NMR: 300 MHz; DMSO-d_6; δ (ppm) = 0.85 (t, 3H), 1.24 (m, 18H), 1.40 (br, 2H), 3.33 (br, 9H), 3.54 (br, 2H), 4.54 (br, 3H)

^{13}C-NMR: 75 MHz; DMSO-$_{d6}$; δ = 68.7, 68.5, 64.3, 58.2, 57.9, 54.7, 27.9, 19.9, 19.2, 13.9

HRMS: ESI+, calc. for $C_{20}H_{44}N_1O_5$ [M+] 378.3214, found 378.3217

10



10

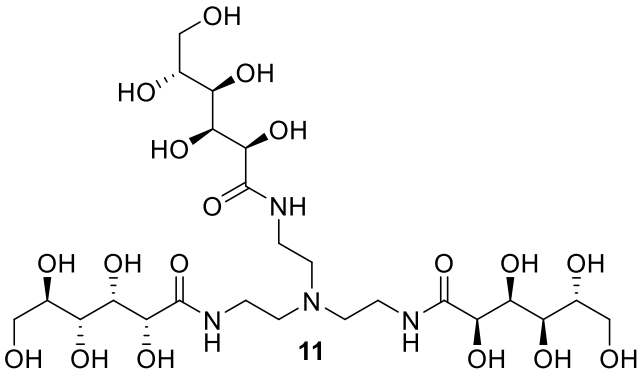
N,N-bis-(ethane)-D-gluconamide methylamine was prepared analogue to *N,N,N*-tris-(ethane)-D-gluconamide with bis(2-aminoethyl)amine and 2 eq. of D-1,5-gluconolacton. (White solid, 3.9 g, 96%)

For its use as catalyst **10-Br** 262 mg of *N,N*-bis-(ethane)-D-gluconamide methylamine and an equimolar amount of HBr (48%wt in water) were mixed in water and used as catalyst without isolation.

^{1}H-NMR: 300 MHz; D_2O; δ (ppm) = 2.28 (s, 3H), 2.59-2.64 (m, 4H), 3.36-3.40 (m, 4H), 3.61-3.65 (m, 2H), 3.72-3.81 (m, 6H), 4.06 (m, 2H), 4.28 (d, 2H)

^{13}CNMR: 75 MHz; D_2O; δ (ppm) = 174.4 (C-6), 73.4 (C-5), 72.1 (C-4), 71.1 (C-2), 70.4 (C-3), 62.7 (C-1), 54.9 (C-8), 41.3 (C-9), 36.2 (C-7)

11 [CAS 1380329-33-8]



N,N,N-Tris-(ethane)-D-gluconamide was prepared after a modified method reported by Ferreira et al.[92] D-1,5-gluconolacton (3 eq, 3.65 g, 20.51 mmol) was added to a solution Tris(2-aminoethyl)amine (1 g, 6.83 mmol, 1 eq) in DMF (50 mL) and stirred for 24 hours at room temperature. The precipitating white solid was filtered of and washed with DMF and ethanol followed by drying in vacuum to yield N,N,N-Tris-(ethane)-D-gluconamide in quantitative yields (4.6 g, 99%) as white, hygroscopic solid. The NMR spectra are in agreement with the literature.[92]

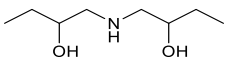
For its use as catalyst **11-Br** 377 mg of *N,N,N*-Tris-(ethane)-D-gluconamide and an equimolar amount of HBr (48%wt in water) were mixed in water and used as catalyst without isolation.

^{1}H-NMR: 300 MHz; D_2O; δ (ppm) = 2.76 (m, 6H), 3.36 (m, 6H), 3.66 (m, 3H), 3.74-3.82 (m, 9H), 4.08 (m, 3H), 4.31 (d, 3H)

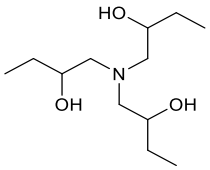
^{13}C-NMR: 75 MHz; D_2O; δ (ppm) = 174.4 (C-6), 73.5 (C-5), 72.2 (C-4), 71.2 (C-2), 70.4 (C-3), 62.7 (C-1), 52.2 (C-8), 36.5 (C-7)

NMR decomposition experiment for 4-Br:

500 mg (5.1 mmol) of NH_4Br and 1.1 g (25.31 mmol) butylene oxide and 100 *µL* deionized water were dissolved in 20 mL THF and refluxed for 5 h. Afterwards, the solvent was removed under reduced pressure and the residue dried vacuum. The obtained clear, viscous liquid was analysed *via* NMR and mass spectroscopy.



HRMS: ESI+, calc. for $C_8H_{20}N_1O_2$ [M+H$^+$]: 162.1489; found 162.1487



HRMS: ESI+, calc. for $C_{12}H_{28}N_1O_3$ [M+H$^+$]: 234.2064; found 234.2060

Preparation of epoxidation catalysts

The catalysts were prepared according to literature.[100,314,315]

$[Me(C_8H_{17})_3N][PO_4(W(O)(O_2)_2)_4]$

12

2.5 g (0.01 mol, 1 eq.) of $WO_3 \cdot H_2O$ was added to 7 mL of H_2O_2 (0.08 mol, 8 eq, 35%wt aqueous solution). The yellow suspension was stirred at 60 ^C for 4 h and then filtered. To the colourless filtrate 25 mL of water and 0.62 mL (0.005 mol, 0.25 eq.) phosphoric acid were added. A solution of 2.1 g (0.005 mol, 0.5 eq.) methyltrioctylammonium chloride in 40 mL CH_2Cl_2 was added. The mixture was stirred for 15 min at room temperature. The phase where separated, the organic phase dried over Na_2SO_4 and the solvent was removed under reduced pressure.

1 g (4 mmol, 1 eq.) of $WO_3 \cdot H_2O$ was added to 2.8 mL of H_2O_2 (32 mmol, 8 eq., 35%wt aqueous solution). The yellow suspension was stirred at 60 °C for 4 h and then filtered. To the colourless filtrate 25 mL of water and 0.25 mL (1 mmol, 0.25 eq.) phosphoric acid were added.

$H_3[PO_4(W(O)(O)_2)_4]$

13

To 1 g (6.95 mmol, 1 eq.) MoO_3 3.43 g (35.53 mmol, 8 eq., 35 %wt aqueous solution) of a solution of H_2O_2.The suspension was stirred for 10 h at 40 °C. The suspension was the filtered and the orange solution was diluted with 6 mL of H_2O.

Catalyst decomposition investigation:

After the epoxidation-carboxylation reaction with catalysts **12** and **15a** as described in the general procedure, all volatiles were removed under reduced pressure. The mixture was separated *via* column chromatography: carbonate and epoxide products were eluted first with hexane/EtOAc. The decomposition products eluted with acetone. Elemental analysis showed that these decomposition products were nitrogen containing compounds:

Element	Measured results **[%]**	Calculated elemental composition of **15b** **[%]**
C	67.20	69.7
H	11.7	12.64
N	6.44	6.50

The mass spectra obtained *via* GC-MS of the catalyst decomposition products are shown below.

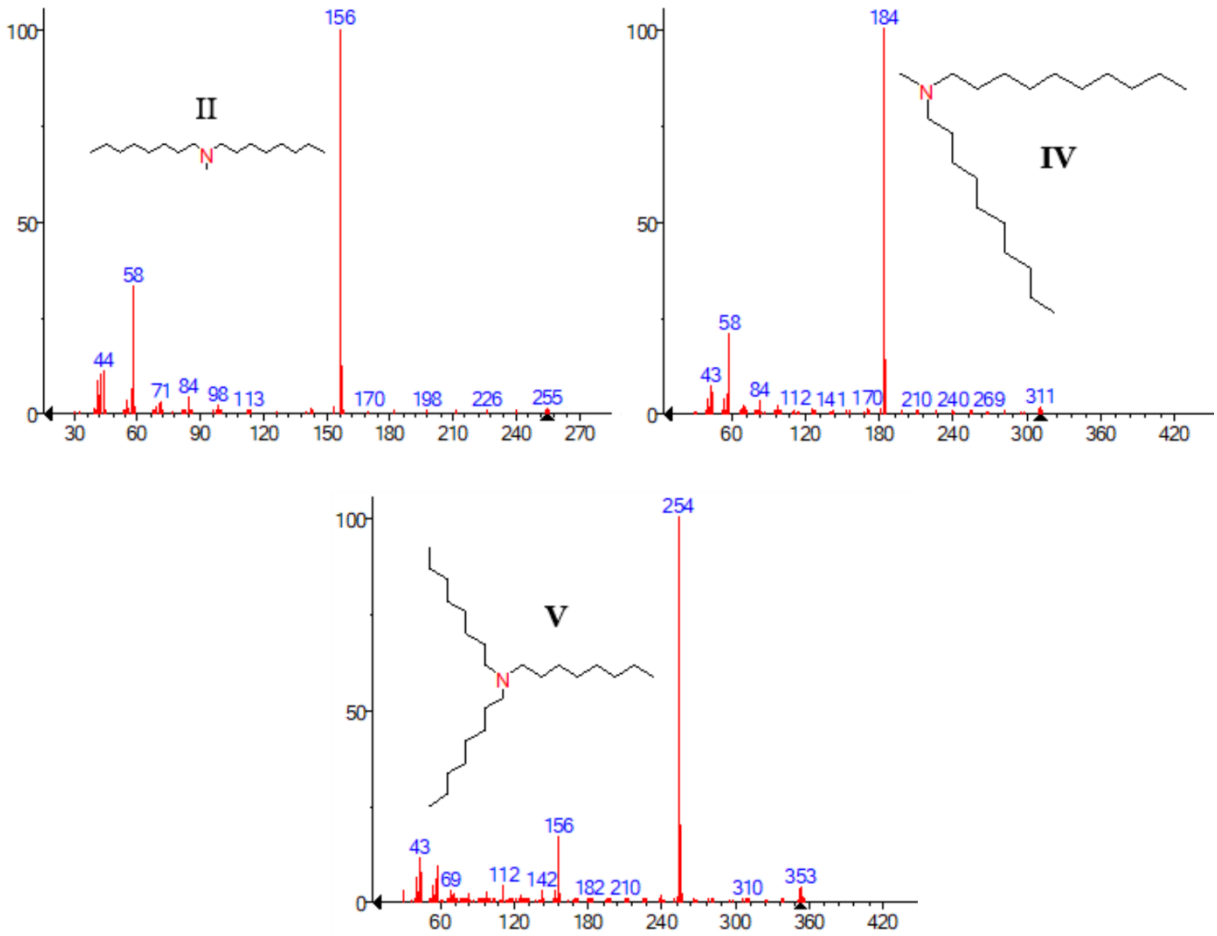
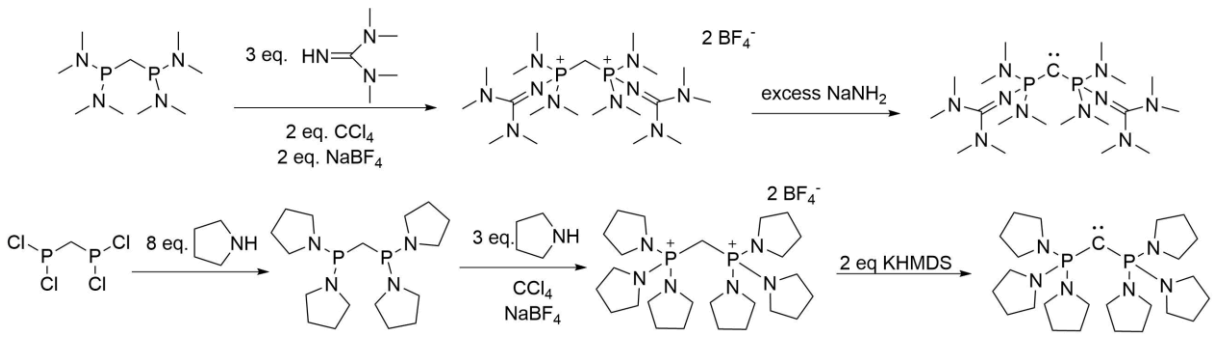


Figure 18: GC-MS spectra of the decomposition products of catalyst 12 and 15b after a typical one pot epoxidation-carboxylation.

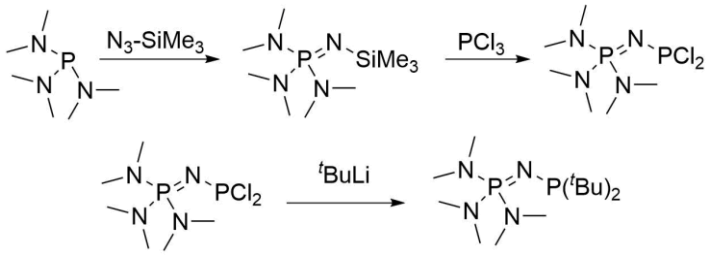
General synthesis of CDP and phosphazenyl phosphine catalyst

The carbodiphosphoranes were provided by IGOR MARTIN.[164] A general scheme based on the works SEBASTIAN ULRICH is given here:

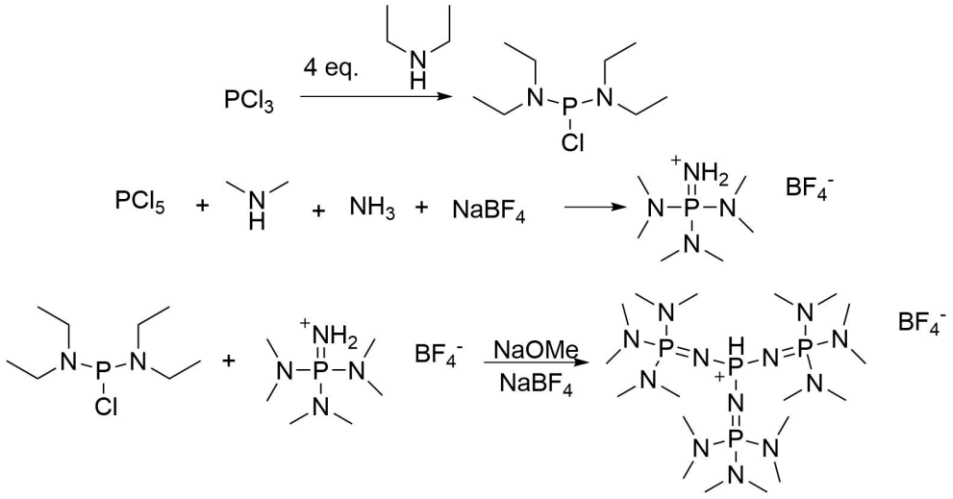


Scheme 125: General synthesis of CDPs.[154]

The phosphazenyl phosphine catalysts were provided by SEBASTIAN WAGNER.[163] A general scheme based on the works SEBASTIAN ULRICH is given here:



Scheme 126: General synthesis of mono phosphazenyl phosphines.[153]



Scheme 127: General Synthesis of phosphazenyl phosphines.[162]

Experimental Part II

9 Experimental Part II

General

All reactions were performed in dry glass ware under Ar atmosphere unless stated otherwise. Solvents were dried prior to use by standard literature procedures. Commercially purchased compounds were used without further purification. Methyl isothiocyanate and ^{t}butyl isothiocyanate, *N,N*-dimethyl thiourea and *N,N*-diisopropyl thiourea were purchased from Sigma Aldrich. *N,N*-diphenyl thiourea was purchased from Acros Organics. *N,N*-di-^{n}butyl thiourea was purchased from Alfa Aesar. solvents were purchased from Eurisotope and Sigma Aldrich and used without further purification. $Pb(HMDS)_2$, $Sn(HMDS)_2$, $Zn(HMDS)_2$, $Mn(HMDS)_2$ were prepared according to known literature procedures. NMR spectra were measured with an AV II 300 MHz spectrometer. NMR spectra were analysed with ACD/Labs. HR-ESI mass spectra were acquired with a LTQ-FT Ultra mass spectrometer (Thermo Fischer Scientific). The resolution was set to 100.000. HR-EI mass spectra were acquired with a AccuTOF GCv 4G (JEOL) Time of Flight (TOF) mass spectrometer. GC analysis was performed with an Agilant 7820A GC system equipped with an FID and HP-5 column (30m x 0.32 mm x 0.25 µm) and an automatic sampler. GC chromatogram signals were assigned and calibrated with prepared or purchased authentic compounds. The calculations were performed with Ecxel. The necessary calibration factors have been determined by external calibration. The calibration curves are listed below. Double injections were performed for calibrations.

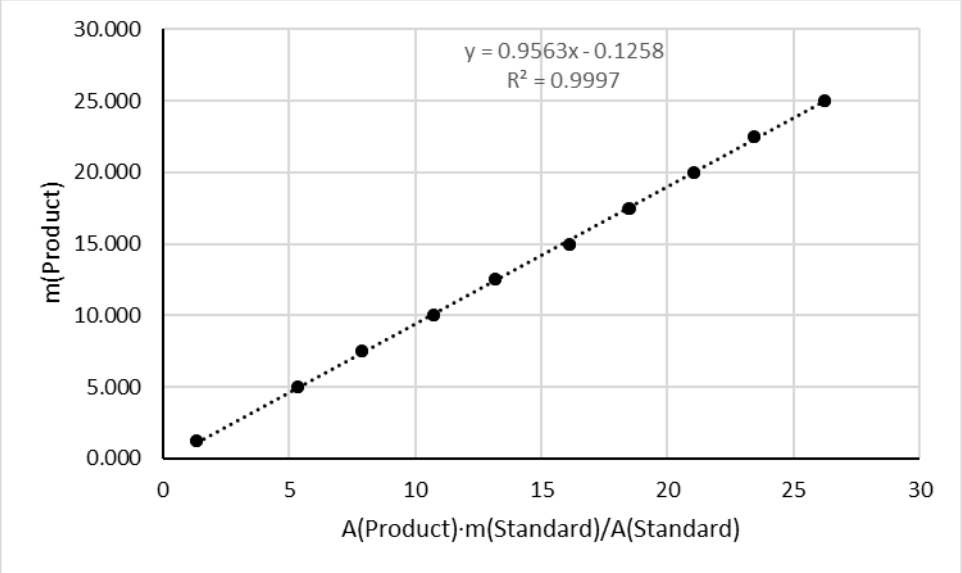


Figure 19: Calibration curve for diisopropyl carbodiimide (DIC).

Yields are determined using following equations:

$$m_{Product} = \frac{m_{Standard} \times \frac{A_{Product}}{A_{Standard}} - b}{r_f}$$

and

$$yield = \frac{m}{m_{max}} \times 100$$

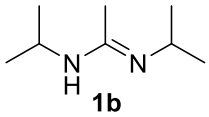
With r_f being the calibration factor determined by calibration.

Experimental Procedures:

Preparation of thioureas:

Unsymmetrical thioureas were prepared by adding 1 eq. of amine to a solution of 1 eq. of methyl or ^{t}butyl isothiocyanate in *n*-hexane. The reaction mixture was stirred overnight at rt, in case of sterically hindered amines under reflux. The thioureas precipitated as white solids which were filtered of, washed with *n*-hexane and pentane and dried in vacuum. Yields were >80 % and most products sufficiently pure for further use. If necessary, further purification was achieved by recrystallisation from hexane/methylene chloride.

1b *N*,*N*-diisopropylacetamidine [CAS 106500-93-0]



1b

Method A: 1 g (6.24 mmol) diisopropyl thiourea **1** and 792 mg (6.24 mmol) $FeCl_2$ were suspended in 50 mL of dry diethyl ether. The mixture was cooled to 0° C and 12 mL (18.72 mmol) of MeLi (1.59 M in Et_2O) was slowly added. The mixture was stirred for 20 h and allowed to reach room temperature. 10 mL of deionized water was added to quench the reaction. The organic phase was decanted of and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 50 °C. Colourless oil, 603 mg, 68% yield.

Method B: 1.5 g (9.36 mmol) diisopropyl thiourea was suspended in 50 mL of dry diethyl ether. 18.3 mL (29 mmol) of MeLi (1.59 M in Et_2O) was slowly added and the mixture was stirred for 20 h. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 50 °C. Colourless oil, 740 mg, 55%.

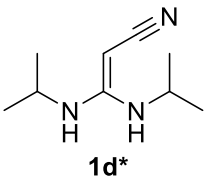
The NMR-spectra are in agreement with the literature.[259]

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 1.07 (d, 12H), 1.76 (s, 3H), 3.62 (br, 2H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 152.7, 65.5, 44.9, 23.6, 14.9

HRMS: ESI calc. for $C_8H_{19}N_2$ ([M+H$^+$]) 143.1543, found 143.1543

1d 3,3-bis(isopropylamino)acrylonitrile



1d*

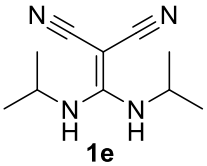
1 g (6.24 mmol) diisopropyl thiourea **1** and 325 µL (6.24 mmol) acetonitrile were suspended in 50 mL dry diethyl ether. The mixture was cooled to -78 °C and 12.15 mL (18.72 mmol) of ^{t}BuLi (1.52 M in pentane) was slowly added. The mixture was stirred for 20 h. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product is purified by crystallisation from CH_2Cl_2/Et_2O (1:1) at -80 °C. Yellow solid, 560 mg, 55% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$ δ (ppm) 1.17-120 (d, 12H), 3.00 (s, 1H), 3.40 (m, 1H), 3.55 (m, 1H), 3.82 (br, 1H), 4.16 (br, NH)

^{13}C-NMR: 75MHz, $CDCl_3$ δ (ppm) 160.3, 123.9, 44.2, 40.1, 22.7

HRMS: (ESI) calc. for $C_9H_{18}N_3$ ([M+H$^+$]) 168.1495, found 168.1496

1e 2-(bis(isopropylamino)methylene)malonitril [CAS 2089439-23-4].



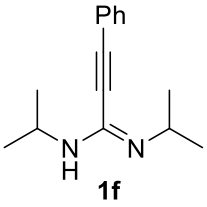
1e

1 g (6.24 mmol) diisopropyl thiourea **1** and 411 mg (6.24 mmol) malononitrile were suspended in 50 mL dry diethyl ether. The mixture was cooled to -78 °C and 12.15 mL (18.72 mmol) of ^{t}BuLi (1.52 M in pentane) was slowly added. The mixture was stirred for 20 h. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product is purified by crystallisation from CH_2Cl_2/Et_2O (1:1) at -80 °C. Yellow solid, 802 mg, 67% yield. The NMR-spectra are in agreement with the literature.[285]

^{1}H-NMR: 300 MHz, $CDCl_3$ δ (ppm) 1.25 (d, 12H), 3.97 (m, 2H), 5.09 (br, 2H)

^{13}C-NMR: 75 MHz, $CDCl_3$ δ (ppm) 162.2, 118.4, 46.1, 33.9, 23.1

1f *N*,*N*-diisopropyl-3-phenyl-propiolamidine [CAS 121948-78-5]



1f

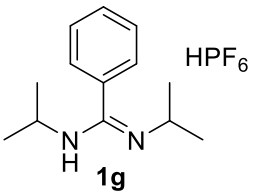
1 g (6.24 mmol) diisopropyl thiourea **1** and 637 mg (6.24 mmol) phenylacetylene were dissolved in 50 mL dry THF. The mixture was cooled to – 78 °C and 12.15 mL (18.72 mmol) ^{t}BuLi (1.52 M in pentane) was slowly added. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product is purified by crystallisation from hexane at -80 °C. Beige solid, 755 mg, 53% yield. The NMR-spectra are in agreement with the literature.[316]

^{1}H-NMR: 300 MHz, $CDCl_3$ δ (ppm) 1.79 (d, 6H), 3.97 (hept, 2H), 7.39 (m, 3H), 7.50 (m, 2H)

^{13}C-NMR: 75 MHz, $CDCl_3$ δ (ppm) 141.2, 131.9, 129.3, 128.4, 121.5, 91.7, 79.3, 23.9

HRMS: (ESI) calc. for $C_{15}H_{21}N_2$ ([M+H$^+$]) 229.1699, found 229.1703

1g *N,N*-diisopropylbenzamidine [CAS 53722-39-7] (free base)



1g

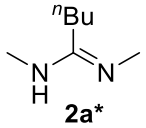
1 g (6.24 mmol) of thiourea **1** was suspended in 50 mL of dry diethyl ether. 19 mL (18.72 mmol) of PhLi (0.98 M in dibutyl ether) was slowly added at room temperature. The mixture was stirred at room temperature for 20 h. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under vacuum. The crude amidine was obtained as yellow oil as described in the literature.[317,318] Benzene and dibutyl ether were the only impurities detected by NMR. The crude product was further purified by dissolution in pentane followed by shaking with an aqueous solution NH_4PF_6. The amidinium salt is obtained as white solid. 1.7 g, 5 mmol, 81% The NMR spectra agree with the literature.[317,318] However, the ^{i}Pr moieties are not equivalent in the protonated form.

^{1}H-NMR: 300 MHz, CD_3CN δ (ppm) 1.22-1.24 (d, 6H), 1.30-1.32 (d, 6H), 3.57 (sept, 1H), 3.93 (sept. 1H), 7.52 (aromatic, 2H), 7.60 (aromatic, 3H)

^{13}C-NMR: 75 MHz, CD_3CN δ (ppm) 163.3, 133.2, 130.1, 128.5, 50.2, 46.3, 22.7, 21.3

HRMS: (ESI) calc. for $C_{13}H_{21}N_2$ ([M+H$^+$]) 205.1699, found 205.1695

2a *N,N*-dimethylpentanamidine



2a*

Method A: 1 g (9.59 mmol) of dimethyl thiourea **2** and 1,22 g (9.6 mmol) $FeCl_2$ were suspended in 50 mL dry diethyl ether. The mixture was cooled to 0 °C and 13.1 mL (28.77 mmol) of ^{n}BuLi (2.2 M in hexane) was slowly added. The mixture was stirred for 20 h and allowed to reach room temperature. 10 mL of deionized water was added to quench the reaction. The organic phase was decanted of and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 60 °C (Colourless solid, 847 mg, 69%).

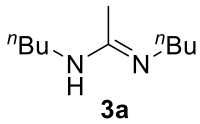
Method B: 1 g (9.59 mmol) of dimethyl thiourea **2** was suspended in 50 mL dry diethyl ether. 13.1 mL (28.77 mmol) of ^{n}BuLi (2.2 M in hexane) was slowly added. The mixture was stirred for 20 h at room temperature. The reaction was quenched with 10 mL 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 60 °C (Colourless solid,774 mg, 63%).

^{1}HNMR: 300 MHz, $CDCl_3$; δ (ppm) 0.90 (t, 3H), 1.33 (m, 2H), 1.49 (m, 2H), 2.16 (t, 2H), 2.84 (s, 6H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 161.7, 36.3, 30.1, 28.7, 22.7, 13.7

HRMS: (ESI) calc. for $C_7H_{17}N_2$ ([M+H$^+$]) 129.1386, found 129.1383

3a *N*,*N*-dibutylacetamidine [CAS 52120-15-7]



3a

Method A: 1 g (5.3 mmol) of dibutyl thiourea **3** and 672 mg (5.3 mmol) $FeCl_2$ were suspended in 50 mL dry ethyl ether. The mixture was cooled to 0 °C and 10 mL (15.9 mmol) of MeLi (1.59 M in Et_2O) was slowly added. The mixture was stirred for 20 h and allowed to reach room temperature. 10 mL of deionized water was added to quench the reaction. The organic phase was decanted of and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 60 °C. (Colourless oil, 515 mg, 57% yield.)

Method B: 1 g (5.3 mmol) of dibutyl thiourea **3** was suspended in 50 mL dry ethyl ether. 10 mL (15.9 mmol) of of MeLi (1.59 M in Et_2O) was slowly added and the mixture was stirred for 20 h at room temperature. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under

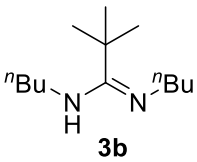
reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 60 °C. Colourless oil, 520 mg, 58% yield. The NMR-spectra are in agreement with literature.[319]

^{1}H-NMR: 300 MHz, $CDCl_3$ δ 0.86 (ppm) (t, 6H), 1.28-1.45 (m, 8H), 1.78 (s, 3H), 3.05 (br, 4H)

^{13}C-NMR: 75 MHz, $CDCl_3$ δ (ppm) 155.3, 65.2, 32.5, 29.9, 15.6, 13.3

HRMS: (ESI) calc. for $C_{10}H_{23}N_2$ ([M+H$^+$]) 171.1856, found 171.1857

3b *N,N*-dibutyl-^{t}butylamidine [CAS 1775-69-5]



3b

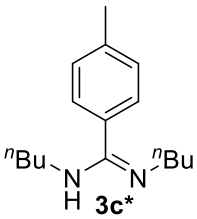
Side product obtained in the preparation of **3c**.

^{1}H-NMR: 300 MHz, $CDCl_3$ δ (ppm) 0.85-0.94 (overlaps with **3c**), 1.17 (s, 9H), 1.32 (m, overlaps with **3c**), 1.50 (m, overlaps with **3c**), 3.15 (br, overlaps with **3c**)

^{13}C-NMR: 75 MHz, $CDCl_3$ δ (ppm) 67.0, 33, 28.7, 21.2, 20.3, 13.9

HRMS: (ESI) calc. for $C_{13}H_{29}N_2$ ([M+H$^+$]) 213.2325, found 213.2324

3c *N,N*-dibutyl-4-methyphenylamidine



3c*

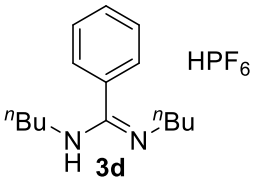
1 g of thiourea **3** was suspended in 50 mL dry diethyl ether. The suspension was cooled to -78 °C. ^{t}BuLi (1.52 M in penatne) was slowly added. The mixture was stirred for 30 minutes. The aryl lithium compound (prepared from 4-bromo toluene and 2 eq. of ^{t}BuLi in ether at -78 °C) was added dropwise *via* transfer canula. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was further purified by condensation into a nitrogen cooled Schlenk flask at 60 °C and 10^{-3} mbar. Attempts to separate **3b** and **3c** by column chromatography resulted in loss of the products.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 0.85-0.94 (overlaps with **3b**), 1.32 (m, overlaps with **3b**), 1.50 (m, overlaps with **3b**), 2.36 (s, 3H), 3.15 (br, overlaps with **3b**), 7.17 (aromatic, 4H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 158.9, 138.4, 133.3, 128.9, 127.5, 67.0, 33.3, 21.2, 20.3, 13.9

HRMS: (ESI) calc. for $C_{16}H_{27}N_2$ ([M+H$^+$]) 247.2169, found 247.2167

3d *N,N*-dibutylbenzamidine [CAS 52120-10-2] (free base)



3d

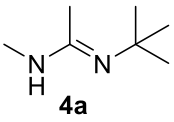
1 g (5.3 mmol) of thiourea **3** was suspended in 50 mL dry diethyl ether. The mixture was cooled to 0 °C and 16.2 mL (16 mmol) PhLi (0.98 M in dibutyl ether) were slowly added. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL 10 %wt $NaOH_{(aq)}$. The phases were separated and the solvent was removed under reduced pressure. The yellow crude oil contained dibutyl ether and benzene as main impurities. The crude product was dissolved in dichloromethane and shaken with $NH_4PF_{6(aq)}$. The phases were separated and the solvent was removed under reduced pressure. The resulting IL was washed with diethyl ether 3 times and then dried under vacuum to give the amidinium salt as yellow oil. 1.4 g, 3.8 mmol, 72%. The spectra are in agreement with the literature[317], however the *n*butyl moieties are not equivalent in the protonated form.

^{1}H-NMR: 300 MHz, CD_2Cl_2; δ (ppm) 0.83 (t, 3H), 0.99 (t, 3H), 1.25 (quint. 2H), 1.48 (quint. 2H), 1.61 (quint. 2H), 1.75 (quint. 2H), 3.34 (t, 2H), 3.49 (t, 2H) 6.62 (br, 1H), 7.09 (br, 1H), 7.51-7.71 (aromatic, 5H)

^{13}C-NMR: 75 MHz, CD_2Cl_2; δ (ppm) 165.3, 133.7, 130.3, 128.2, 125.4, 46.8, 46.0, 43.5, 32.1, 30.1, 20.3, 19.9, 13.6

HRMS: (ESI) calc. for $C_{15}H_{25}N_2$ ([M+H$^+$]) 233.2012, found 233.2010

4a *N*-*t*butyl-*N*-methylacetamidine [CAS 76893-99-7]



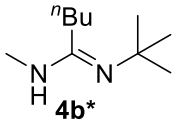
4a

Method B: 500 mg (3.42 mmol) *N*-*t*butyl-*N*-methyl thiourea **4** was suspended in 50 mL dry diethyl ether. 6.45 mL (10.26 mmol) of MeLi (1.59 M in Et_2O) was slowly added. The reaction was stirred for 20 h at room temperature. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 40 °C. Colourless oil, 560 mg, 64% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 1.18 (s, 9H), 1.59 (s, 3H), 2.77 (s, 3H)

^{13}C-NMR: 75 MHz, $CDCl_3$ δ (ppm) 155.6, 65.2, 49.9, 36.0, 28.6, 16.4, 14.7

4b *N*-*t*butyl-*N*-methylpentanamidine



4b*

Method A: 1 g (6.84 mmol) *N*-*t*butyl-*N*-methyl thiourea **4** and 866 mg (6.84 mmol) $FeCl_2$ were suspended in 50 mL dry diethyl ether. The mixture was cooled to 0 °C and 8.14 mL (20.52 mmol) of *n*BuLi (2.2 M in hexane) was slowly added. The reaction was stirred for 20 h and was allowed to reach room temperature. 10 mL of deionized water was added to quench the reaction. The organic phase was decanted of and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 40 °C. Colourless oil, 638 mg, 55% yield.

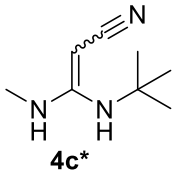
Method B: 1 g (6.84 mmol) *N*-*t*butyl-*N*-methyl thiourea **4** was suspended 50 mL dry diethyl ether. The mixture was cooled to 0 °C and 8.14 mL (20.52 mmol) of *n*BuLi (2.2 M in hexane) was slowly added. The reaction was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL of 10wt% $NaOH_{(aq)}$ and the phases were separated. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The solvent was removed under reduced pressure and the residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 40 °C. Colourless oil, 885 mg, 76% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$ δ (ppm) 0.91 (t, 3H), 1.30 (s, 9H), 1.33-1.43 (m, 4H), 2.05 (t, 2H), 2.94 (s, 3H)

^{13}C-NMR: 75 MHz, $CDCl_3$ δ (ppm) 159.3, 65.7, 50.3, 35.9, 30.2, 29.0, 22.6, 15.1, 13.8

HRMS: (ESI) calc. for $C_{10}H_{23}N_2$ ([M+H$^+$]) 171.1856, found 171.1855

4c *N*-methyl-*N*-*t*butyl-acrylonitrile-1,1-diamine



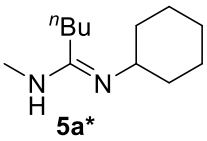
4c*

1 g (6.84 mmol) of thiourea **4** and 360 µL (280 mg, 6.84 mmol) were suspended in 50 mL of dry diethyl ether. The mixture was cooled to -78 °C. 13.5 mL (20.52 mmol) of *t*BuLi (1.52 M in pentane) were slowly added. The mixture was stirred for 20 h and allowed to reach room temperature. The reaction was quenched with 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the solvent was removed under reduced pressure. Purification of the yellow crude product was attempted by crystallisation, condensation into a nitrogen cooled Schlenk flask and by column chromatography (silica and AlO_X). Impurities were not removed by crystallisation and

condensation attempts resulted in decomposition or other side reactions. Column chromatography resulted in total loss of the crude product. The crude product was therefore analysed by mass spectrometry.

HRMS: (ESI): calc. for $C_8H_{16}N_3$ ([M+H$^+$]) 154.1339, found 154.1336

5a *N*-cyclohexyl-*N*-methylpentanamidine



5a*

Method A: 1 g (5.84 mmol) of *N*-cyclohexyl-*N*-methyl thiourea **5** and 735 m (5.84 mmol) $FeCl_2$ were suspended in 50 mL dry diethyl ether. The mixture was cooled to 0 °C. 7.9 mL (17.4 mmol) of ^{n}BuLi (2.2 M in hexane) was slowly added. The reaction was stirred for 20 h and was allowed to reach room temperature. 10 mL of deionized water was added to quench the reaction. The organic phase was decanted of and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 60 °C. White solid, 570 mg, 50% yield.

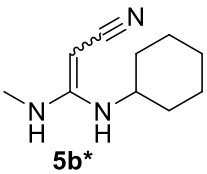
Method B: A: 1 g (5.84 mmol) of *N*-cyclohexyl-*N*-methyl thiourea **5** was dissolved in 50 mL dry THF. 7.9 mL (17.4 mmol) of ^{n}BuLi (2.2 M in hexane) was slowly added. The reaction was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 60 °C. White solid, 860 mg, 75% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 0.93 (t, 3H), 1.18-1.83 (m, 14H), 2.16 (t, 2H), 2.88 (s, 3H), 3.46 (br, 1H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 159.6, 34.3, 29.2, 25.7, 25.0, 22.6, 13.8

HRMS: (ESI) calc. for $C_{12}H_{25}N_2$ ([M+H$^+$]) 197.2012, found 197.2012

5b *N*-methyl-*N*-cyclohexyl-acrylonitrile



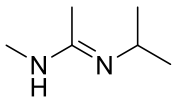
5b*

1 g (5.8 mmol) of thiourea **5** and 305 *µL* (238 mg, 5.8 mmol) acetonitrile suspended in 50 mL of dry diethyl ether. The mixture was cooled to -78 °C and 11.4 mL (17.4 mmol) of ^{t}BuLi (1.52 M in pentane) was slowly added. The mixture was stirred for 20 h and allowed to reach room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. Purification of the yellow crude product was

attempted by crystallisation, condensation into a nitrogen cooled Schlenk flask and by column chromatography (silica and AlO_X). Impurities were not removed by crystallisation and condensation attempts resulted in decomposition or other side reactions. Column chromatography resulted in total loss of the crude product. The crude product was therefore analysed by mass spectrometry.

HRMS: (ESI): calc. for $C_{10}H_{18}N_3$ ([M+H$^+$]) 180.1495, found 180.1494

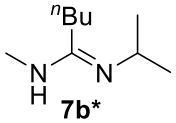
7a *N*-isopropyl-*N*-methylacetamidine [CAS 779998-19-5]


7a

Method B: 1 g (7.56 mmol) of thiourea **7** was suspended in 50 mL dry diethyl ether. 14.3 mL (22.68 mmol) of MeLi (1.59 in Et_2O) was slowly added. The mixture was stirred for 20 h at room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 50 °C. The NMR spectrum is in agreement with the literature.[320] White solid, 370 mg, 43% yield.

^{1}H-NMR: 300MHz, $CDCl_3$; δ (ppm) 1.09-1.11 (d, 6H), 1.82 (s, 3H), 2.85 (s, 3H), 3.73 (br, 1H)

7b *N*-isopropyl-*N*-methylpropanamidine


7b*

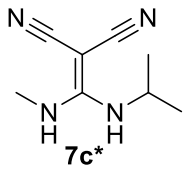
Method B: 1 g (7.56 mmol) *N*-isopropyl-*N*-methyl thiourea **7** was suspended in 50 mL dry diethyl ether. The suspension was cooled to 0 °C and 10.3 mL (22.68 mmol) ^{n}BuLi (2.2 M in hexane) was slowly added. The reaction was stirred for 20 h and allowed to reach room temperature. The reaction was quenched with 10 mL 10%wt $NaOH_{aq}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by condensation into a nitrogen cooled flask at 10^{-3} mbar and 50 °C. White solid (melts to a colourless oil), 970 mg, 82% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 0.84 (t, 3H), 1.02 (d, 6H), 1.27-1.42 (m, 4H), 2.07 (t, 2H), 2.78 (s, 3H), 3.70 (m, 1H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 159.4, 43.2, 32.8, 30.2, 28.9, 22.3, 13.4

HRMS: (ESI) calc. for $C_9H_{21}N_2$ ([M+H$^+$]) 157.1699, found 157.1696

7c 2-((isopropylamino)(methylamino)methylene)malonodinitril



7c*

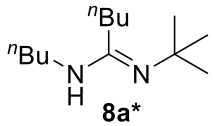
1 g (7.56 mmol) of thiourea **7** and 500 mg (7.56 mmol) of malonodinitrile were suspended in 50 mL dry diethyl ether. The mixture was cooled to -78 °C and 15 mL (22.68 mmol) of ^{t}BuLi (1.52 M in pentane). The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography. Yellow solid, 300 mg, 24% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 1.27-1.29 (d, 6H), 3.01 (s, 3H), 3.99 (m, 1H), 4.90 (br NH), 5.65 (br, NH)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 163.8, 118.4, 46.0, 33.8, 30.4, 23.3

HRMS: (ESI) calc. for $C_8H_{12}N_4Na$ ([M+Na^+]) 187.0954, found 187.0959

8a *N*-^{t}butyl-*N*-butylpentanamidine



8a*

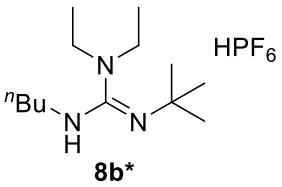
Method B: 1 g (5.3 mmol) of thiourea **8** was suspended in 50 mL of dry diethyl ether. The mixture was cooled to 0 °C. (15.9 mmol) of ^{n}BuLi (2.2 M in hexane) were slowly added. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by condensation into a nitrogen cooled Schlank flask (60 °C, 10^{-3} mbar). White solid (melts to a colourless oil), 970 mg, 82% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 0.91 (t, 3H), 1.32 (s, 9H), 1.34-1.35 (m, 8H), 2.03 (t, 2H), 3.13 (t, 2H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 156.9, 50.2, 48.3, 34.6, 28.9, 22.5, 20.5, 13.9

HRMS: (ESI) calc. for $C_{13}H_{29}N_2$ ([M+H^+]) 213.2325, found 213.2321

8b *N*-^{t}butyl-*N*-^{n}butyl-diethylguanidine



8b*

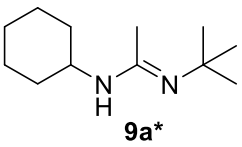
1 g (5.3 mmol) of thiourea **8** was suspended in 50 mL of dry diethyl ether. 550 µL (388 mg, 5.3 mmol) dry diethyl amine was added. The mixture was cooled to-78 °C. 7.7 mL (11.66 mmol) of ^{t}BuLi (1.52 M in pentane) was slowly added. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under vacuum. The crude product was obtained as colourless oil and showed only small amounts of impurities. **8b** was further purified by dissolving in pentane and shaking with a solution (~10 %wt) of NH_4PF_6. The precipitating white solid was filtered of and washed with diethyl ether and water and dried under vacuum. Isolated as HPF_6 salt, white solid, 1.2 g, 60% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 0.93 (t, 3H), 1.19 (t, 6H), 1.29-1.39 (sext, 2H, overlaps with the ^{t}Bu-group), 1.41 (s, 9H), 1.64 (q, 2H), 3.22 (t, 2H), 3.33 (quart, 4H), 5.36 (br, 2H, NH, NH^+)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 158.0, 54.3, 45.5, 43.8, 31.5, 29.6, 19.9, 13.4, 12.5

HRMS: (ESI) calc. for $C_{13}H_{30}N_3$ ([M+H^+]) 228.2434, found 228.2431

9a *N*-^{t}butyl-*N*-cyclohexylacetamidine



9a*

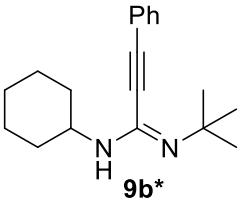
Method B: 1 g (4.66 mmol) of thiourea **9** was suspended in 50 mL of dry diethyl ether. 8.8 mL (14 mmol) of MeLi (1.59 M in Et_2O) were slowly added. The mixture was stirred 20 h at room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. Crude **9a** was obtained as colourless oil and was almost NMR pure. The crude product was purified by condensation into a nitrogen cooled Schlenk flask (60 °C, 10^{-3} mbar).nColourless oil, 815 mg, 89% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 1.26-1.28 (m, 5H), 1.31 (s, 9H), 1.57 (m, 3H), 1.70 (s, 3H), 1.73 (m, 2H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 150.9; 67.6; 56.5; 50.4; 34.8; 28.9; 25.9; 24.5; 15.7

HRMS: (ESI) calc. for $C_{12}H_{25}N_2$ ([M+H^+]) 197.2012, found 197.2013

9b *N*-^{t}butyl-*N*-cyclohexyl-3-phenyl-propiolamidine



9b*

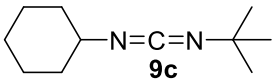
1 g (4.66 mmol) of thiourea **9** was suspended in 50 mL dry diethyl ether. 510 µL (476 mg, 4.66 mmol) of phenylacetylene was added. The mixture was cooled to -78 °C and 9.2 mL (14 mmol) of ^{t}BuLi (1.52 M in pentane) was slowly added. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. Purified by column chromatography (hexane/EtOAc). Yellow oil, 670 mg, 73% yield.

^{1}H-NMR: 300MHz, $CDCl_3$; δ (ppm) 1.19-1.73 (m, 19H, signals overlap), 3.56 (m, 1H), 7.38 (m, 3H), 7.51 (m, 2H)

^{13}C-NMR: 75MHz, $CDCl_3$; δ (ppm) 140.3; 132.2, 128.9, 122.2, 91.4, 80.8, 51.8; 35.2, 31.7, 29.9; 26.4, 25.3, 16.5

HRMS: (ESI) calc. for $C_{19}H_{27}N_2$ ([M+H^{+}]) 283.2169, found 283.2161

9c *N*-^{t}butyl-*N*-cyclohexylcarbodiimide [CAS 1202-53-5]



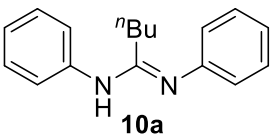
9c

1 g (4.66 mmol) of thiourea **9** was suspended in 50 mL of dry diethyl ether. 5.8 mL (9.32 mmol) of MeLi (1.59 M in Et_2O) was slowly added. The mixture was stirred for 20 h at room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, yielding NMR pure **9c**. Colourless liquid, 750 mg, 89% yield. The NMR-spectra are in agreement with the literature.[321]

^{1}H-NMR: 300MHz, $CDCl_3$; δ (ppm) 1.25 (s+br, 15H), 1.78 (m, 2H), 1.88 (m, 2H), 3.16 (m, 1H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 139.4, 55.7, 54.7, 34.9, 31.2, 29.1, 25.4, 24.6

10a *N,N*-diphenylpentamidine [CAS 35189-93-6]



10a

1 g (4.38 mmol) of diphenyl thiourea **10** was dissolved in 50 mL of dry toluene. 6 mL (13.14 mmol) of ^{n}BuLi (2.2 mmol in hexane) was slowly added. The mixture was stirred for 30 min at room temperature and then refluxed for 3 h. After cooling down, the reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4.

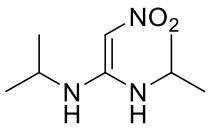
The solvent was removed under reduced pressure. The NMR-spectra are in agreement with the literature.[322] White solid, 800 mg, 72% yield.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ (ppm) 0.80-0.85 (t, 3H), 1.23-1.35 (sext, 2H), 1.52-1.62 (quint, 2H), 2.37-2.42 (t, 2H), 7.12-7.46 (aromatic, 10H)

^{13}C-NMR: 75 MHz, $CDCl_3$; δ (ppm) 129.1, 124.1, 121.3, 30.3, 29.2, 22.2, 13.4

HRMS: (ESI) calc. for $C_{17}H_{21}N_2$ 253.1699 ([M+H$^+$]), found 253.1698

N,N-diisopropyl-2-nitroethene-1,1-diamine



1 g of (6.24 mmol) of thiourea **1** was suspended in 50 mL dry diethyl ether. 335 *µL* (380 mg, 6.24 mmol) of dry nitromethane was added. The mixture was cooled to -78 °C and 12.3 mL (18.7 mmol) of ^{t}BuLi (1.52 M in pentane) were slowly added. The mixture was stirred for 20 h and was allowed to reach room temperature. The reaction was quenched by addition of 10 mL of 10 %wt $NaOH_{(aq)}$. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the yellow crude product was attempted by condensation into a nitrogen cooled Schlenk flask, however only decomposition crude product occurred. Column chromatography or crystallization was unsuccessful as well. A mass spectrum was obtained after TLC.

TLC-MS: (ESI) calc. for $C_8H_{17}N_3O_2Na$ 210.1213 ([M+Na$^+$]), found 210.1217

10 Literature

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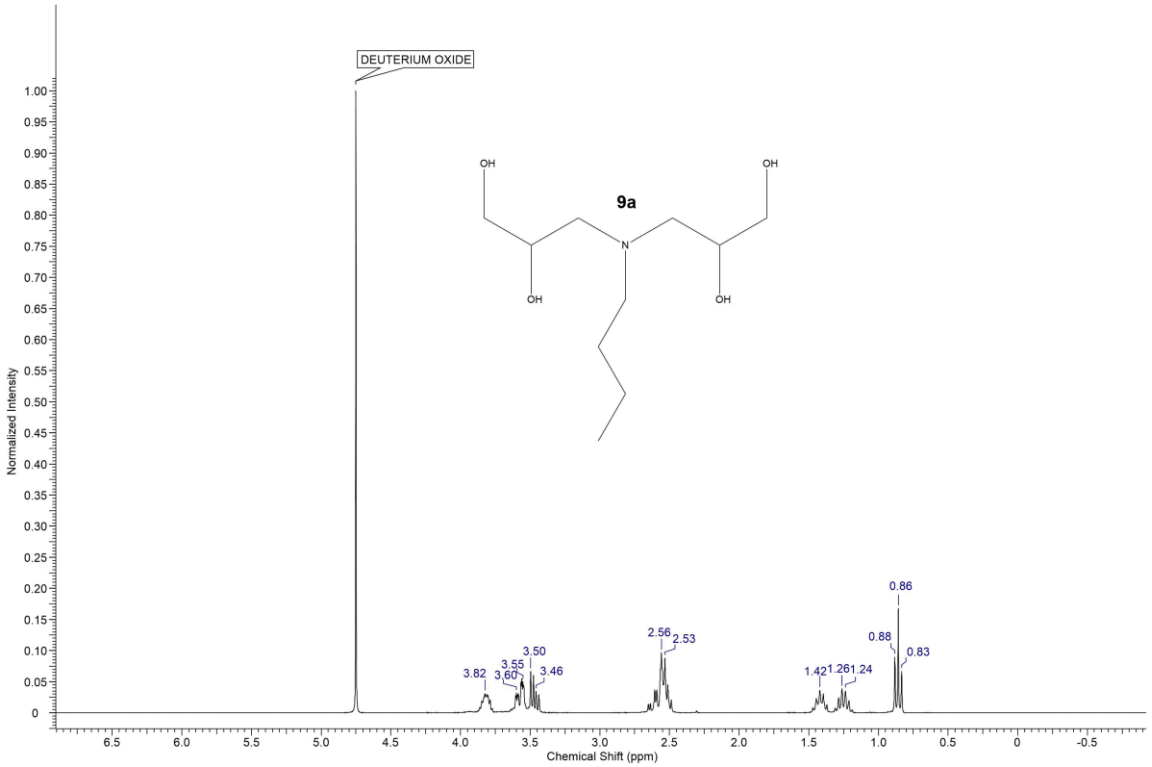
11 Appendix

Part I:



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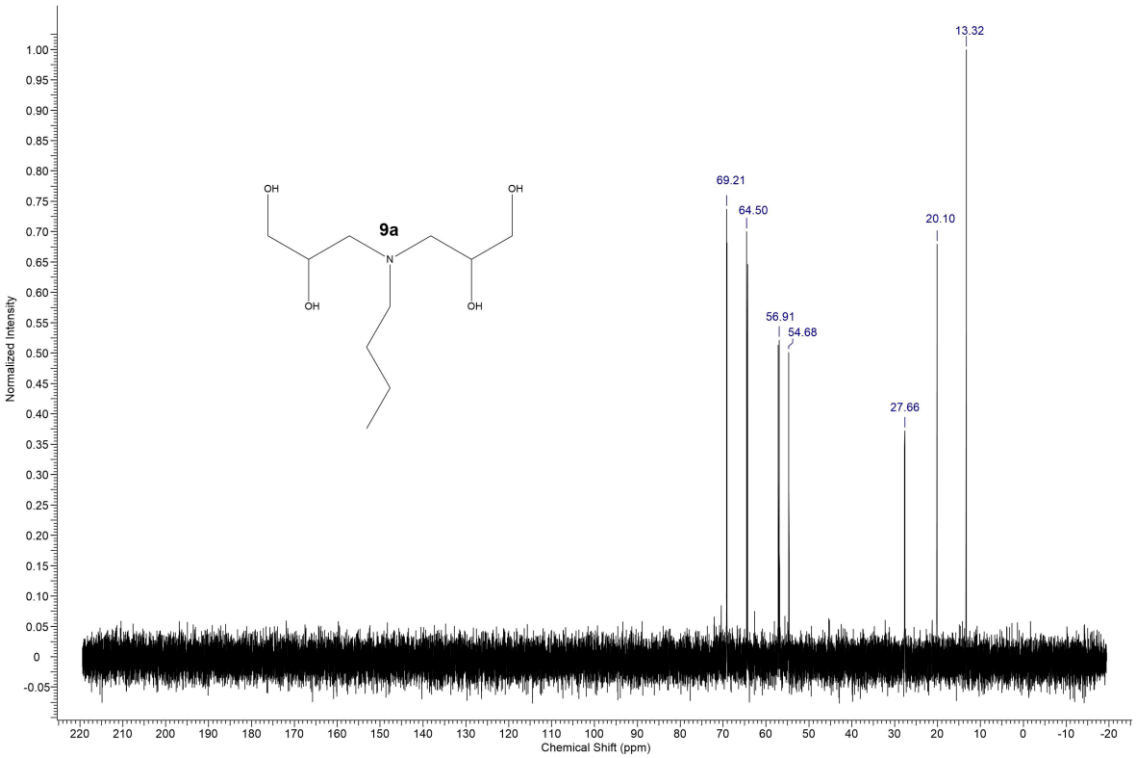

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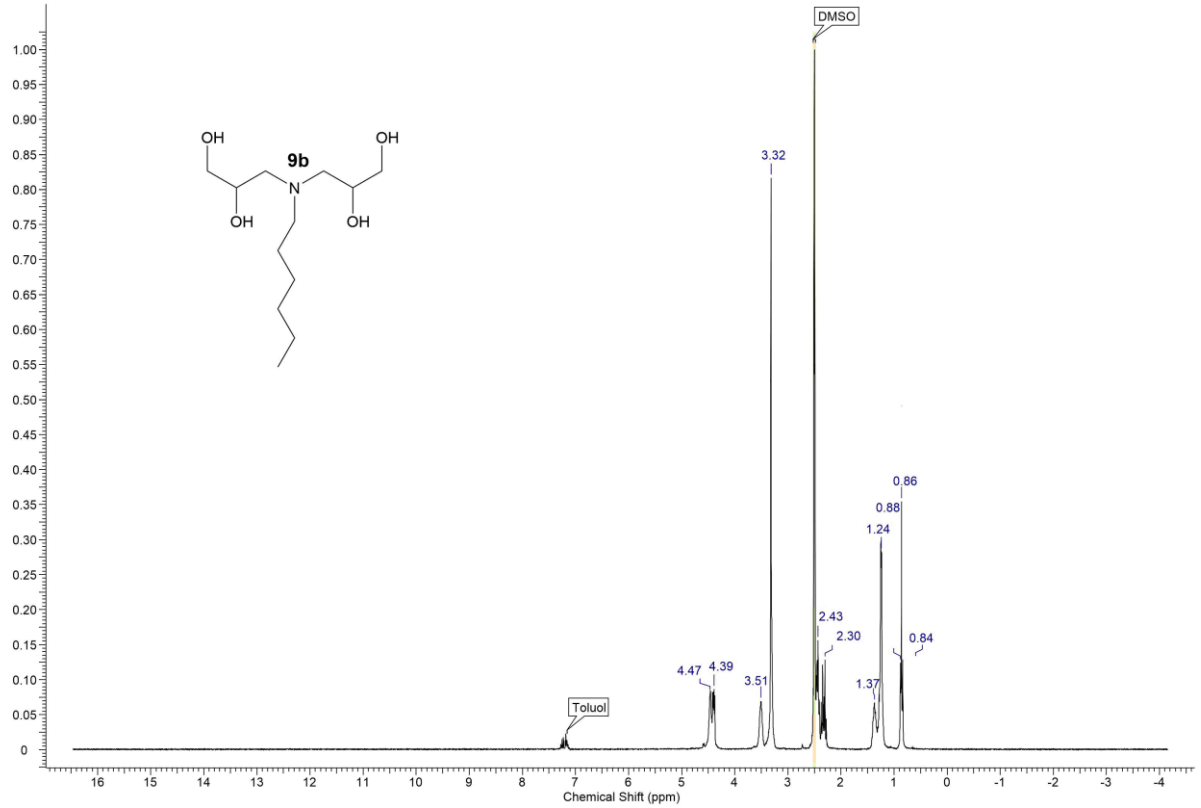

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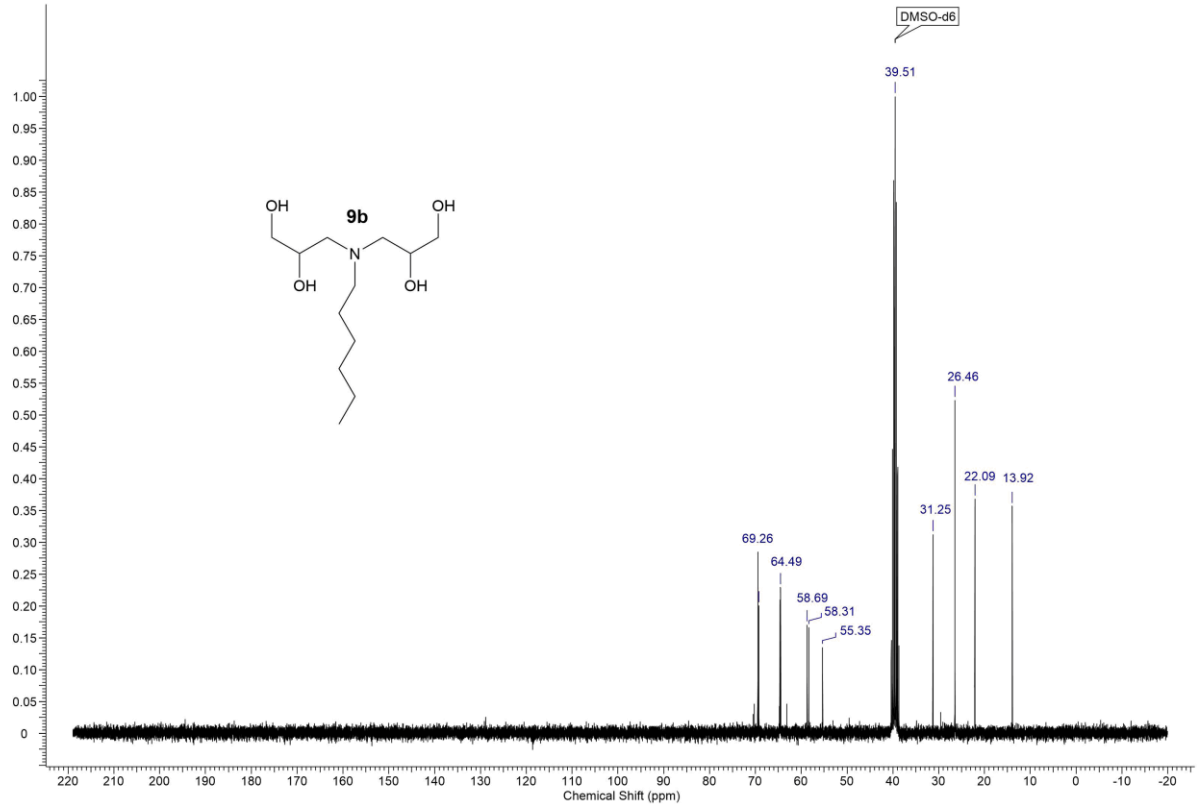

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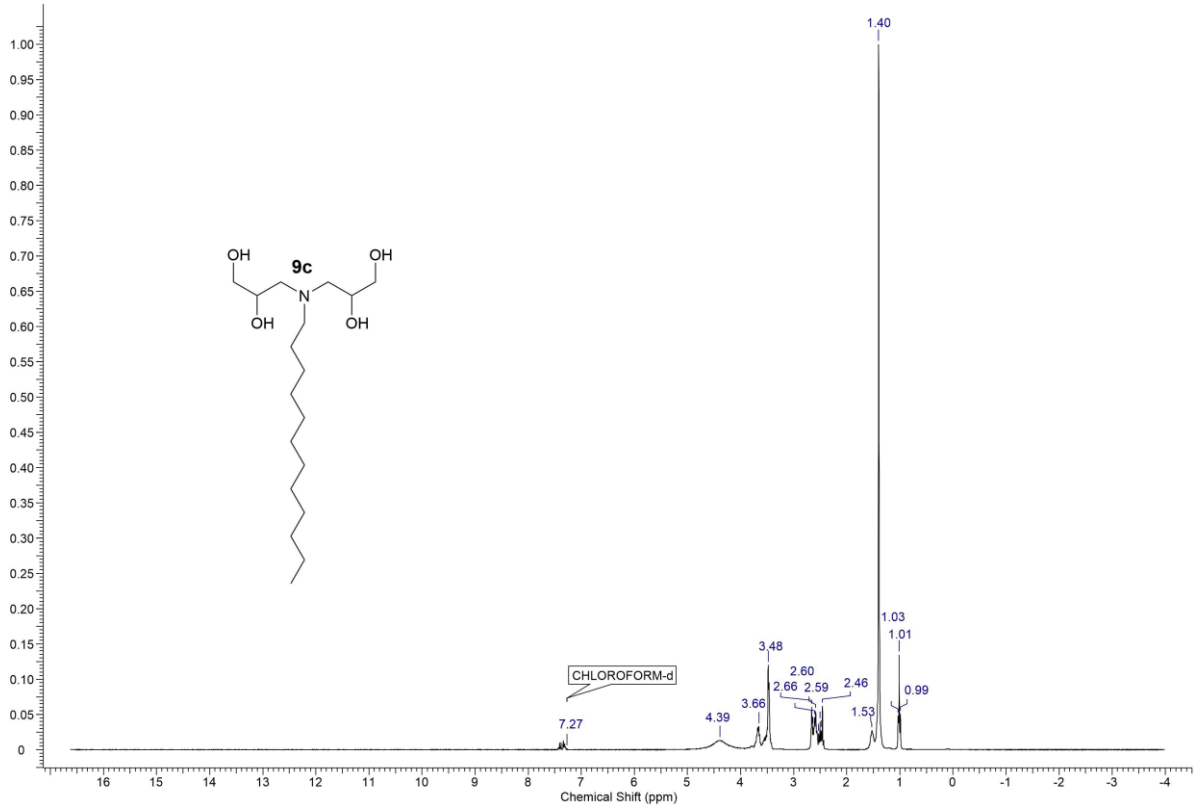

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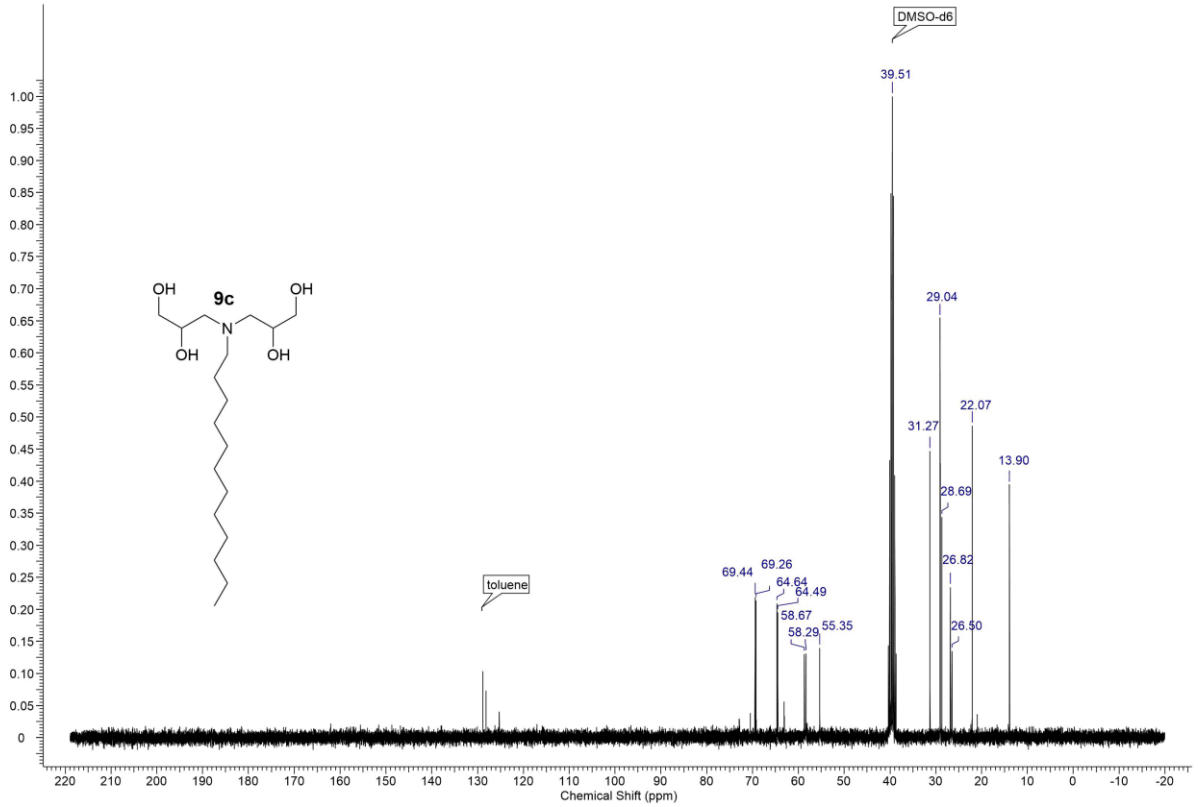

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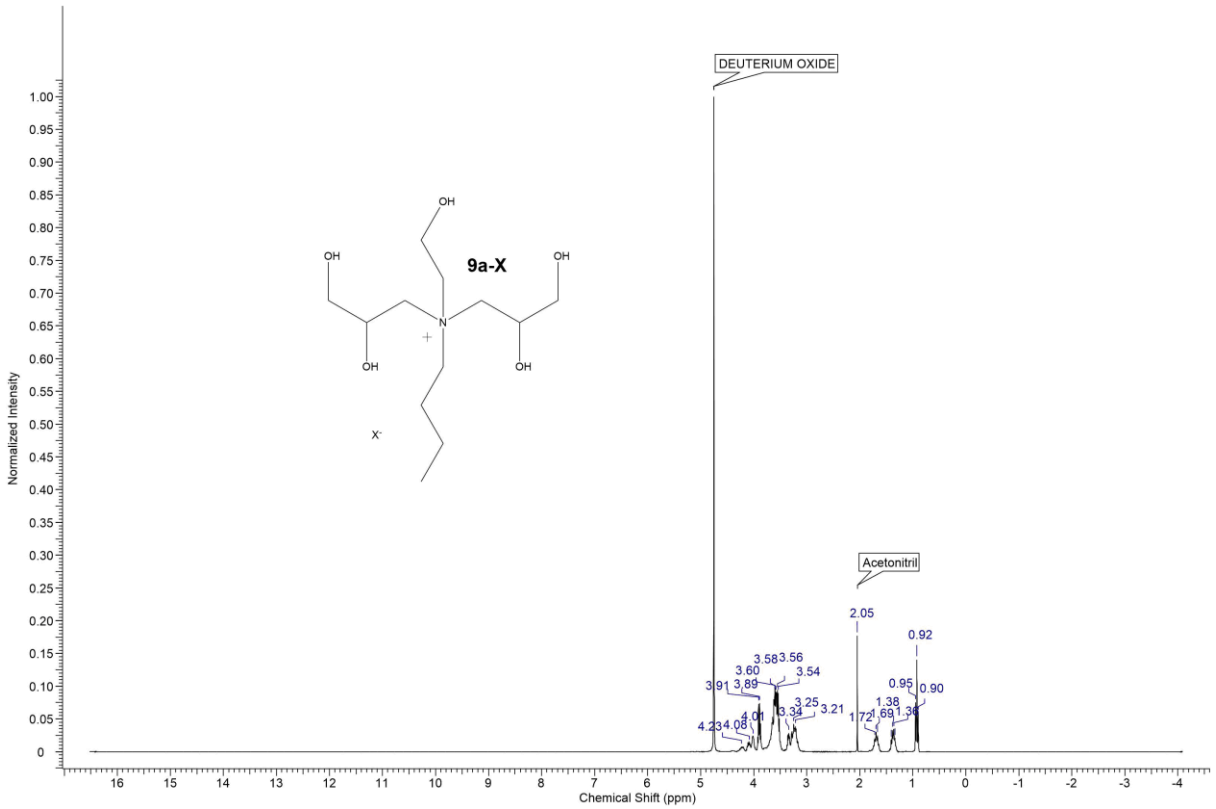

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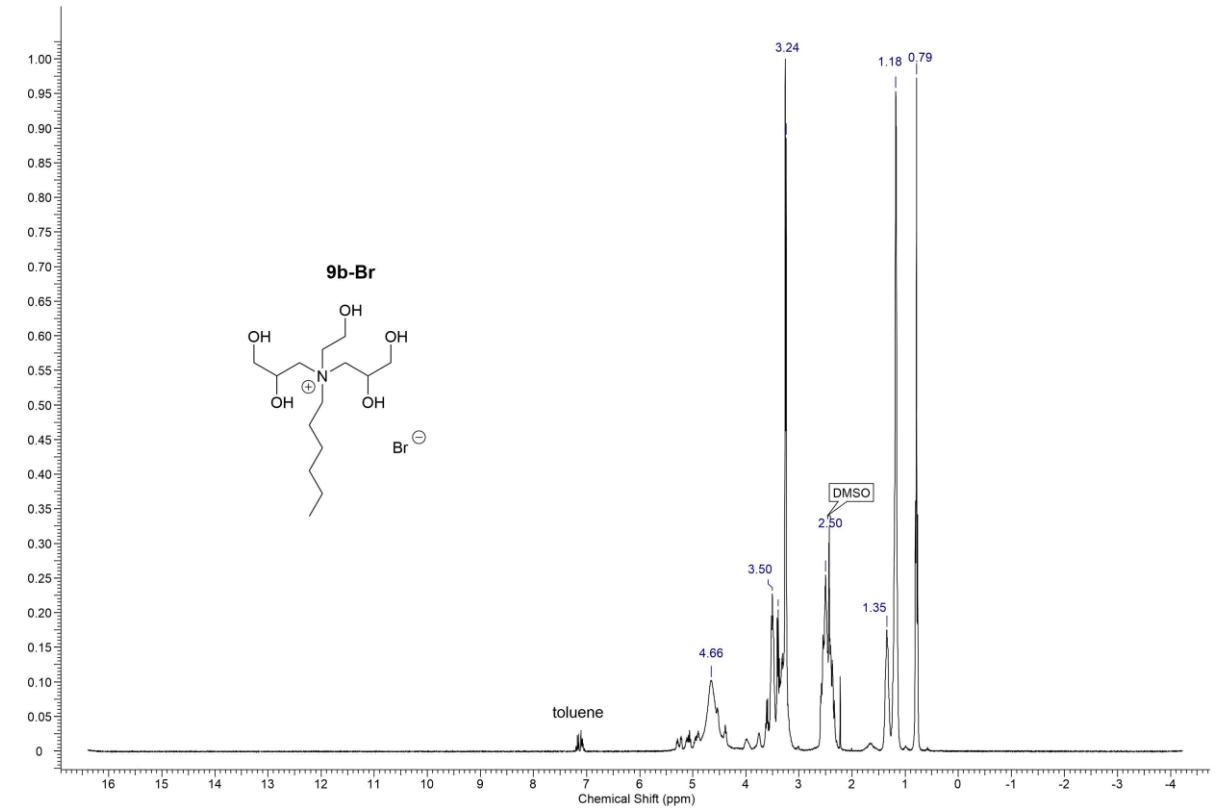

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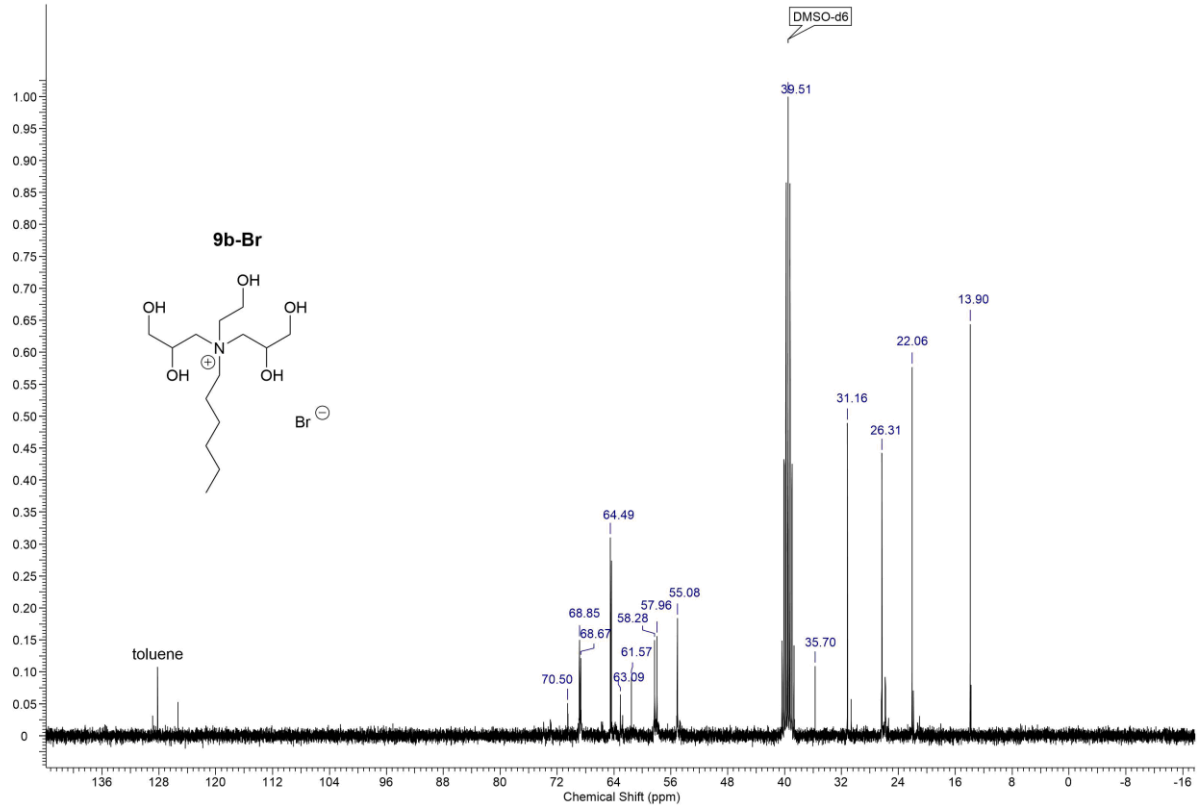

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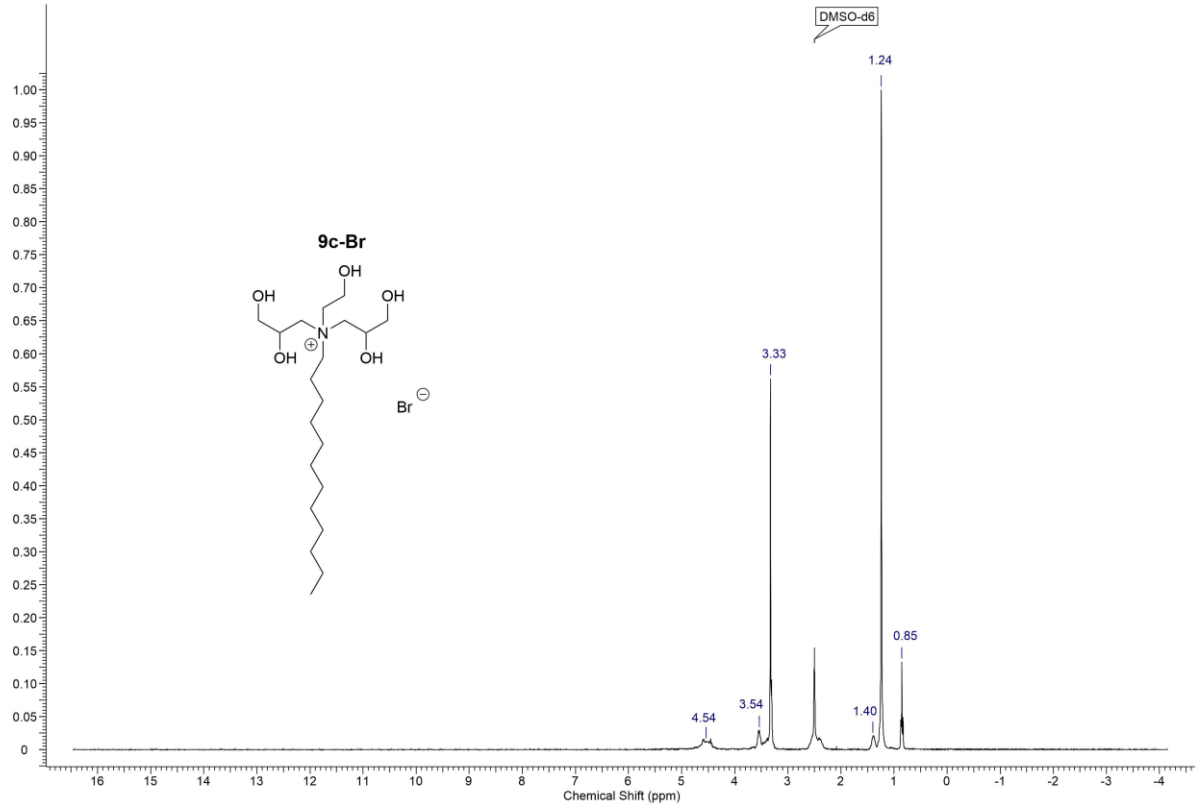

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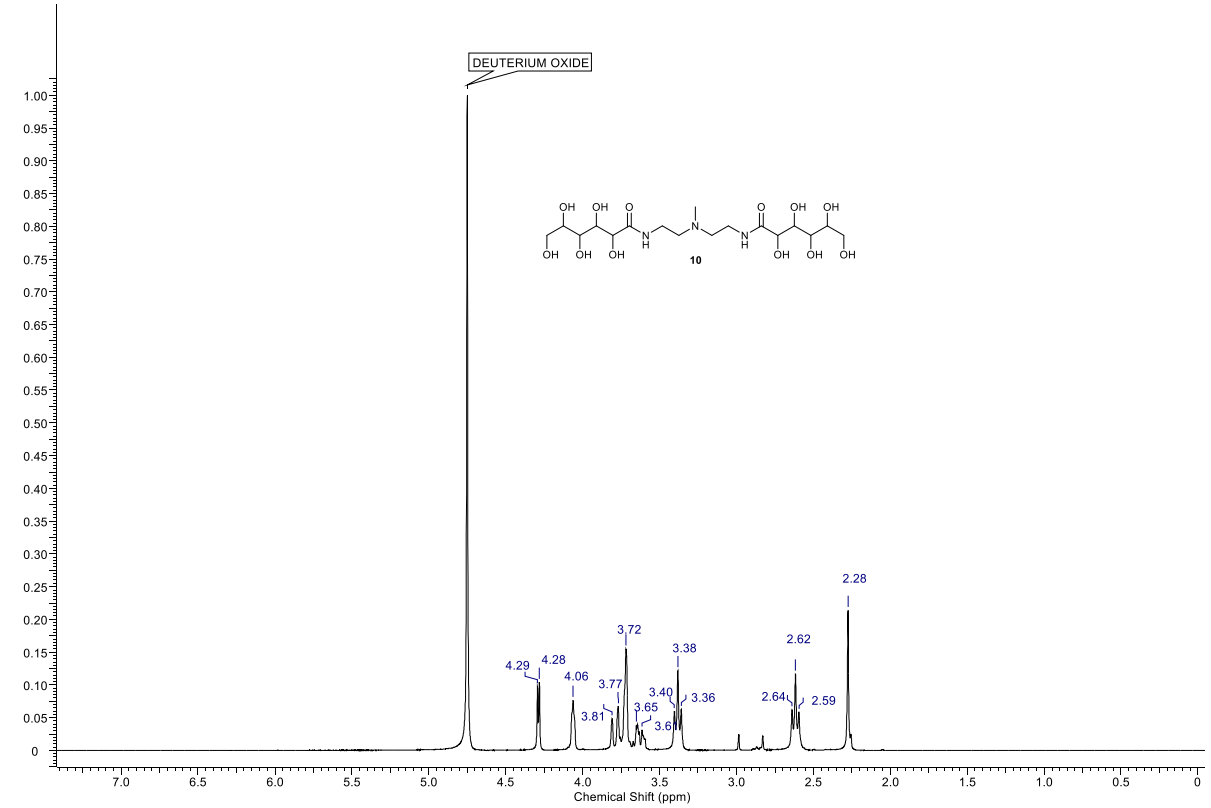

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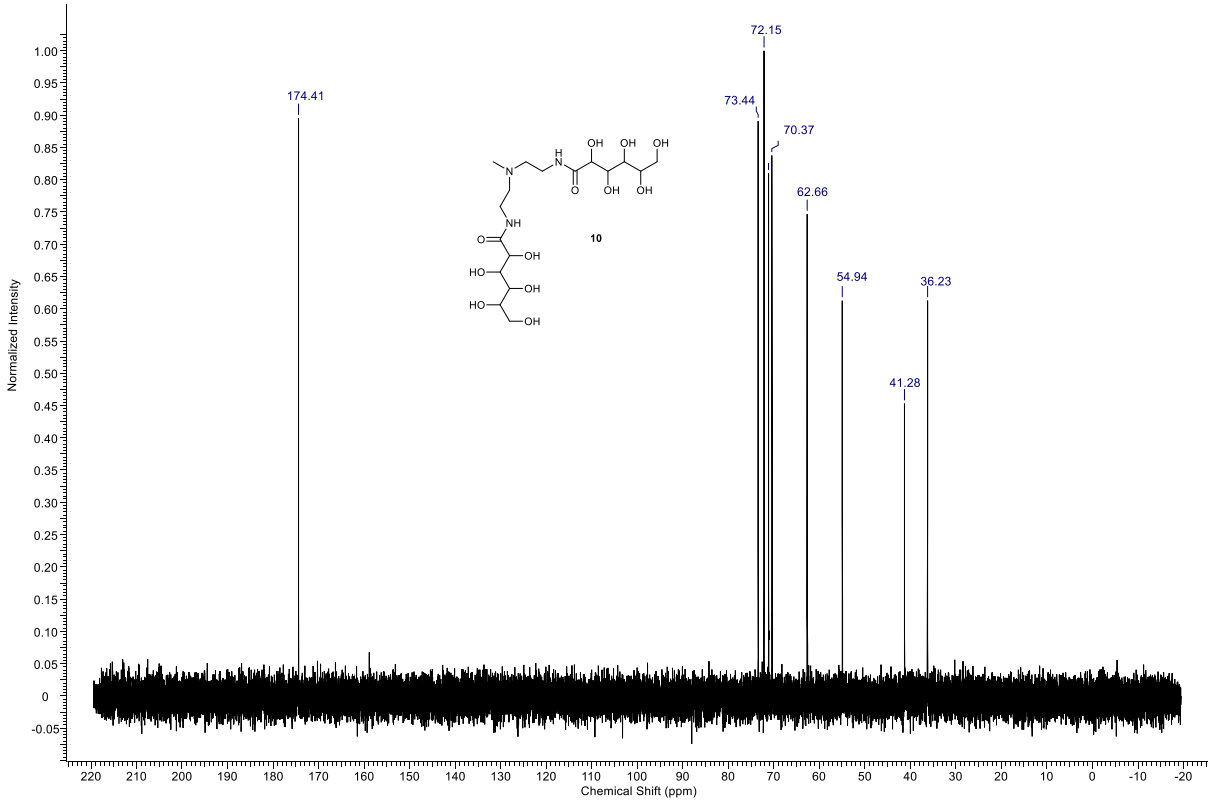

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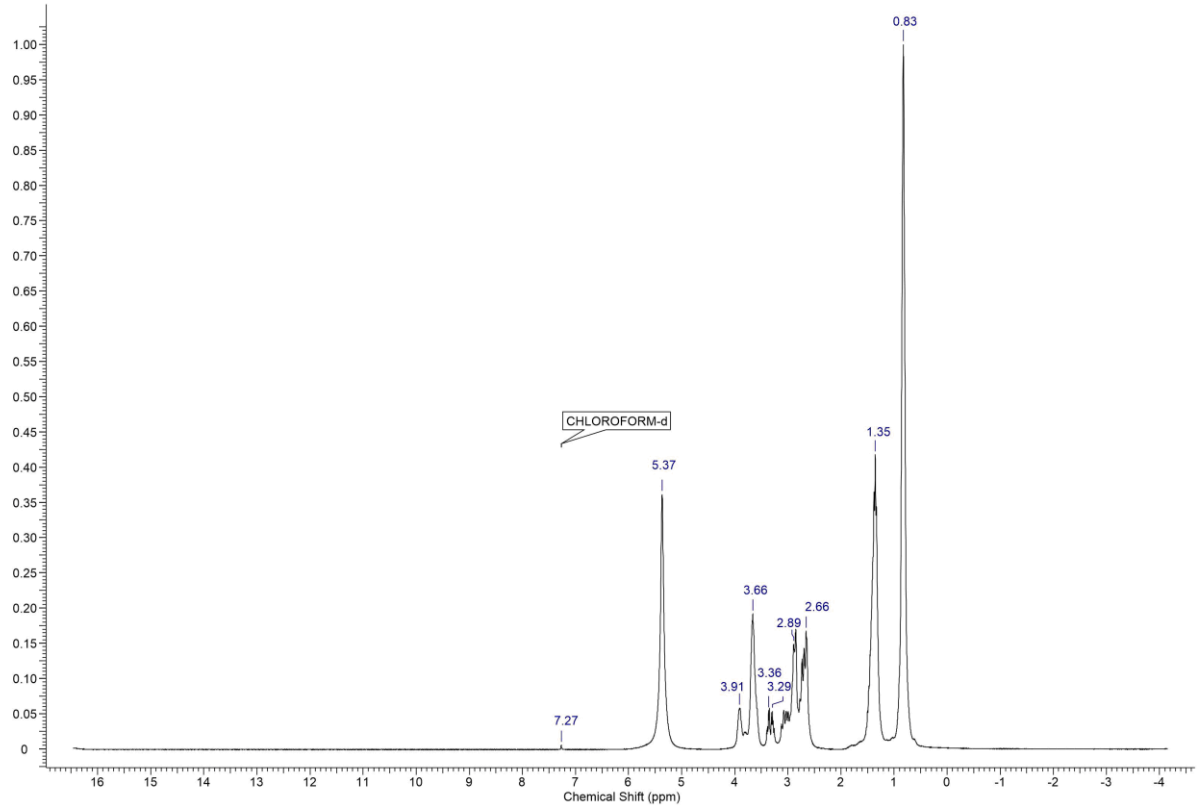

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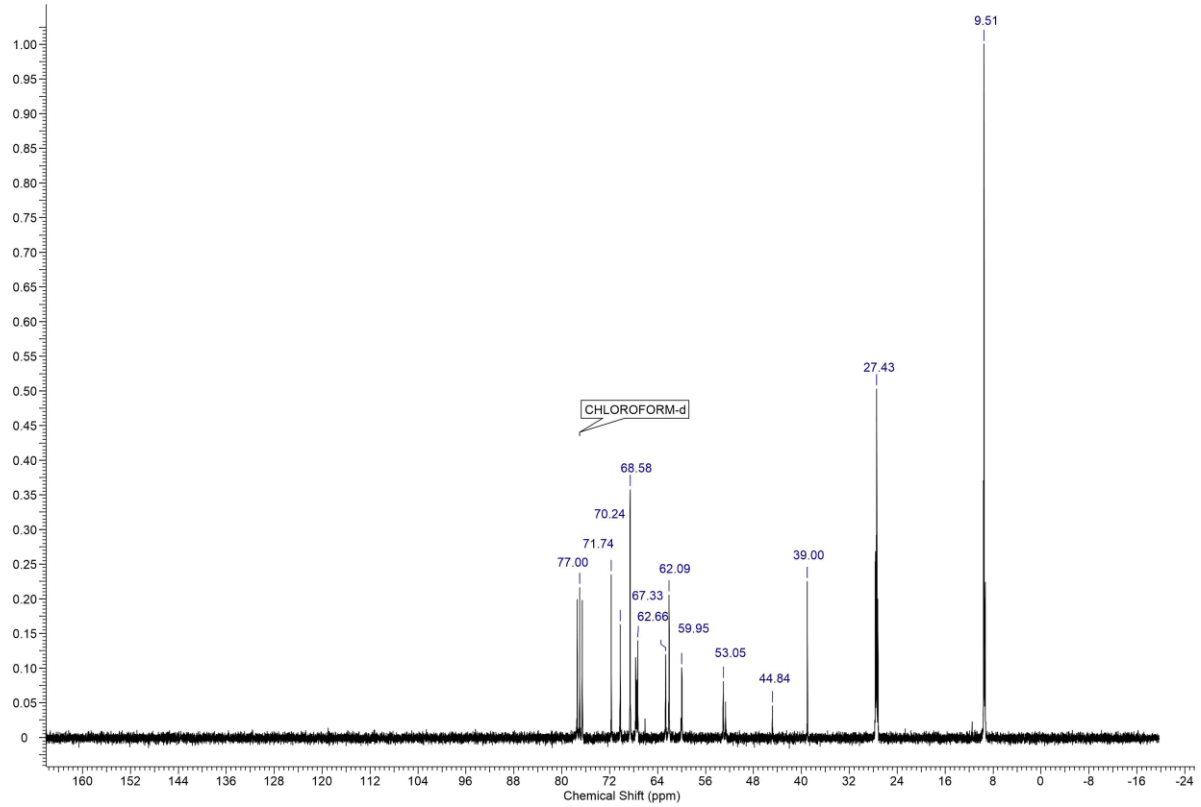

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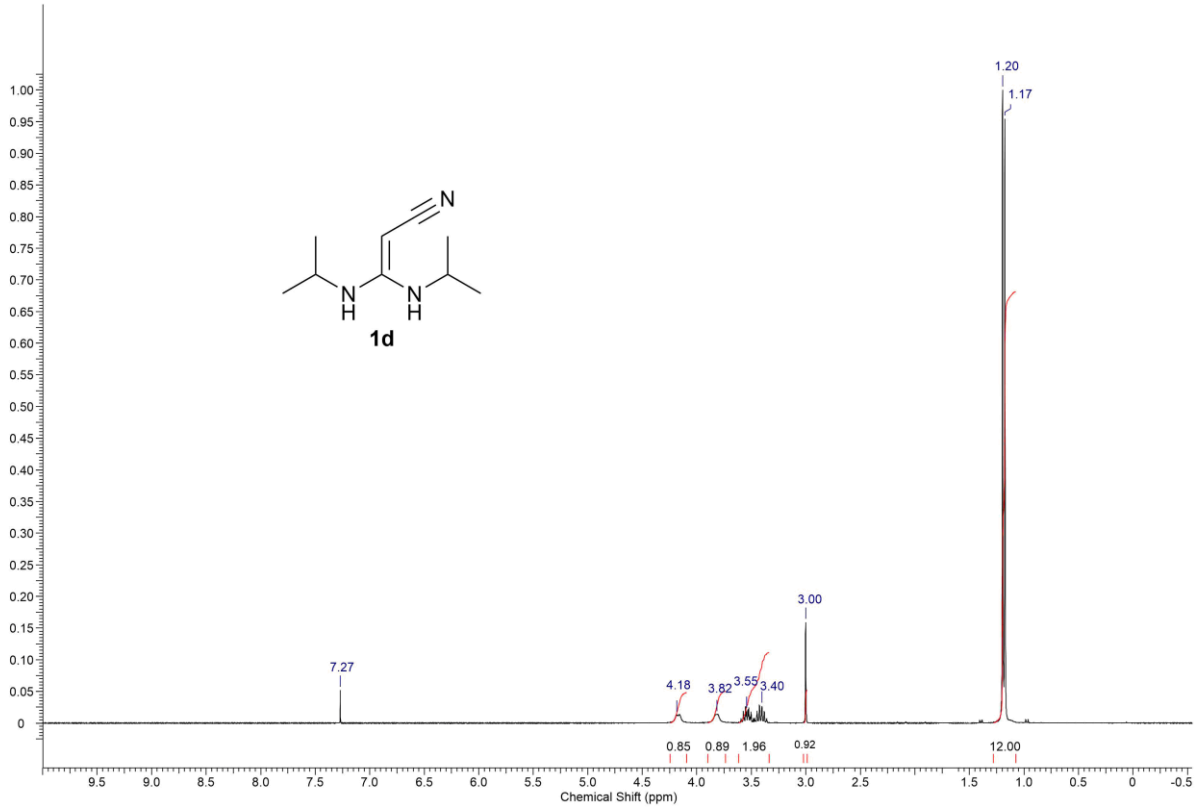
Part II:



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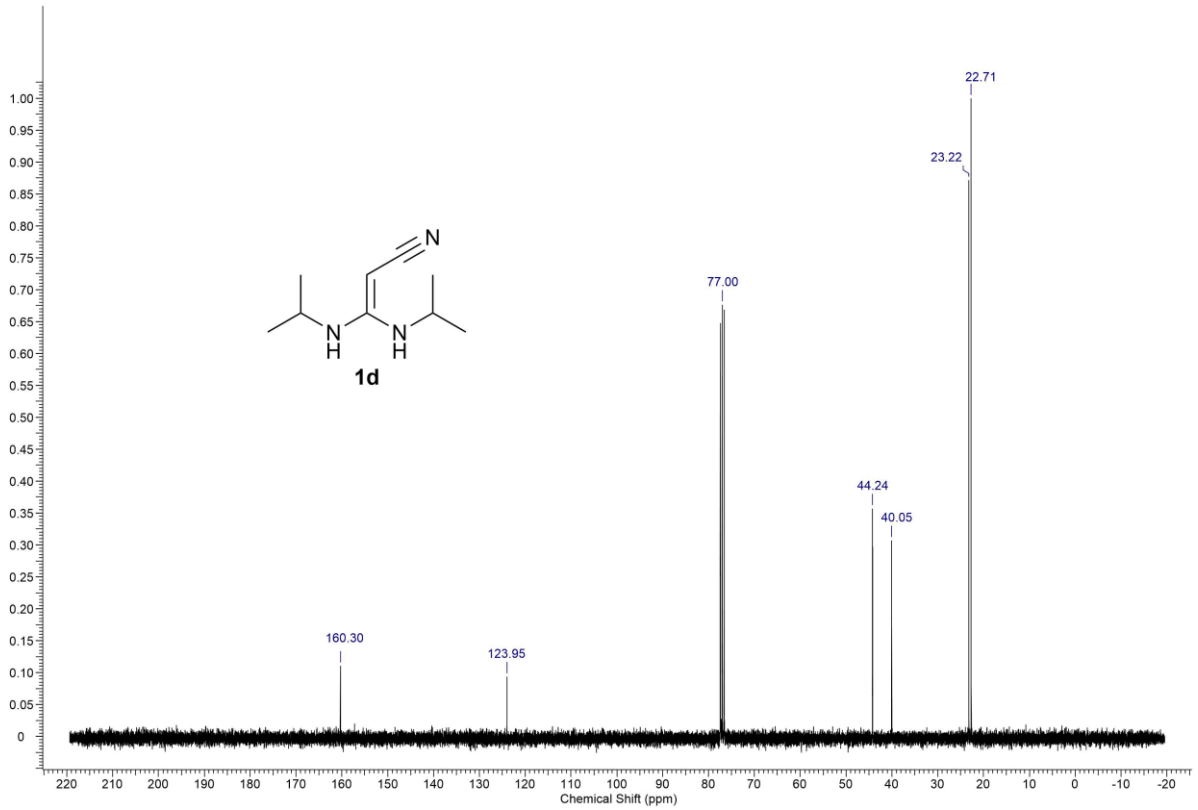

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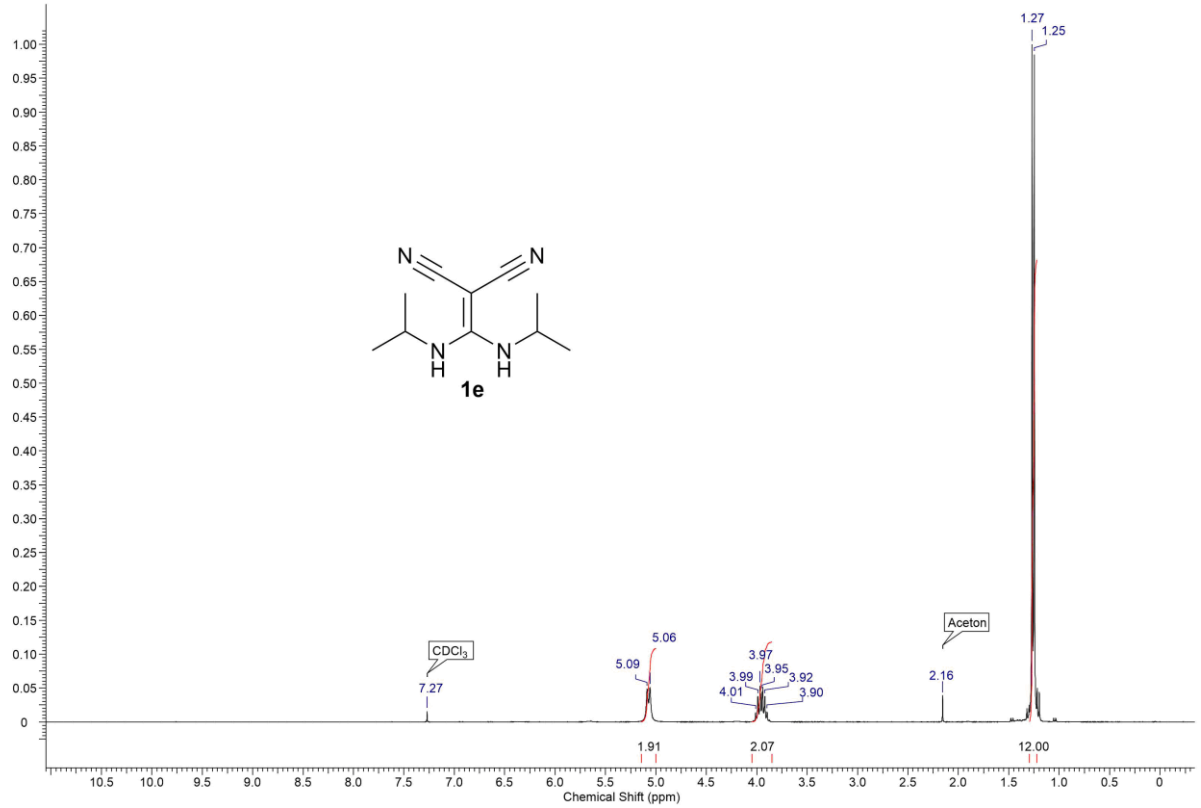

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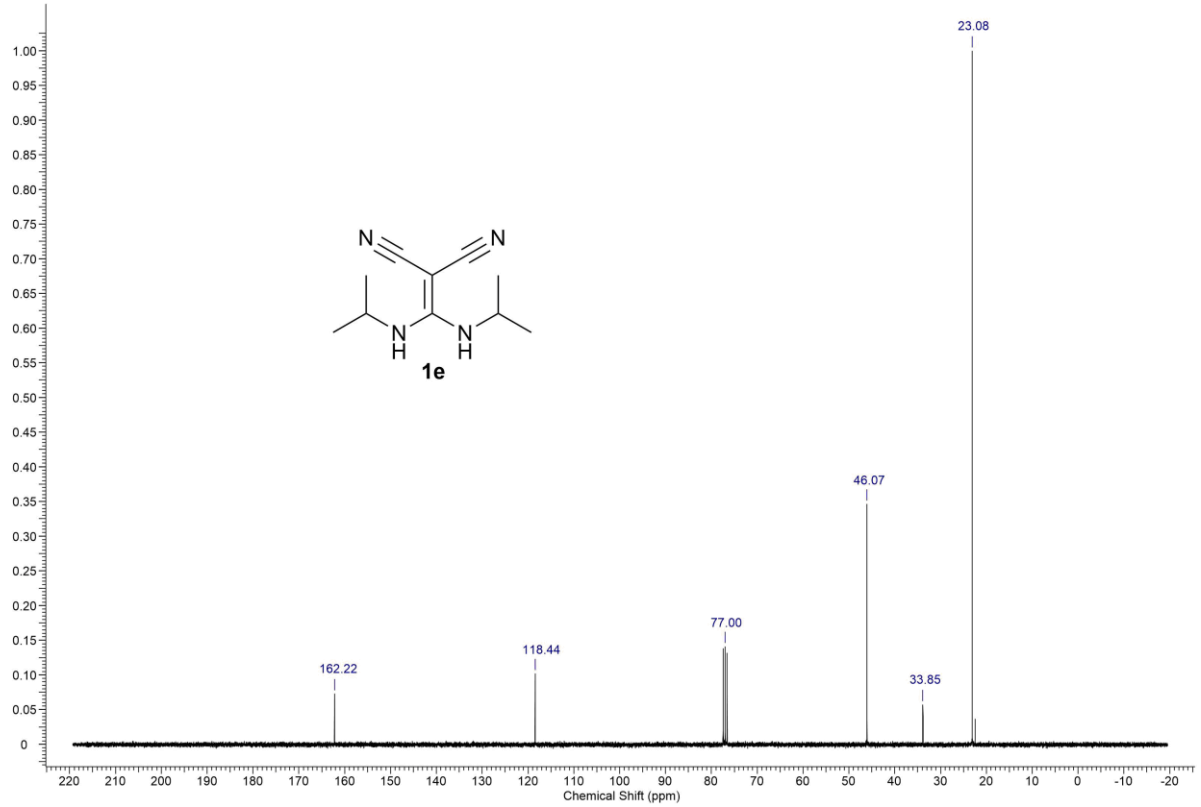

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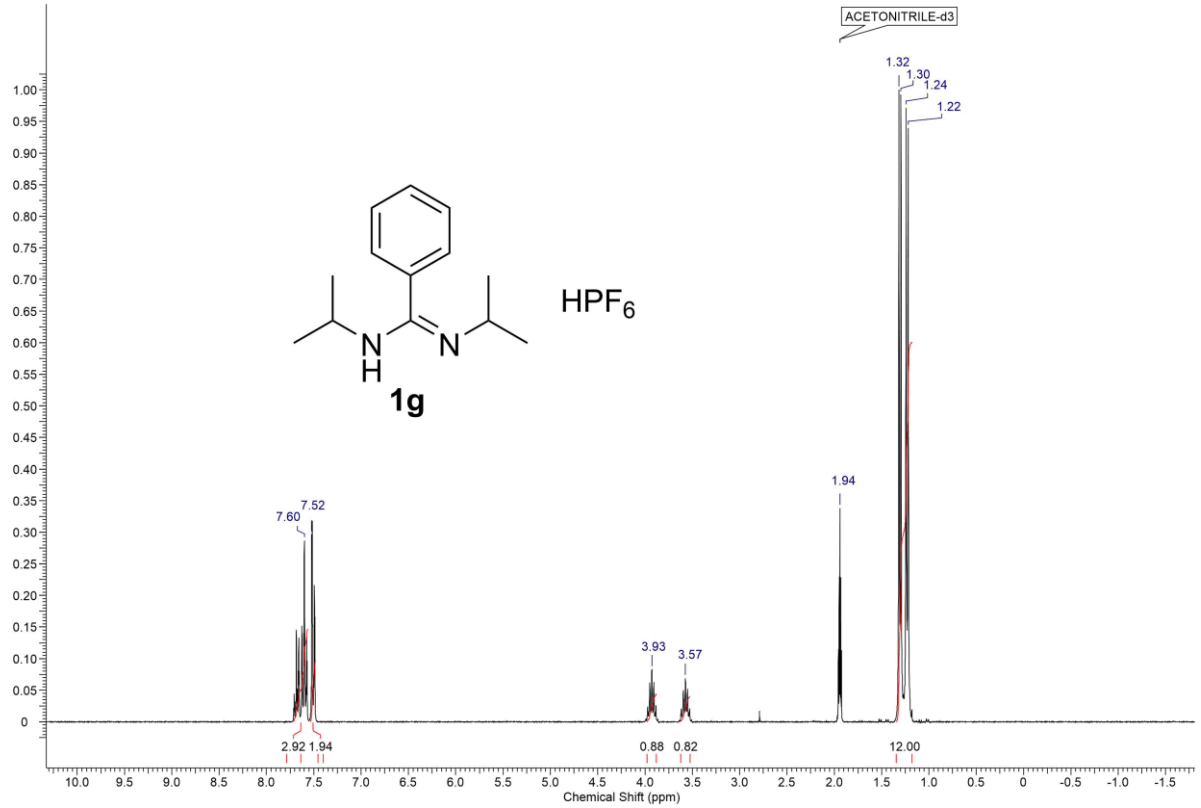

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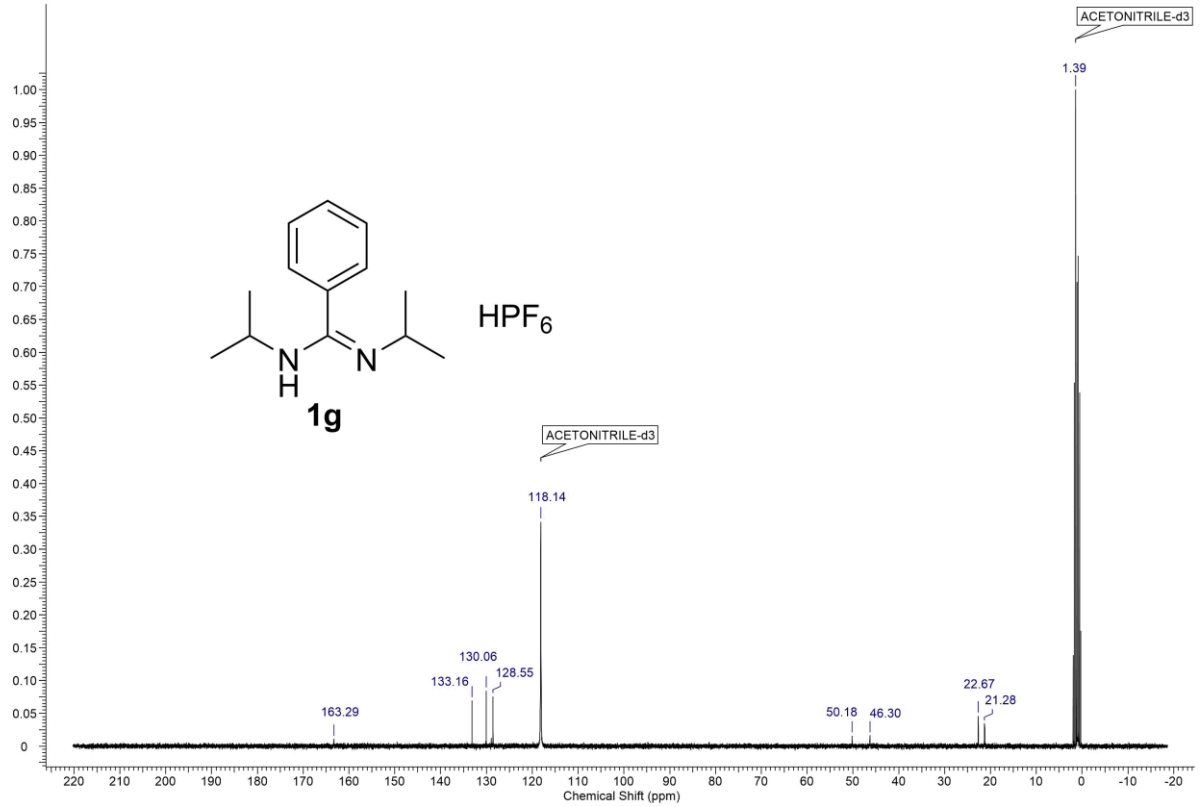

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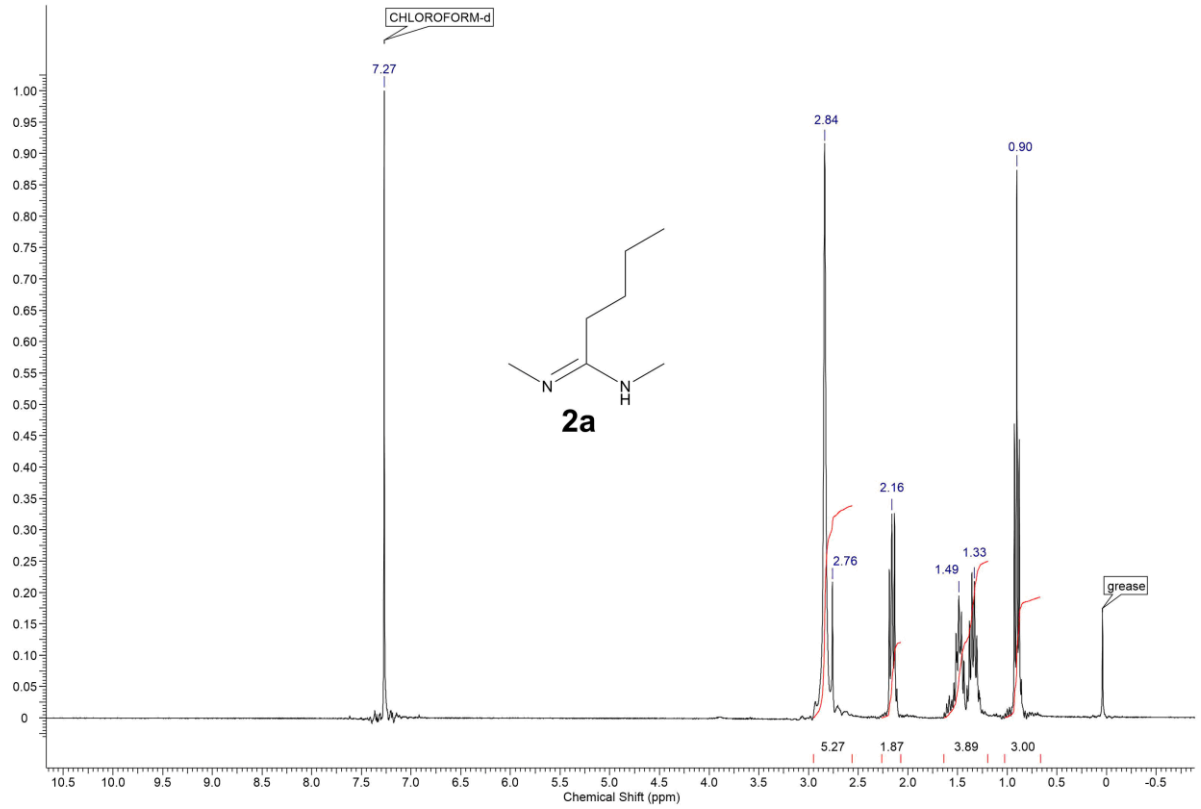

2a

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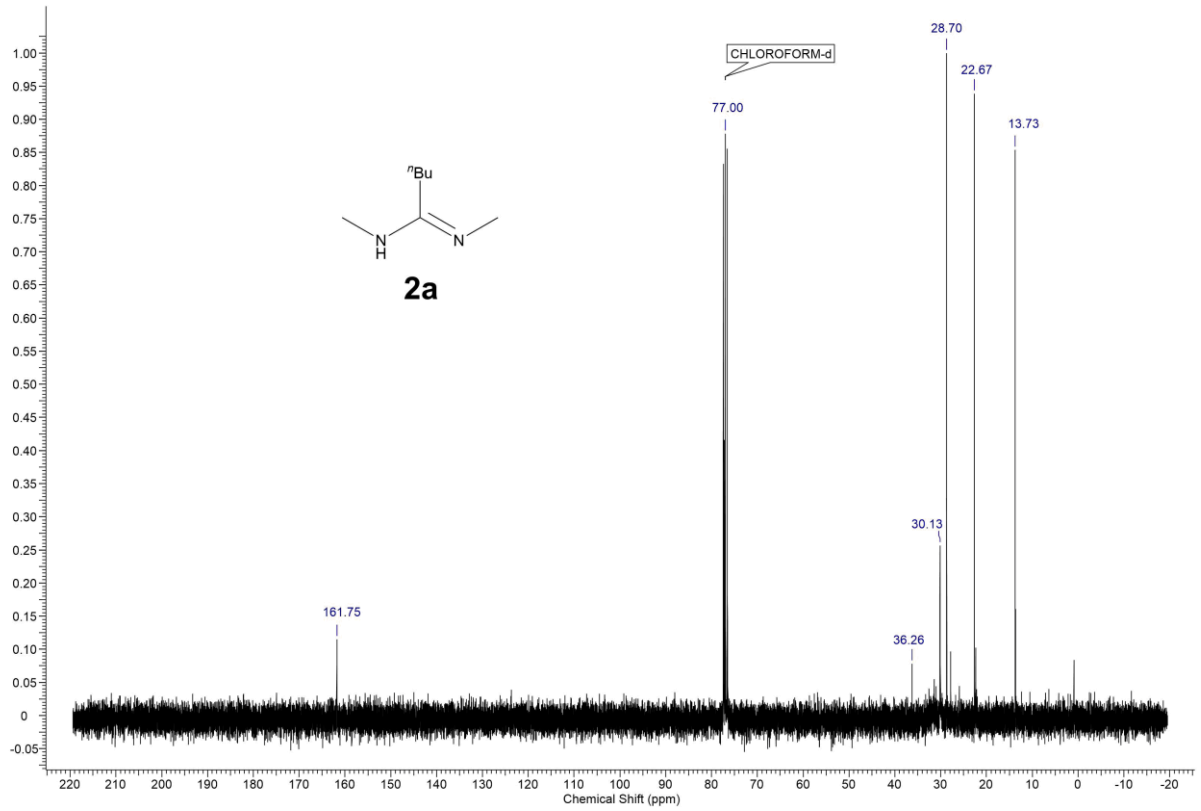
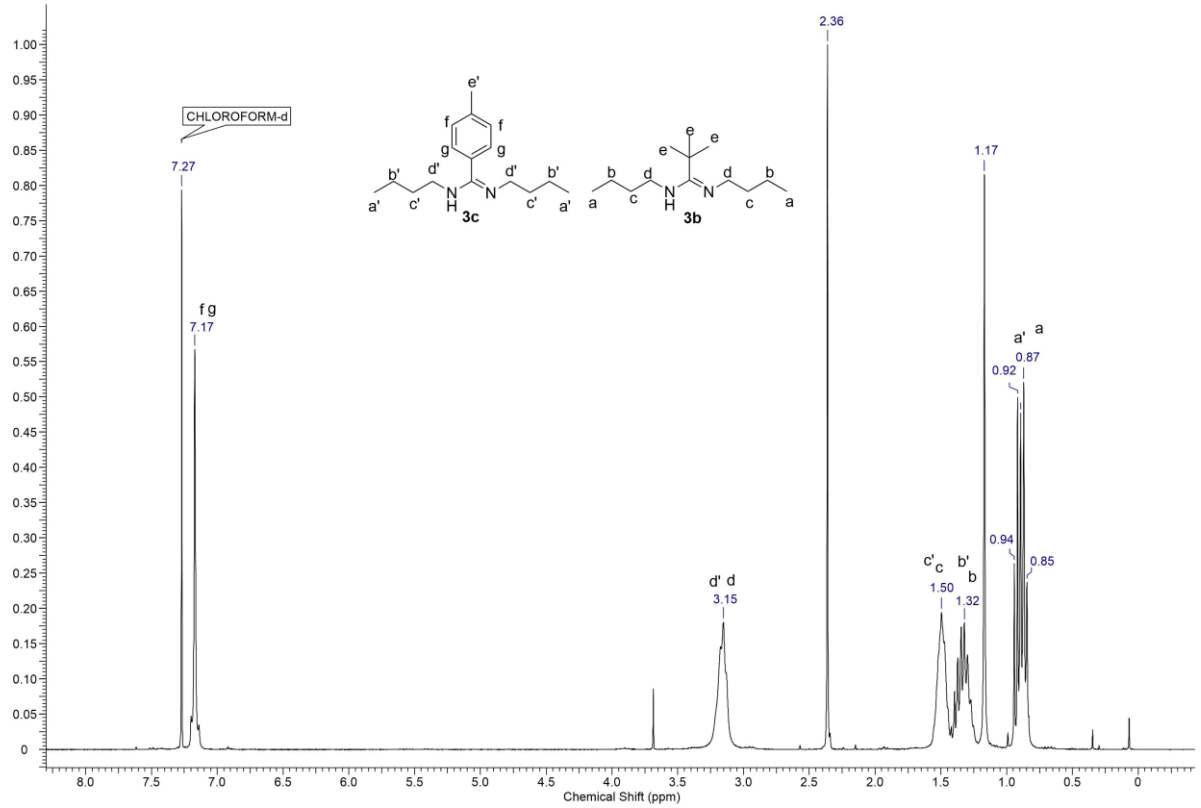


2a



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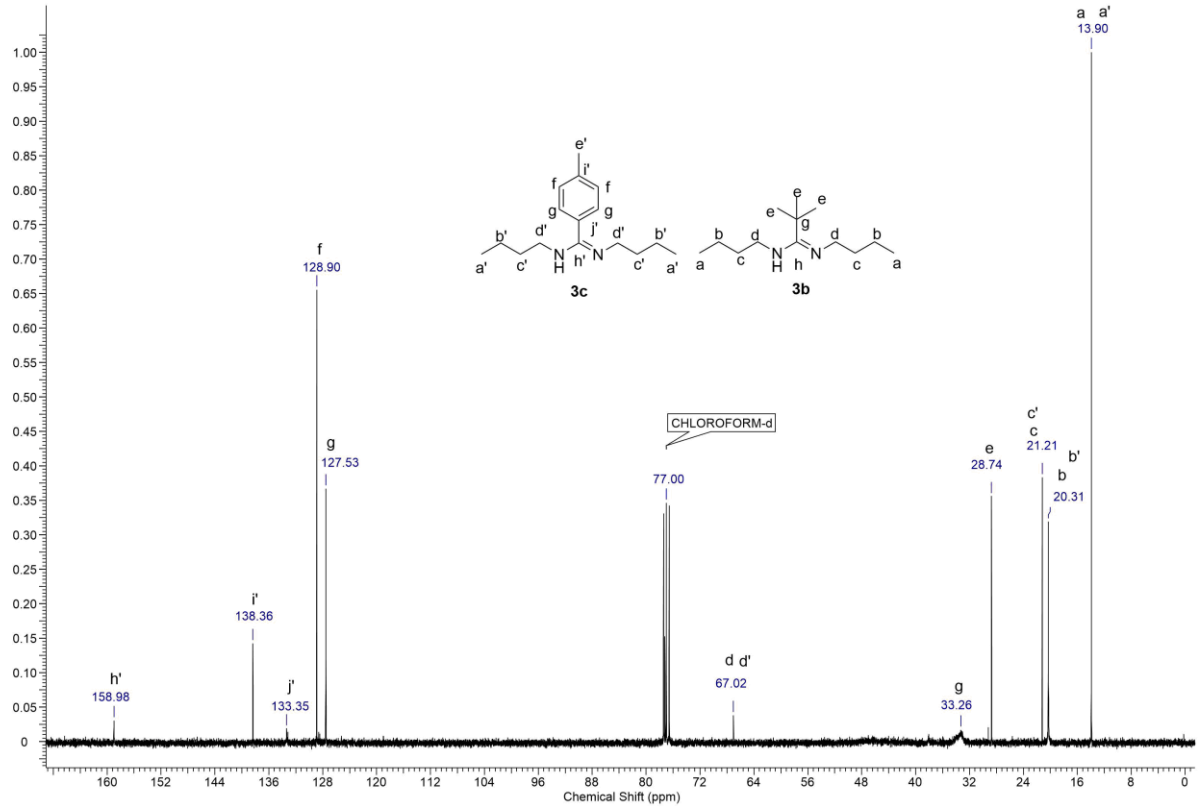

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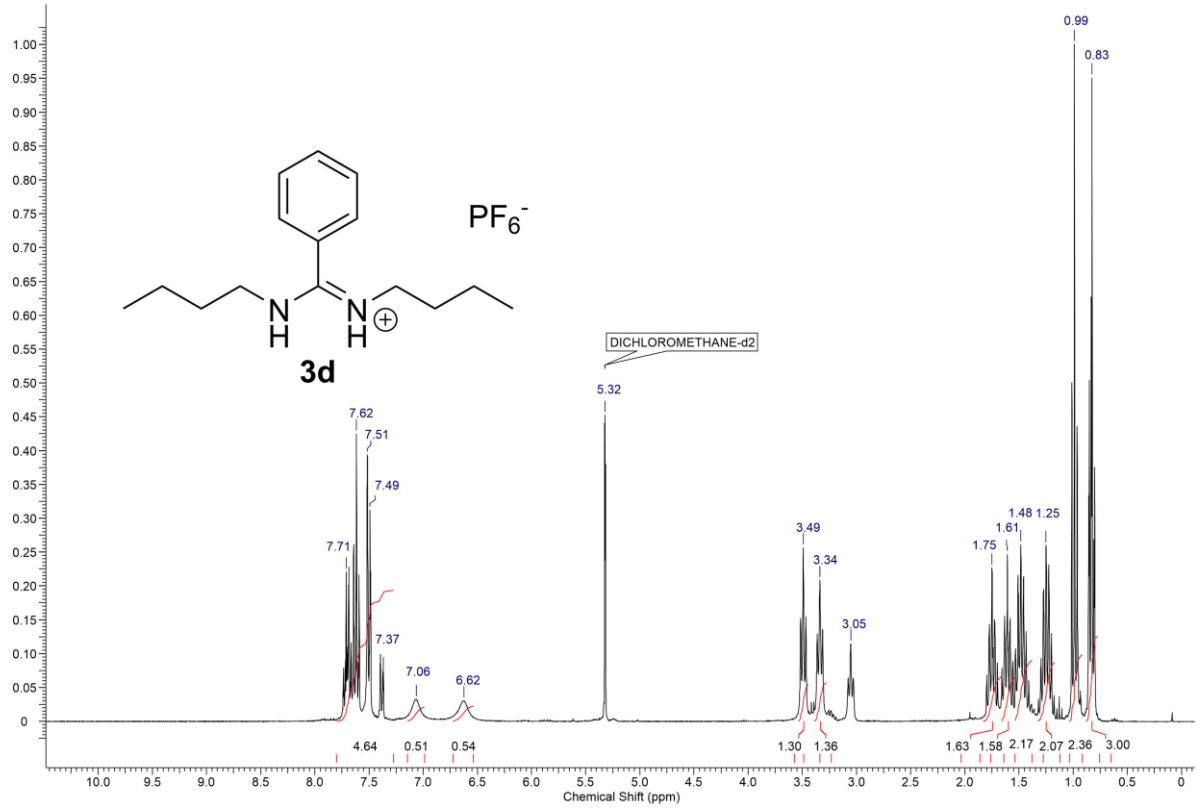

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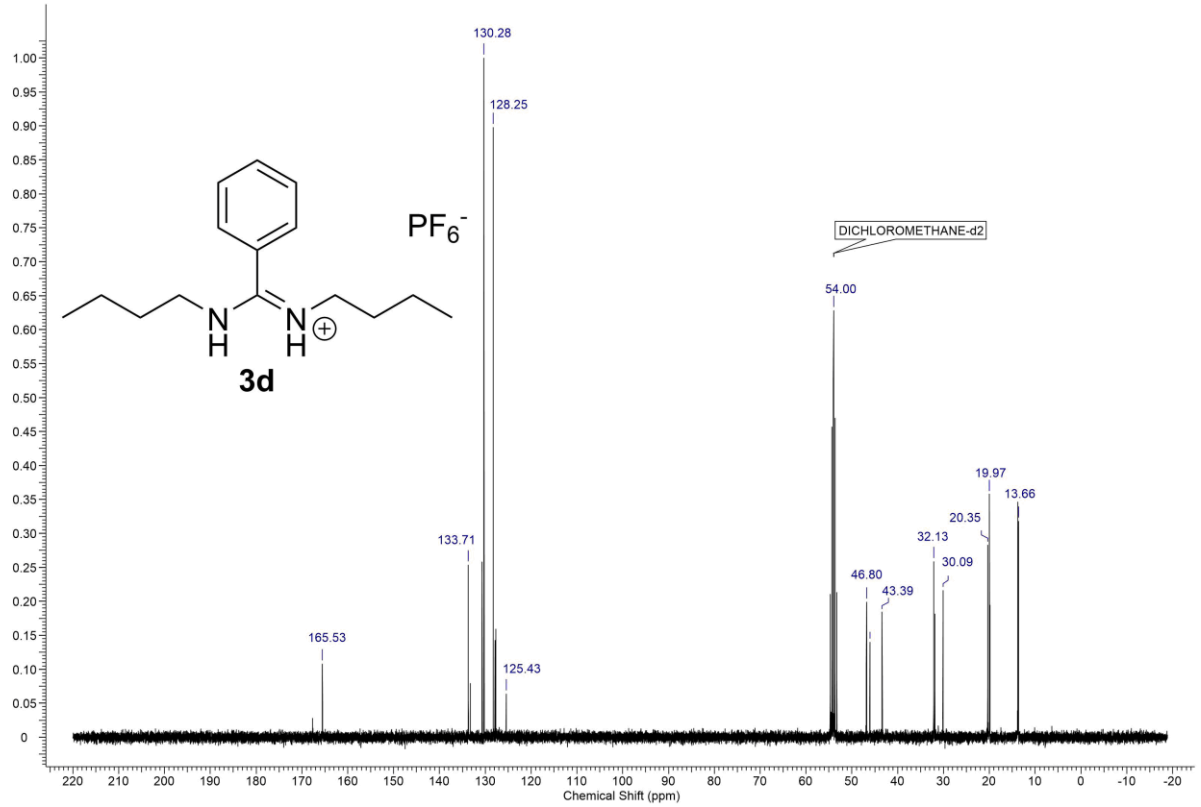

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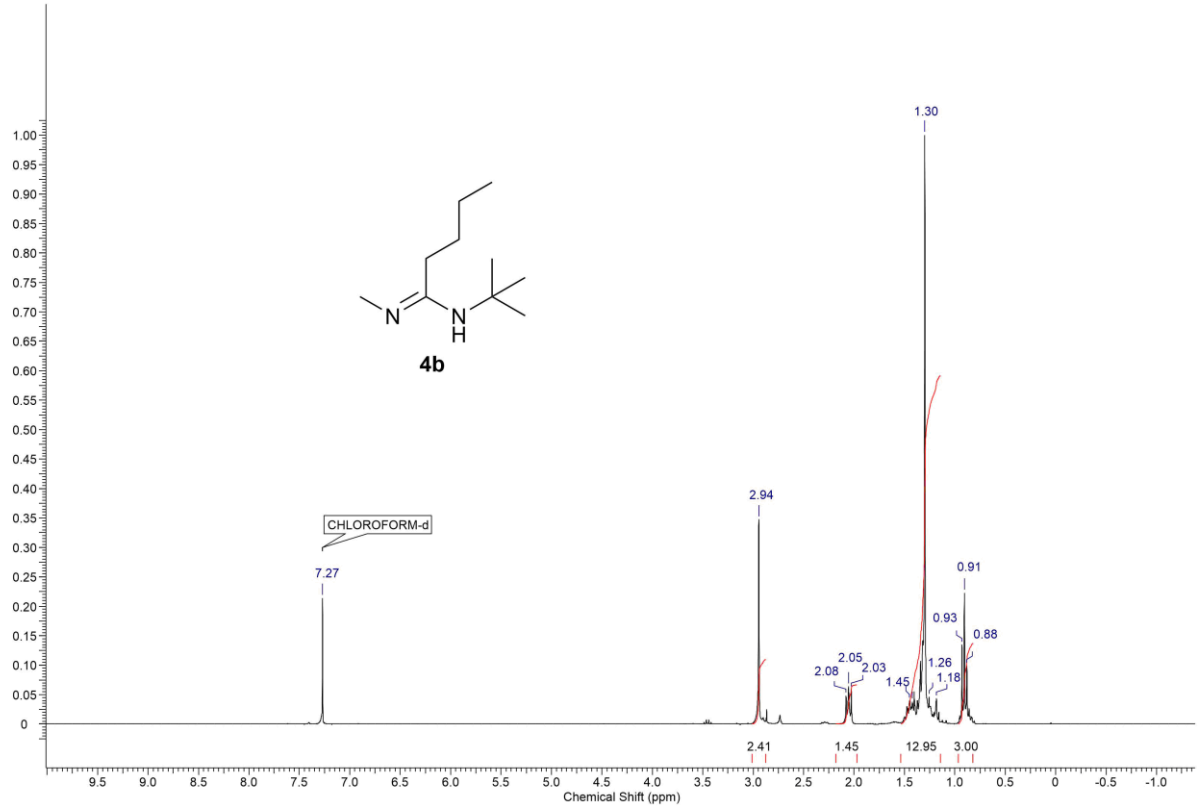

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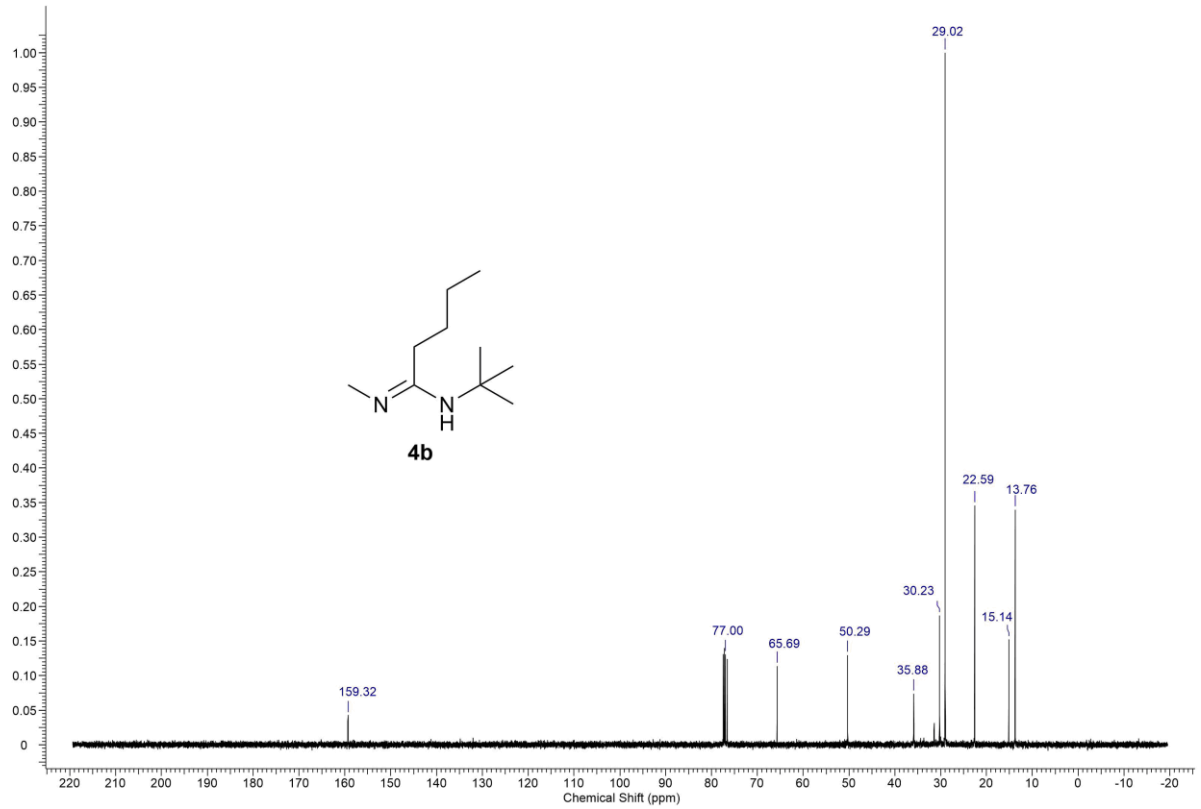

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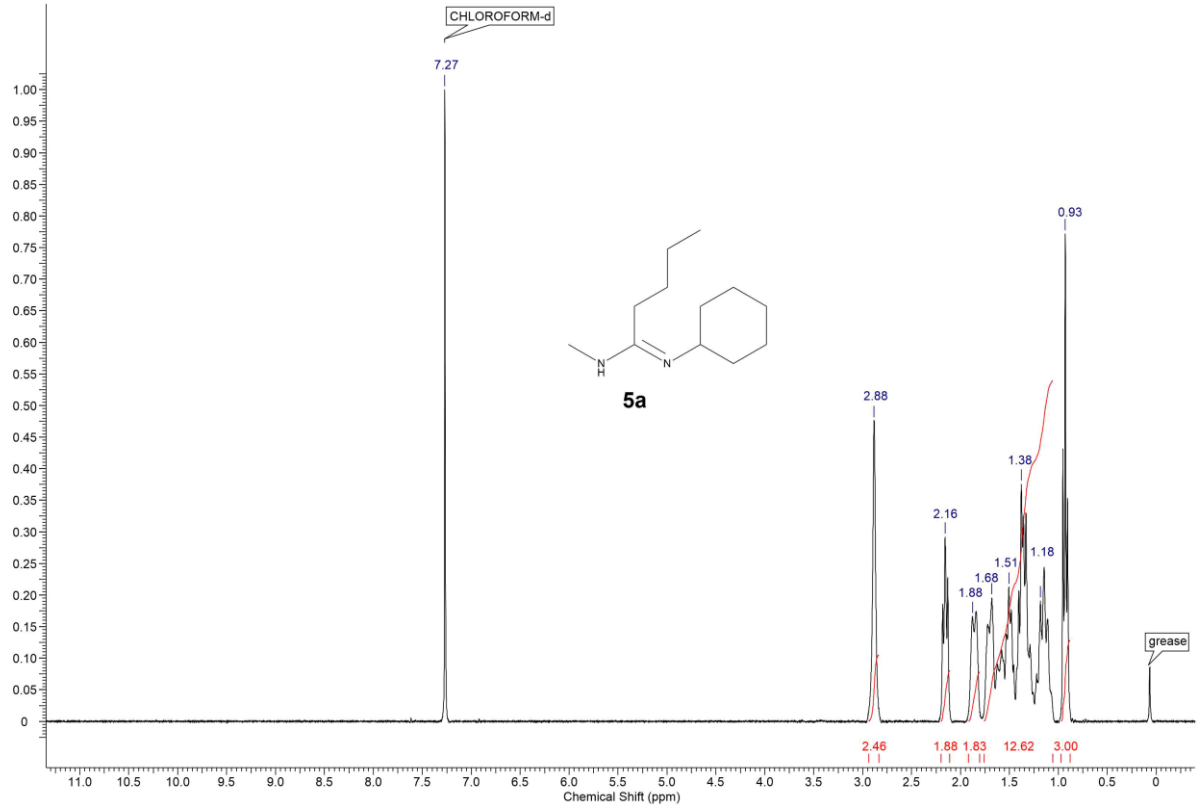

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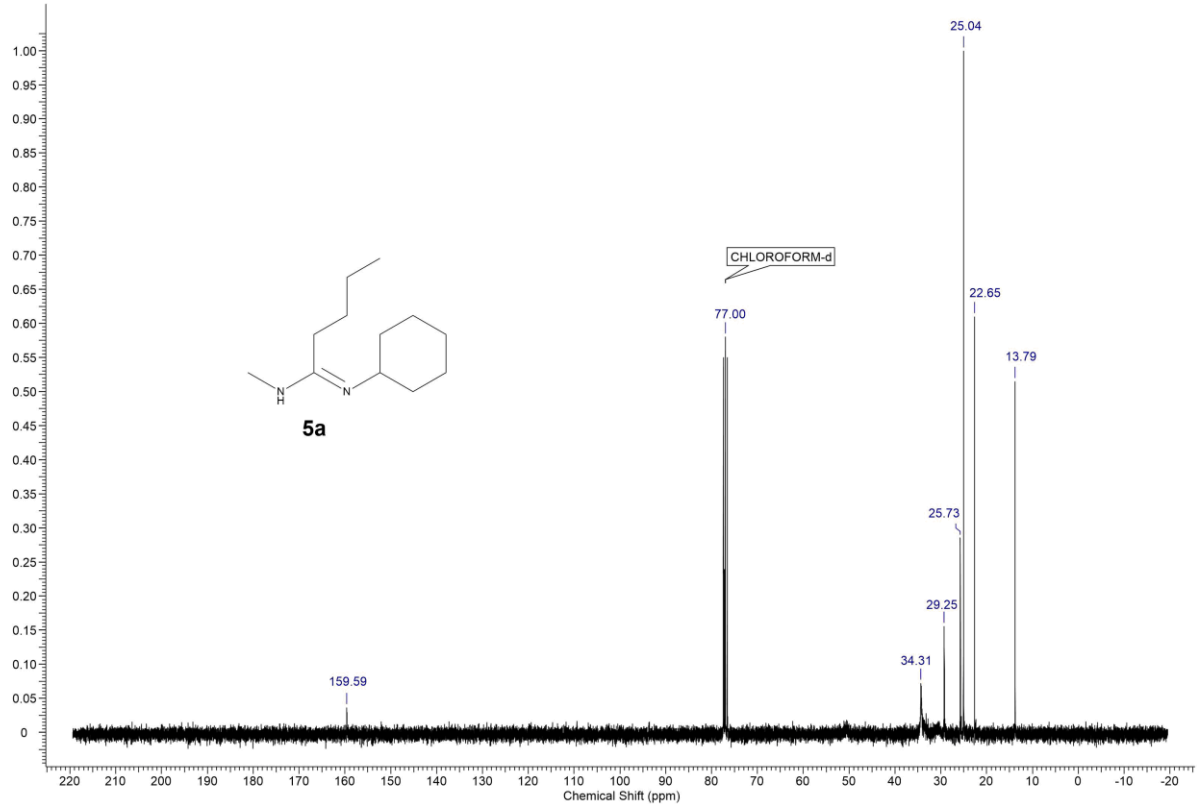

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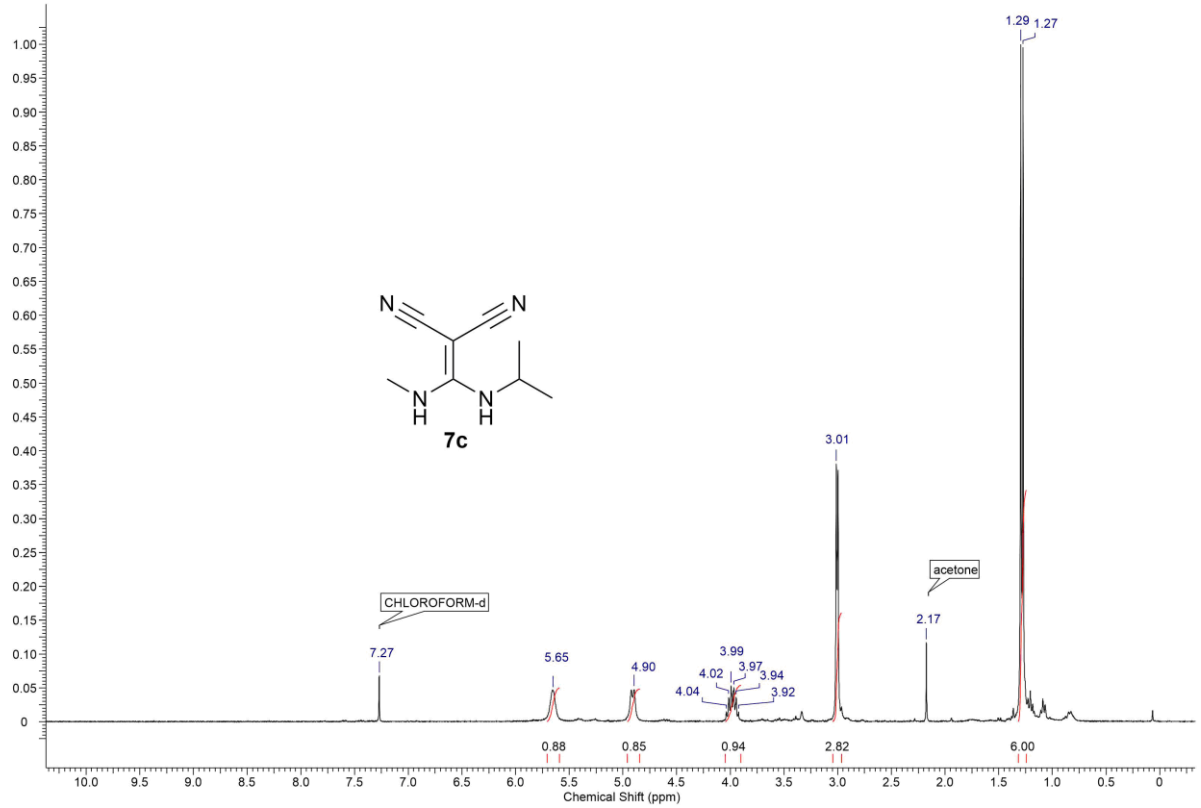

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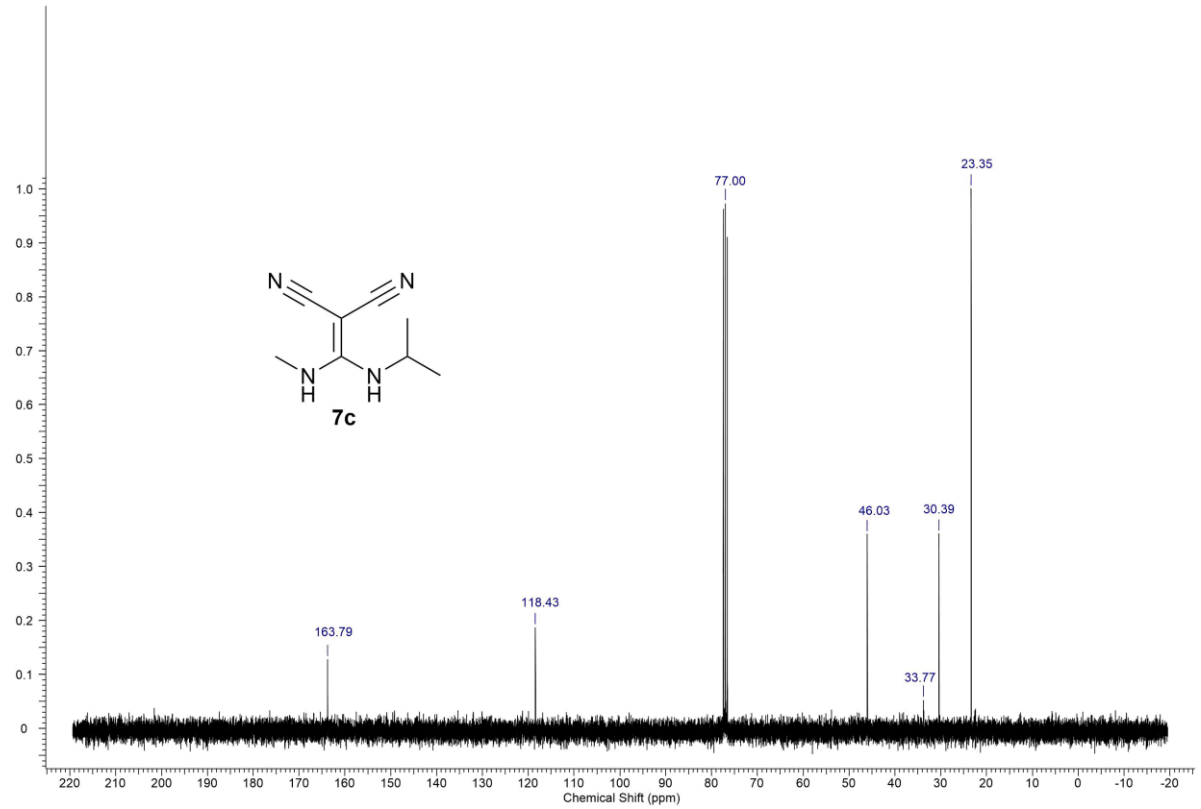

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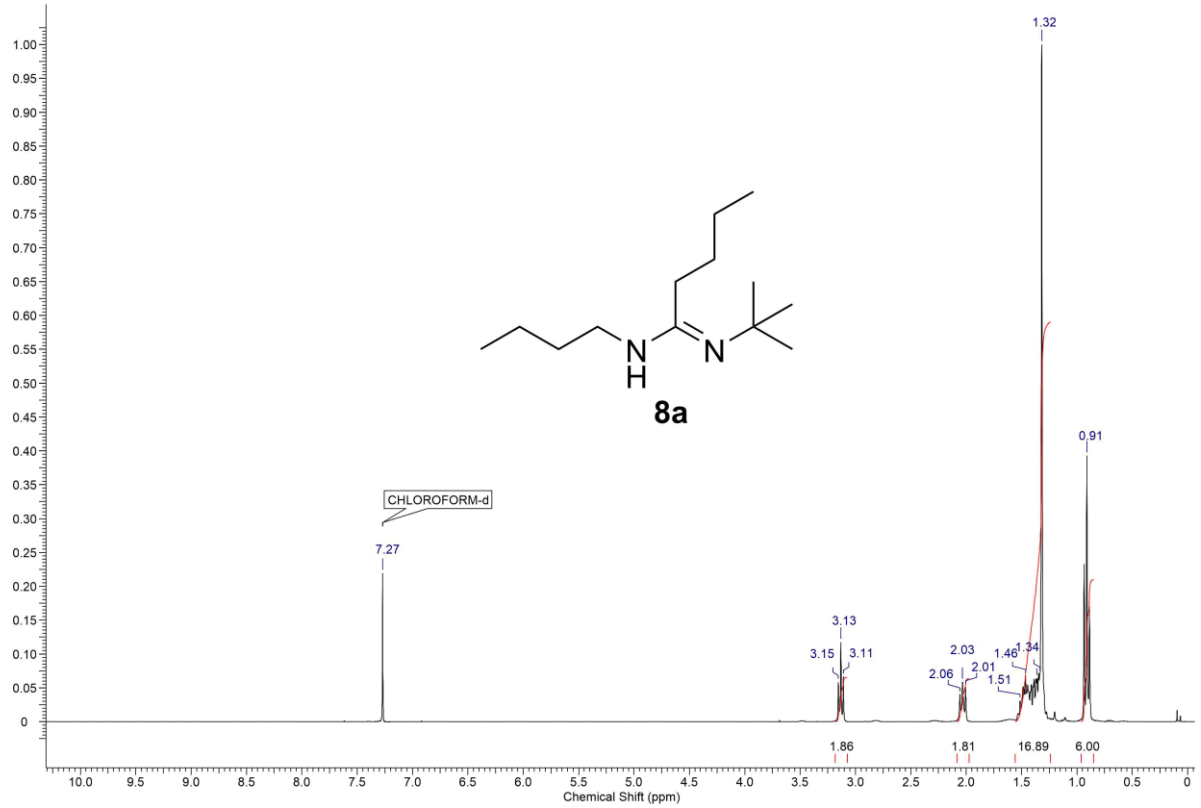

8a

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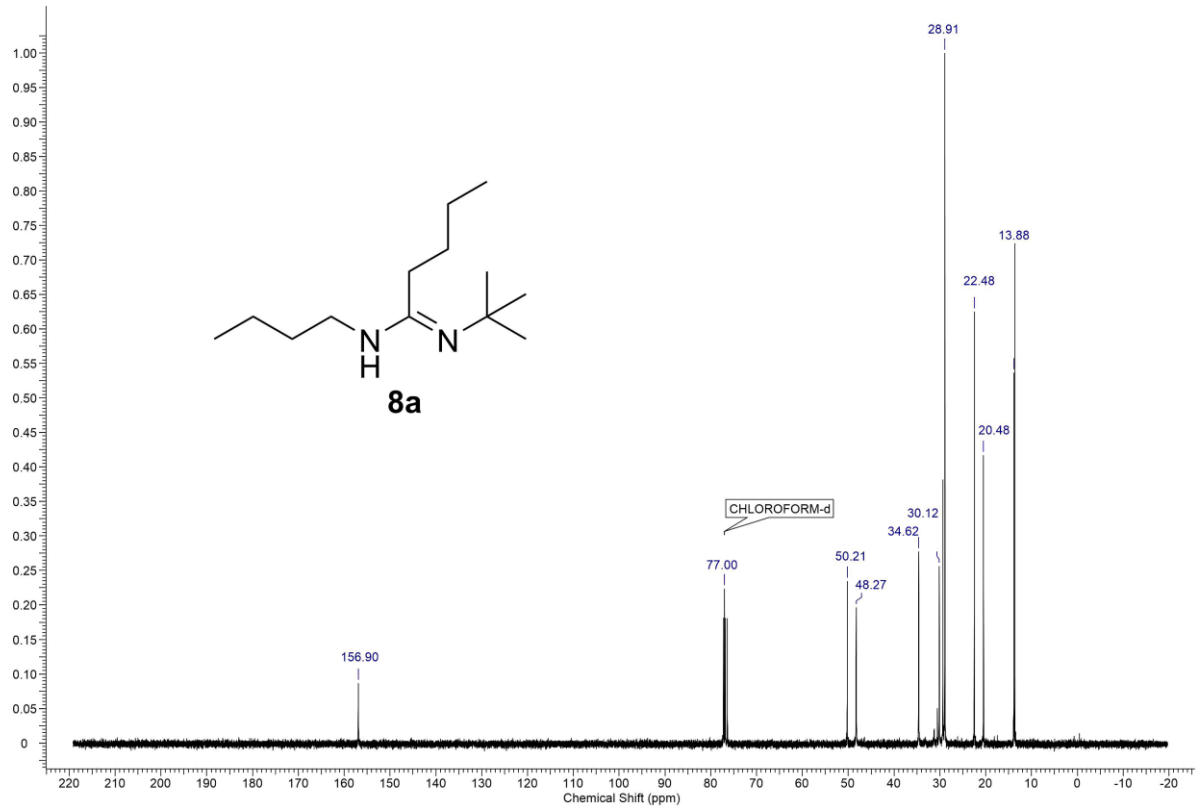

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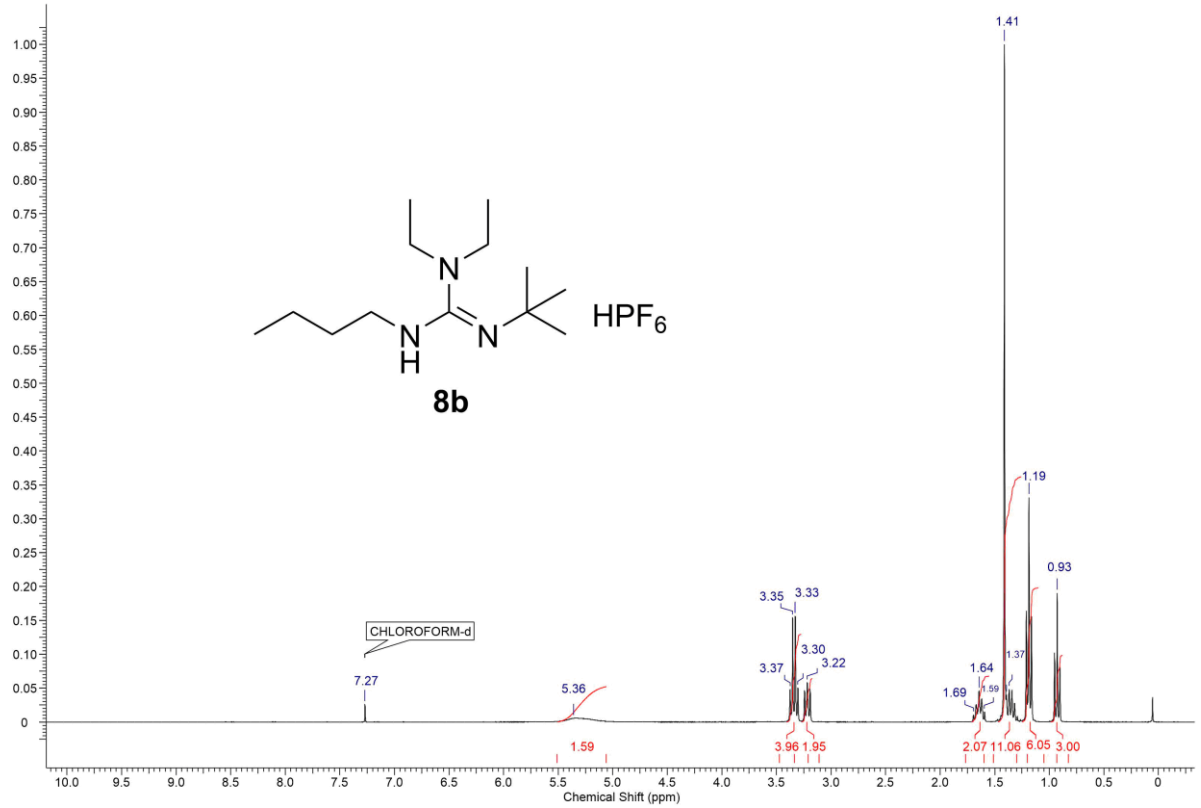

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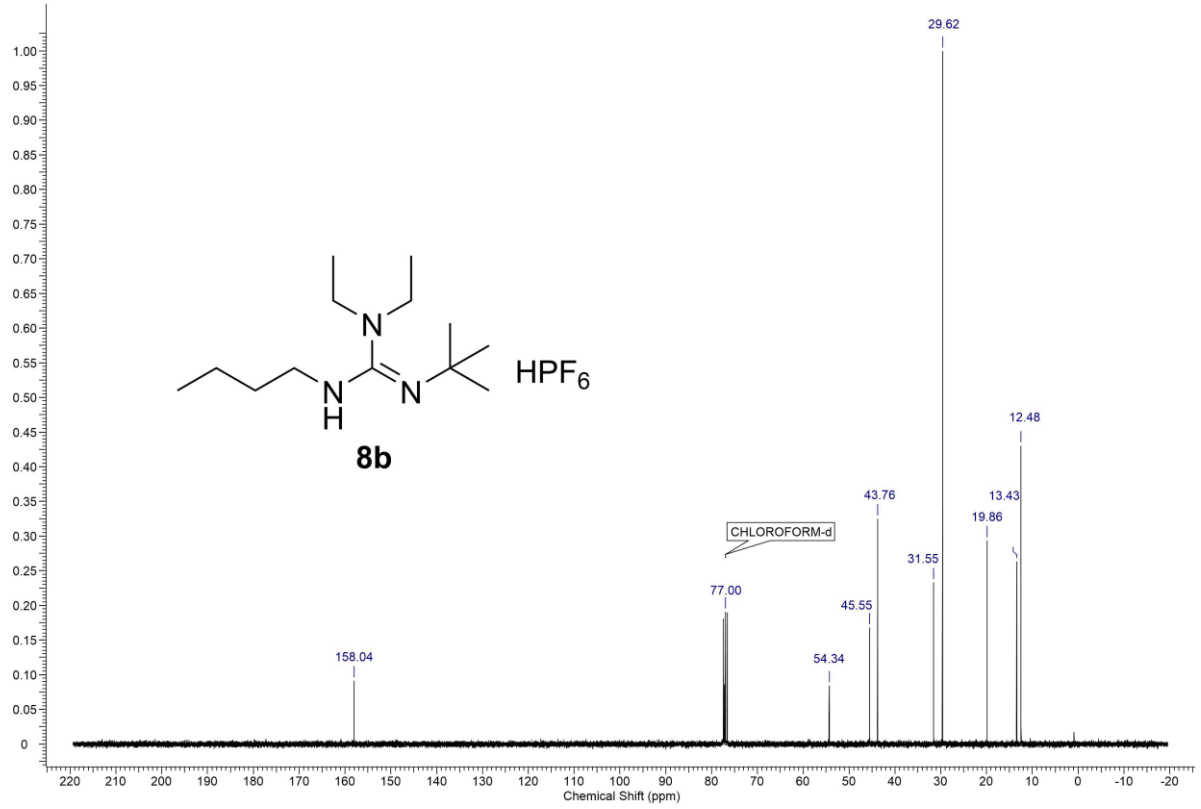

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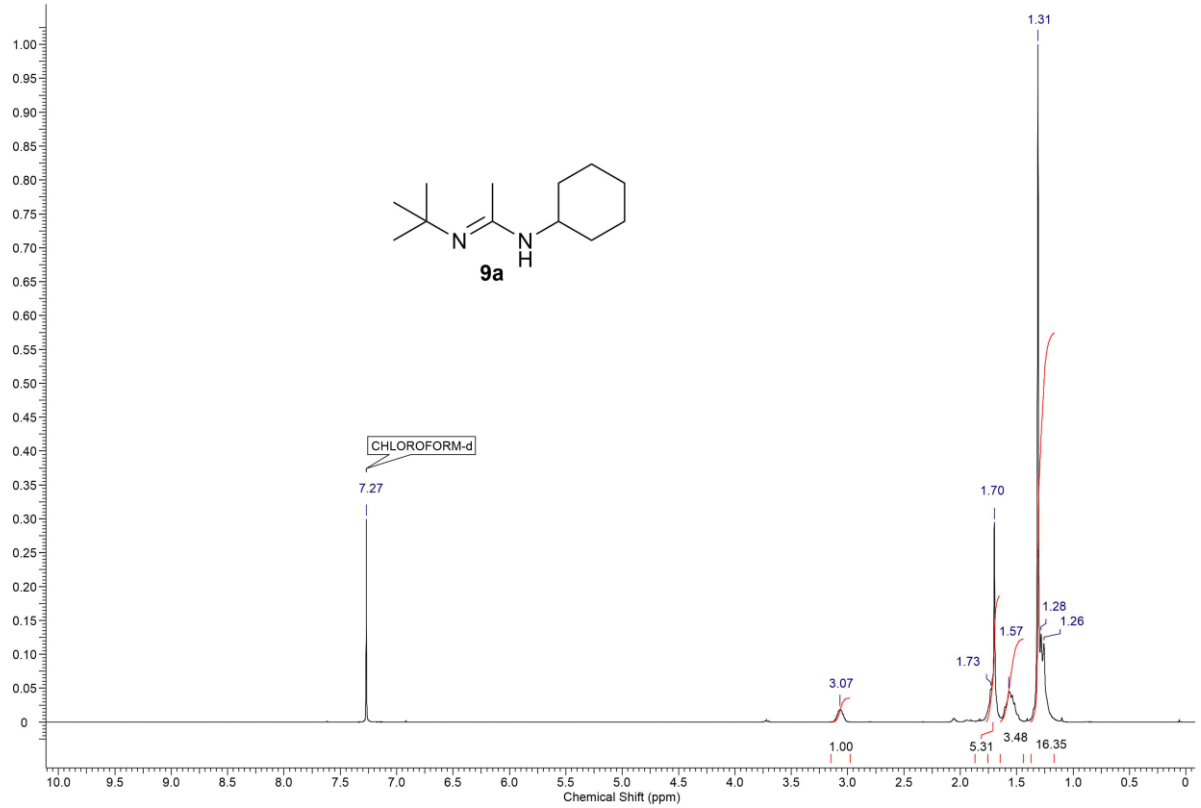

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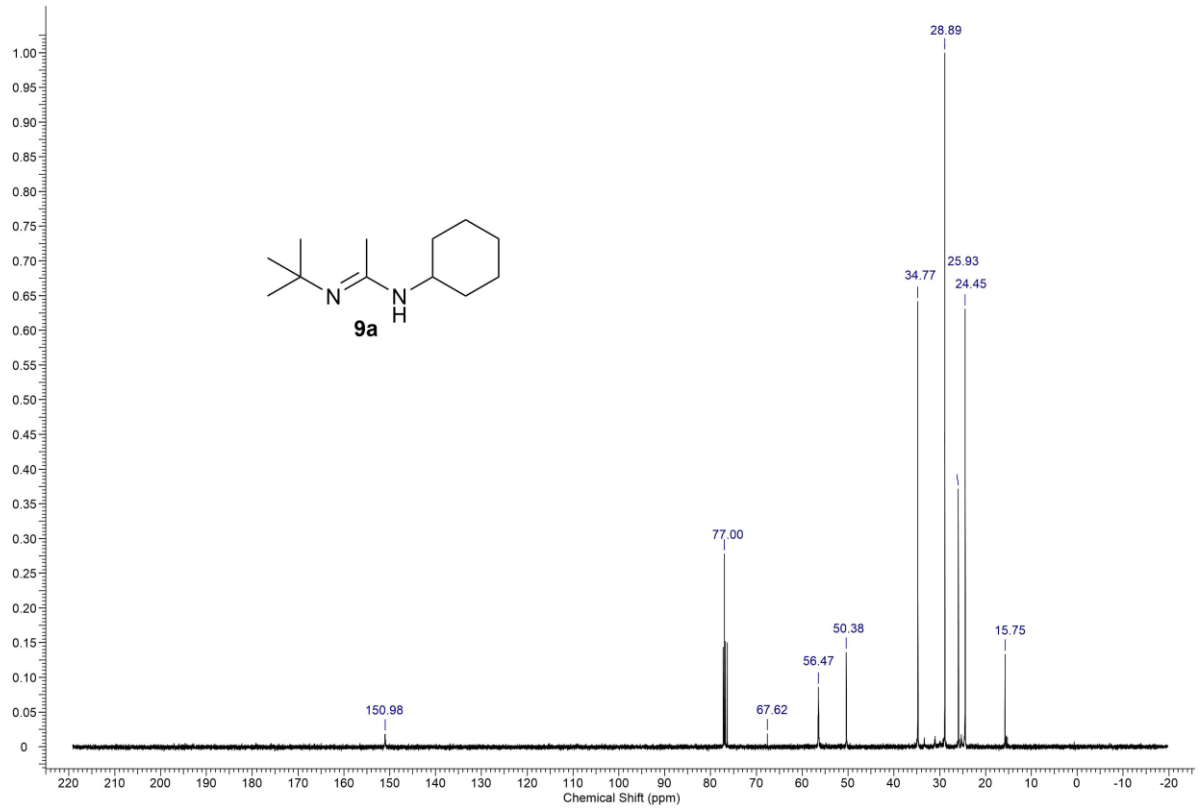

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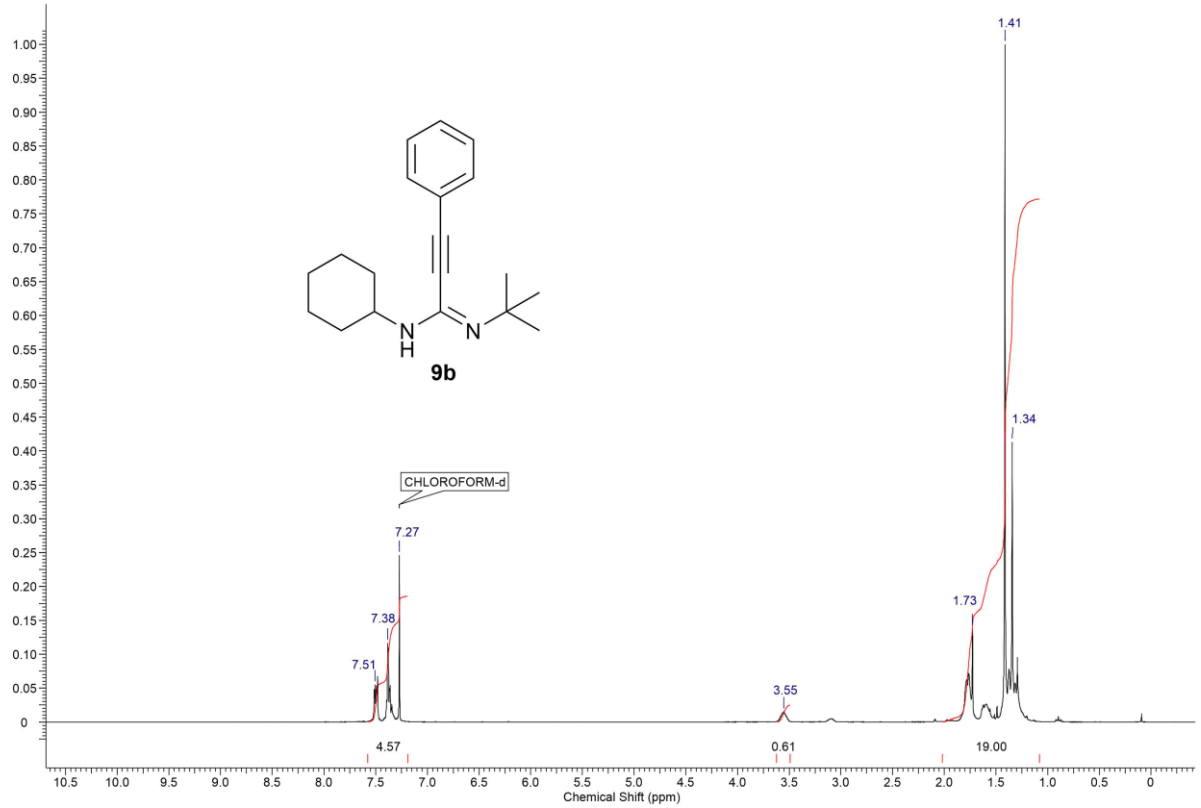

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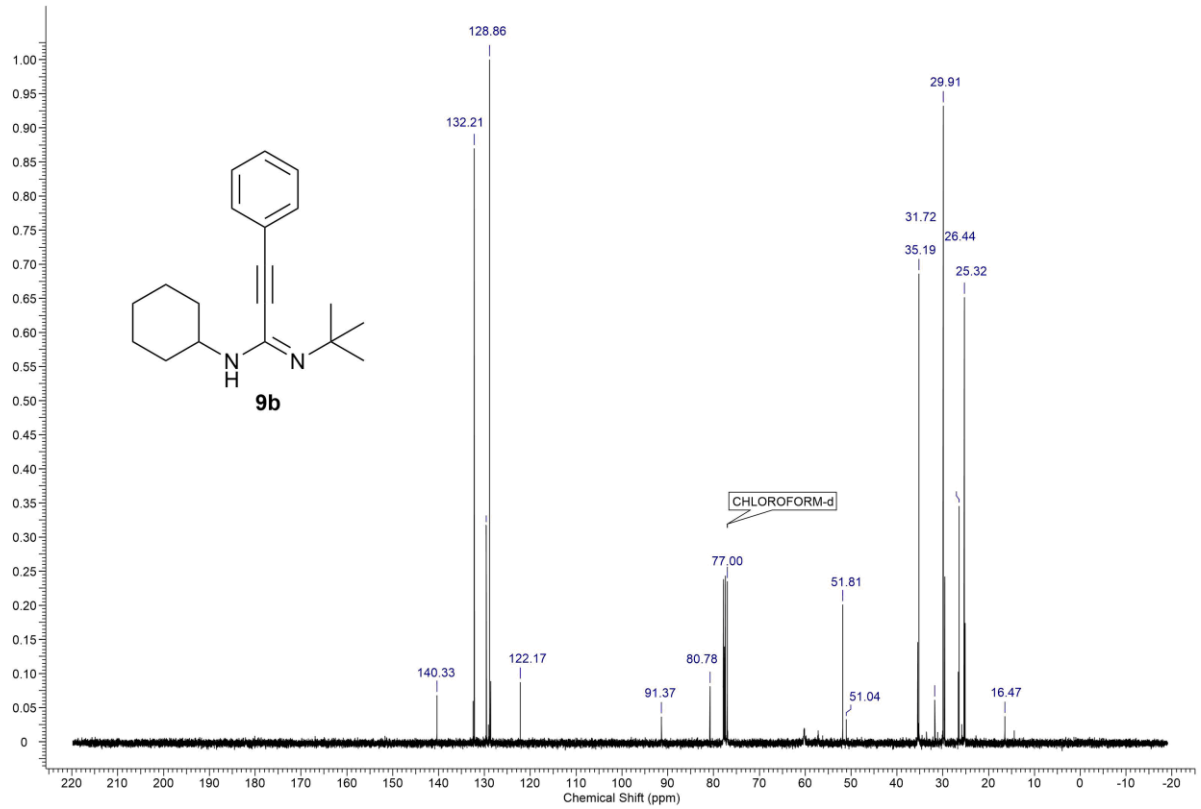

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