Opportunities for organocatalysis in polymer synthesis via step-growth methods

Progress in Polymer Science

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Abstract

Organocatalysis has emerged as an invaluable tool for polymer synthesis and has already demonstrated versatility for replacing organometallic catalysts in many polymerization reactions. The overall ease of removal and lower toxicity of organocatalysts relative to their common metal counterparts has also nurtured development especially in chain growth polymerizations to achieve precision macromolecular architectures for application in the biomedical space. The application of organocatalysts in step-growth polymerizations of polymers, including polyesters, polycarbonates, and polyurethanes, has garnered fewer studies in spite of the large array of benefits that could be achieved. Step-growth polymers account for nearly 20 wt. % of the Word Plastic Production and play a vital role in many technologies as engineering plastics and high performance polymeric materials with outstanding thermomechanical performance. Step-growth polymerizations are achieved using monomers with a diversity of chemical functionality. Consequently, a vast array of polymeric structures are attainable and will impact diverse applications in energy, aerospace, medicine, transportation, and construction. This review article will highlight the recent advances in organocatalysis in step growth polymerizations. We will primarily focus our review on the synthesis of commercially important polyesters and polyurethanes using organocatalysis, however, the review will also emphasize recent literature describing less explored polymers, such as polyethers, polycarbonates, and polybenzoins, which have recently employed organocatalysts. Moreover, the article will draw attention to recent efforts in the use of carbon

dioxide as a monomer for the preparation of step-growth polymers in the presence of organocatalysis.

Abbreviations: AcOH, acetic acid; ADMET, α,ω-dienemetathesis polymerization; AMP, Acetal Metathesis Polymerization; BAIL, [BBSIm]Tf_2N, 4-(3'-butyl-1'-imidazolio)-1-butanesulfonic acid bis(trifluoromethylsulfonyl)imidide; Brønsted acid ionic liquid; BDMAEE, 2,2′-bis-(dimethylaminoethyl ether); BF_3OEt_2, boron trifluoride diethyl ether complex; BHET, bis(2-hydroxyethyl)terephtalate; bis-MPA, 2,2-bis(hydroxymethyl)-propionic acid; bis-MPA-TEMPO, 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate; BEMP, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; CSA, camphor-10-sulfonic acid; Đ, dispersity; DABCO, 1,4-diazabicyclo [2,2,2]octane; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBSA, dodecylbenzenesulfonic acid; DBTDL, dibutyltin dilaurate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DES, diethylstilbestrol; DFT, density functional theory; DOX, doxorubicin; DMAP, 4-dimethylaminopyridine; DMC, dimethyl carbonate; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; DMT, dimethyl terephthalate; DPC, diphenyl carbonate; DPP, diphenyl phosphate; EG, ethylene glycol; Et-MDEA, *N*,*N*-bis(2-hydroxyethyl)-*N*-methylbutan-1-aminium bromide; Hex-MDEA, *N*,*N*-bis(2-hydroxyethyl)-*N*-methylhexan-1-aminium bromide; HCl, hydrochloric acid; HMDI, hexamethylene diisocyanate; H_3PO_4, phosphoric acid; H_2SO_4, sulfuric acid; IPDI, isophorone diisocyanate; KHMDS, potassium bis-(trimethylsilyl)amide; KOMe, potassium methoxide; KO-*t*-Bu, potassium *tert*-butoxide; LCST, lower critical solution temperature; MDA, 4,4'-diaminodiphenylmethane; MDEA, *N*-methyldiethanolamine; MeCN, acetonitrile; MeOTF, trifluoromethanesulfonate; M_n, number-average molar mass; MRI, magnetic resonance imaging; MSA, methanesulfonic acid; MTBD, *N*-methyl 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; M_w, weight-average molar mass; Nf_2NH, bis(1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl)imide; NfOH, 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonic acid; NHC, *N*-heterocyclic carbene; NHC-CO_2, azolium-2-carboxylate; NIPU, non-isocyanate polyurethane; NMP, *N*-methyl-2-pyrrolidone; [OBSIm]Tf_2N, 4-(3'-octyl-1'-imidazolio)-1-butane-sulfonic acid bis(trifluoromethylsulfonyl) imidide; P_2-Et, 1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene); PCS, pyridinium camphorsulfonate; PEG, polyethylene glycol; PEO, polyethylene oxide; PET, poly(ethyleneterephtalate); Ph_3P, triphenylphosphine; PHU, poly(hydroxyurethane); PHUU, poly(hydroxyurea–urethane); PPV, poly(1,4-phenylenevinylene); PPY, 4-pyrrolidinopyridine; PTMO, poly(tetramethylene oxide); PTSA, *p*-toluene sulfonic acid; PTSAA, *p*-toluene sulfonic anhydride; PTS, pyridinium *p*-toluenesulfonate; p-TsOH, *p*-toluene sulfonic acid monohydrate; PU, polyurethane; PVA, polyvinyl alcohol; REMP, ring expansion metathesis polymerization; ROIP, ring opening insertion metathesis polymerization; ROP, ring-opening poylmerization; RT, room temperature (23 ± 5 °C); SP, (+)-sparteine; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; *t*-BuP_1, *tert*-butylimino-tris(dimethylamino)phosphorene; *t*-BuP_2, 1-*tert*-Butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene); *t*-BuP_4, 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene); TEA, triethylamine; TFA, trifluoroacetic acid; Tf_2NH, bis(trifluoromethanesulfonyl)imide; TfOH, triflic acid; THF, tetrahydrofuran; $Ti(OBu)_4$, titanium(IV) butoxide; TMC, trimethylene carbonate; TMG, 1,1,3,3-tetramethylguanidine; TMS, trimethylsilyl; TU, thiourea.

1. Introduction: Step-growth vs. Chain growth polymerization

The beginning of the 20th century marked the development of the first synthetic plastics, ingraining polymers as ubiquitous in our daily life. Their production has increased over the past decades from 15 million tons in 1964 to 311 million tons in 2014 and is expected to increase above 500 million tons by 2050. The production of polymers comprises two distinctive polymerization mechanisms, chain growth and step-growth polymerization. The largest difference between step-growth and chain growth encompasses the molecular weight dependence on extent of monomer conversion. During chain growth polymerization process, a reactive intermediate (*i.e.* radical, anion, cation or metallocene) forms through an initiation step. This reactive center reacts with a monomer, most often alkene derivatives, in a propagation step transferring the reactive center to the end of the chain. Molecular weight growth occurs through consecutive addition of monomers until termination consumes the reactive center. This polymerization does not proceed through reaction with different polymer chains as this would result in termination of the reactive end. As such, high molecular weight polymers form early in the reaction and shorter polymer chains at the end, lowering the average molar mass, thus, the overall concentration of high molecular weight polymer chains and polymer dispersity index becoming reliant on % conversion (**Figure 1b**) [1]. One alternative to chain growth polymerization is the so-called living chain growth polymerization where the molecular weight increases linearly with the conversion (**Figure 1c**). Although this type of polymerization has gained a great interest in the polymer community due to the ability of obtaining narrower dispersities in comparison with conventional chain growth and step growth polymerizations, it is out of the scope of this review and therefore will not be discussed here.

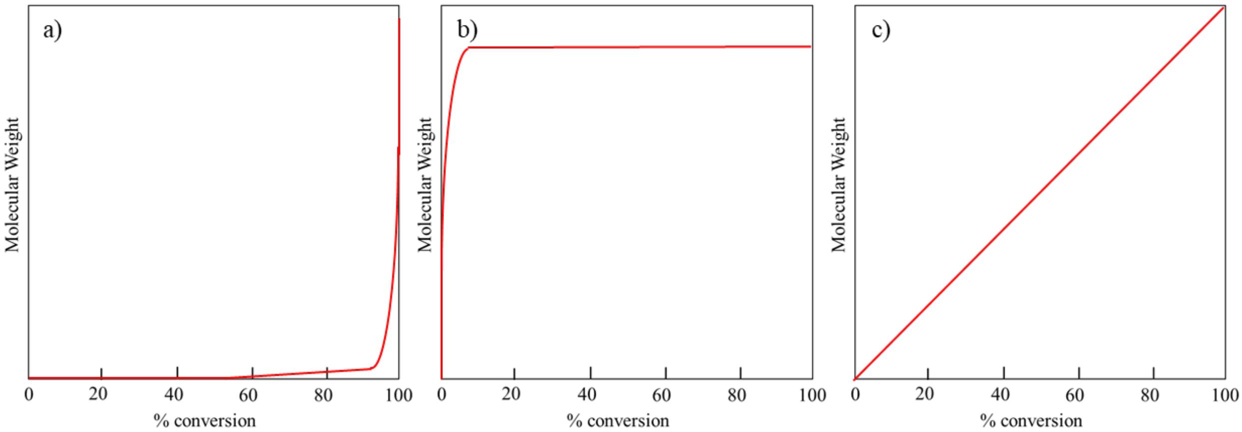


Figure 1. Molecular weight dependence on extent of conversion in different polymerization mechanisms a) step-growth b) chain growth and c) living.

In contrast, the mechanism of growth in step-growth polymerizations begins with the formation of dimers from monomers then systematically increases in size to trimers and tetramers until high molecular weights are achieved (**Figures 1a and 2**). In the case of a polymerization between two bifunctional monomers AA + BB, where A functional group reacts with B functional group, the reactive end-groups enable chains of varying sizes to couple together eventually forming high molecular weight species when larger chains couple [1]. This process also proceeds with AB type monomers enabling homopolymerization through one monomer. Studies on polyesters demonstrated that the increasing chain molecular weight does not perturb the reactivity of the end-groups. Carothers explained this extent of conversion dependence through the development of equation 1, where X_n represents the degree of polymerization, ρ denotes the extent of conversion, and f_{avg} indicates the average functionality of the polymer system.

$$X_{n,\, step-growth} = \frac{2}{2 - \rho f_{avg}} \qquad (1)$$

Figure 1a graphically depicts this dependence and demonstrates that high molecular weight is only achieved at high reaction conversions [1,2]. This being said, it must be pointed out that achieving high molecular weight with step-growth polymerization is non-trivial and requires six essential criteria unlike chain growth polymerizations:[3]

1. Monomer functionality (*f*) of 2.0.
2. Stoichiometry of functional groups equivalent to 1.0.
3. Absence of side-reactions that would reduce monomer functionality and impact stoichiometry.
4. High reaction conversions (>99.9%).
5. Accessibility of reactive groups.
6. Efficient removal of condensates when applicable.

It should be noted that in step-growth polymerizations when the average functionality of monomers employed is greater than 2, cross-linked materials can be obtained. In these cases, obtaining high monomer conversions is not crucial to achieve high molecular weight polymers and factors such as gel point or crosslinking density should be evaluated. These factors are extremely important in step-growth polymers but has not been considered in detail within this review as it focuses especially on the catalysis of thermoplastic polymers.

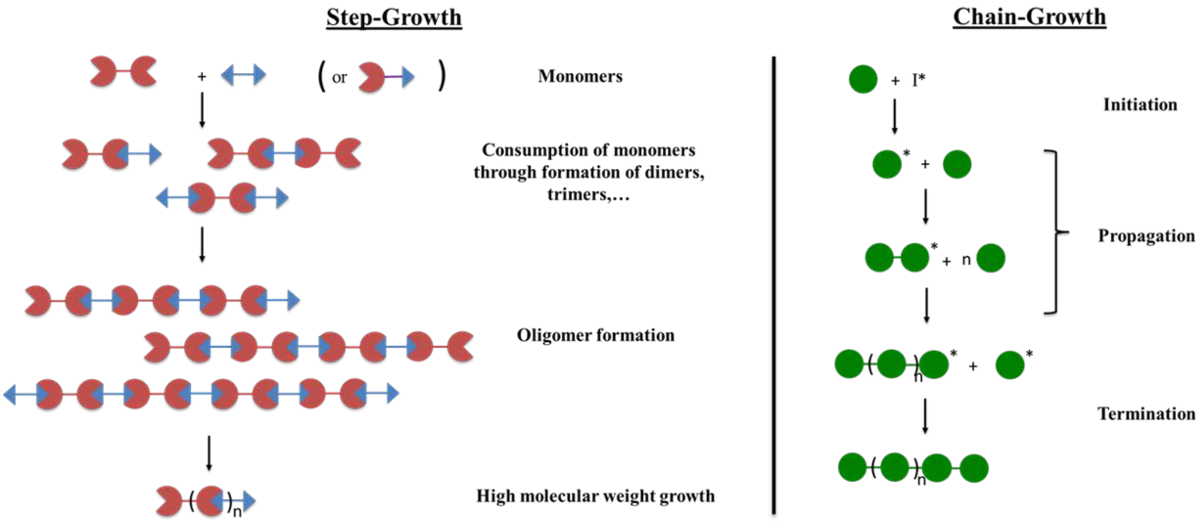


Figure 2. Illustration of mechanistic difference between step-growth polymerization and chain growth polymerization.

Step-growth polymers comprise almost all high performance polymers in production with chain-growth polymers making up 80 % of the currently utilized commodity polymers. While both of these polymer systems contribute to the quality, safety, and health of our modern life, step-growth polymers exhibit a marked improvement in toughness, stiffness, and thermal stability when compared to early free-radical derived polymers. For these reasons, many polymers obtained by step-growth method (e.g. polyetherketones, polysulfones, polyimides) comprise the top of the pyramid of added value polymers with high mechanical performance.

Step-growth polymerization first gained notoriety through DuPont's commercialization of Nylon-6,6, following Carothers pioneering work to elucidate the polycondensation process [4,5]. Traditionally this polymerization method occurs through a reaction between two different functional groups utilizing quantitative reactions, such as esterification, amidation, nucleophilic aromatic substitution, and urethane/urea formation with isocyanates [1,3]. Considering Carothers equation, for an organic reaction to be considered a suitable candidate for polymerization, the reaction must proceed in a quantitative fashion (> 99%). In the case of polyesters, the transesterification reaction achieves high conversion under proper conditions making it a suitable reaction for step-growth polymerization [6].

However, several issues perturb the course of a step-growth polymerization. For instance,

- The harsh conditions, such as high pressures and temperatures, facilitate monomer decomposition during the polymerization resulting in loss of the reaction stoichiometry.
- Unwanted side reactions involving functional groups can occur (e.g. cyclization, decarboxylation from COOH end groups, etc.) affecting the A to B monomer ratio and diminishing the molecular weight.
- Polymerization can reach an unfavorable equilibrium with no means to eliminate the side product (reversible polycondensation) limiting high conversions and consequently high molecular weight.

Thus, most step-growth polymerizations require a catalyst to mediate the polymerization, increase the rate of reactions, and push the conversion above 99 %, in order to reduce the potential side reactions. Small organic molecules synthesis employs a diverse range of catalysts to improve selectivity of enantiomers and increase reaction rates. These reactions often draw inspiration from nature with the use of enzymes to catalyze biochemical reactions [7,8]. Flory initially studied the use of Lewis acidic/basic catalysts for quantitative ester interchange kinetics for use in high molecular weight polyester synthesis [9]. Until recently, metal based catalysts have comprised the majority of systems utilized in step-growth polymerization focusing on a variety of metal complexes, bases, and acids. Organocatalysis has emerged in this field with the potential to improve upon these long studied processes. [3].

2. Organocatalysis vs. Metal Catalysis in step-growth polymerizations

The first notorious examples about the importance of metal catalysis for the preparation of well defined polymers were based on chain-growth polymerization. Among them, Ziegler-Natta catalysts comprise the most widely used polymer catalysts due to their use in the commercialized synthesis of polyethylene, polypropylene, and polyolefin copolymers. These materials encompass over 50 % of the total non-fiber plastics produced since 1950 and generated an estimated 184 Mt of global primary plastic production in 2015 [10]. Developed in the 1940’s, these systems comprised titanium compounds and organoaluminum derivatives as co-catalysts. They allow triggering the polymerization through a coordination mechanism resulting in insertion of the catalyst across the double bond. Further development resulted in the formation of single-site catalysts using metallocene structures, often incorporating Zr or Hf as the metal center [11,12]. Metathesis based polymerizations represent another mechanism of catalysis for chain growth reactions. Originally developed for ring opening polymerizations of structures exhibiting significant ring strain, i.e. norbornene, these catalysts include transition metal centers observed in the Schrock or Grubbs catalyst in **Figure 3** [11,13,14]. These catalysts expanded their use into a wide variety of polymerization including ring opening insertion metathesis polymerization (ROIP), ring expansion metathesis polymerization (REMP), and α,ω-dienemetathesis polymerization (ADMET) [15,16]. Cyclic monomers, such as lactones and epoxides, also undergo a ring opening polymerization following chain growth kinetics due to the repeated addition of the monomer to the active chain ends. Catalysis of these polymerizations traditionally occur through the use of metal alkoxide catalysts that undergo a "coordination-insertion" mechanism and use a diverse array of metals such as, Al, Mg, Zn, Ca, Sn, Fe, Y, Sm, Lu, Ti, and Zr [17].

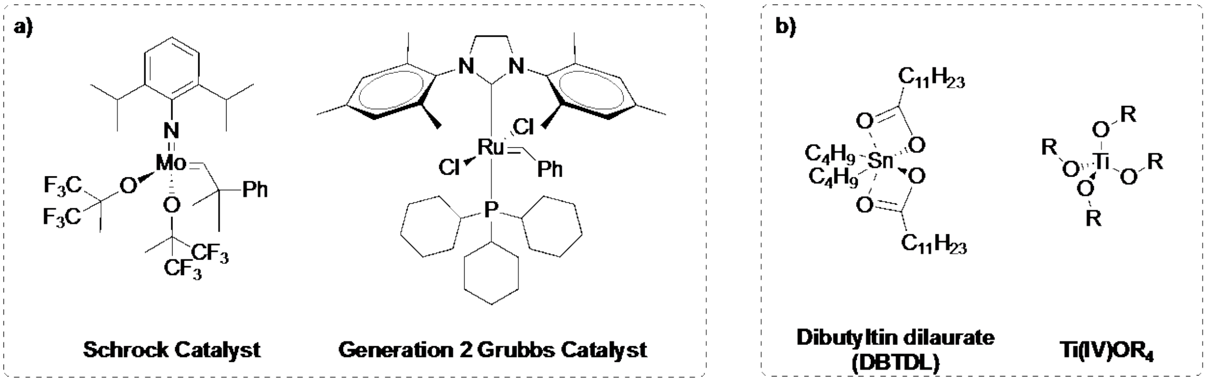


Figure 3. Examples of typical a) transition metal-based catalysts for metathesis polymerization and b) organometallic catalysts for step-growth polymerization.

Metal catalysis also have shown significant importance for the development of step-growth polymers. One of the gold standars for step growth polymerization of polyurethanes are organotin compounds such as dibutyltin dilaurate. They act as Lewis acids toward the polymerization with remarkable catalytic activity and they are used in most of polyurethane preparation. The second highly employed catalyst in step-growth polymerization of polyesters, specially for the polymerization of polyethyleneterephtalate (PET) are antimony trioxide based compounds. The harsh polymerization conditions, being high vacuum in combination with high temperatures, are key factor in producing polymers with high molecular weights and good mechanical properties an antimony trioxide is currently the best suited for these polymerizatin conditions.

While these catalysts enable the achievement of high molecular weight polymers, the accompanying issues that arise with their use present a variety of challenges. The initial use of organocatalysts for polymer synthesis largely stemmed from the necessity for a non-toxic catalyst, to synthesize polymers for biomedical applications and/or microelectronics [17]. The initial focus was directed towards chain growth polymerizations, specifically ring opening polymerization of lactones and epoxides [17]. Over the last ten years, an emerging focus on the use of organocatalysts in step-growth polymerization has appeared in the literature.

Organocatalysts comprise an area of polymer catalysis that exclusively utilize non-metal atoms[18–22]. The use of organocatalysis in chain growth polymerization primarily revolves around ring-opening polymerization (ROP) and occurs through four main activation mechanisms. Imidazoles, *N*-heterocyclic carbenes, phosphines, and pyridine derivatives undergo activation through a nucleophilic monomer activation mechanism. This occurs when the catalyst attacks the carbonyl carbon of the monomer resulting in ring-opening and the formation of a zwitterionic intermediate. The intermediate proceeds to deprotonate an initiating or propagating alcohol resulting in an alkoxide chain end that undergoes acylation with the carbonyl releasing the catalyst. Organic acids, such as trifluoromethanesulfonic acid (TfOH), trifluoromethanesulfonate (MeOTf), and $HCl\cdot Et_2O$, utilize the second activation mechanism, electrophilic monomer activation [23,24]. This involves activation of the carbonyl either by protonation or by interaction by hydrogen bonding, facilitating nucleophilic attack of the chain-end (ROH). General base chain-end activation comprises the third catalytic mechanism. Activation of the chain-end (H-OR) occurs through deprotonation to form an alkoxide or H-bonding to increase the nucleophilicity of the alcohol. The chain-end then attacks the carbonyl carbon causing a ring-opening reaction to form an ester and reform the activated alcohol species. Pyridine derivatives, such as dimethylaminopyridine (DMAP), demonstrate mechanistic competition between this mechanism and nucleophilic activation [25]. Finally, bifunctional activation encompasses the last mechanism for ROP, which simultaneously activates the monomer through electrophilic activation of the carbonyl and activation of the chain end/initiator through a general base mechanism [17]. It is hypothesized that 1,5,7-triazabicyclododecene (TBD) catalyzes ROP through this unique dual-activation mechanism. This explains the observation of higher turnover frequency during the ROP of lactides and higher reactivity in comparison to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *N*-methyl-1,5,7-triazabicyclododecene (MTBD), structures illustrated in **Figure 4** [26,27].

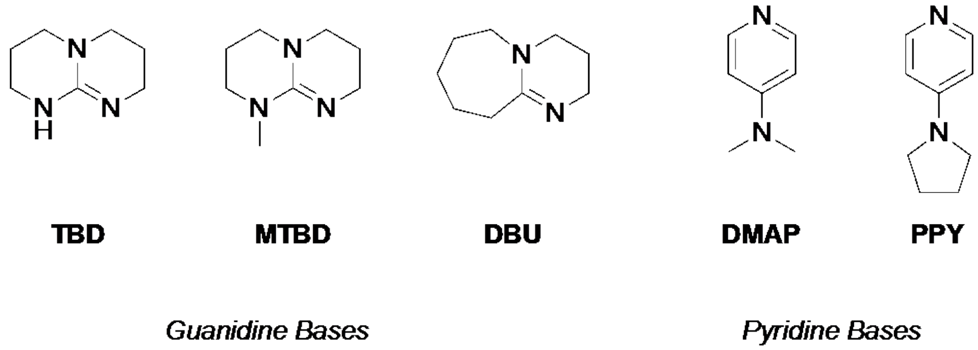


Figure 4. Structures of organocatalysts bases selected from guanidine or pyridine derivatives.

Due to the similarity between the functional groups used in step-growth polymerization and ROP, many of the organocatalysts used in ROP represent possible catalytic systems for step-growth polymerizations. N-heterocyclic carbenes (NHCs), over the last 16 years, developed into a widely used range of organocatalysts for step-growth polymerization [28]. Polycarbonates, polyesters, polybenzoins, and oxa-Michael addition polymerizations all utilized derivatives of NHCs to achieve high molecular weight polymers (**Figure 5**) [28–32]. In these polymerizations, carbenes were generated in- situ through deprotonation of imidazolium salts with a base, like potassium *tert*-butoxide, resulting in a nucleophile more active than tertiary amines or phosphines. This nucleophilic species activates the monomer through attack of the carbonyl carbon forming a salt with the resulting alkoxide and enabling attack from a propagating alcohol (nucleophilic monomer activation) [28]. Studies of transesterification reactions demonstrated that the bulkiness/ structure of the NHC influences the selectivity of the catalyst, limiting reactions with secondary alcohols, representing a unique tunable feature not present in metal based catalysts [30,31].

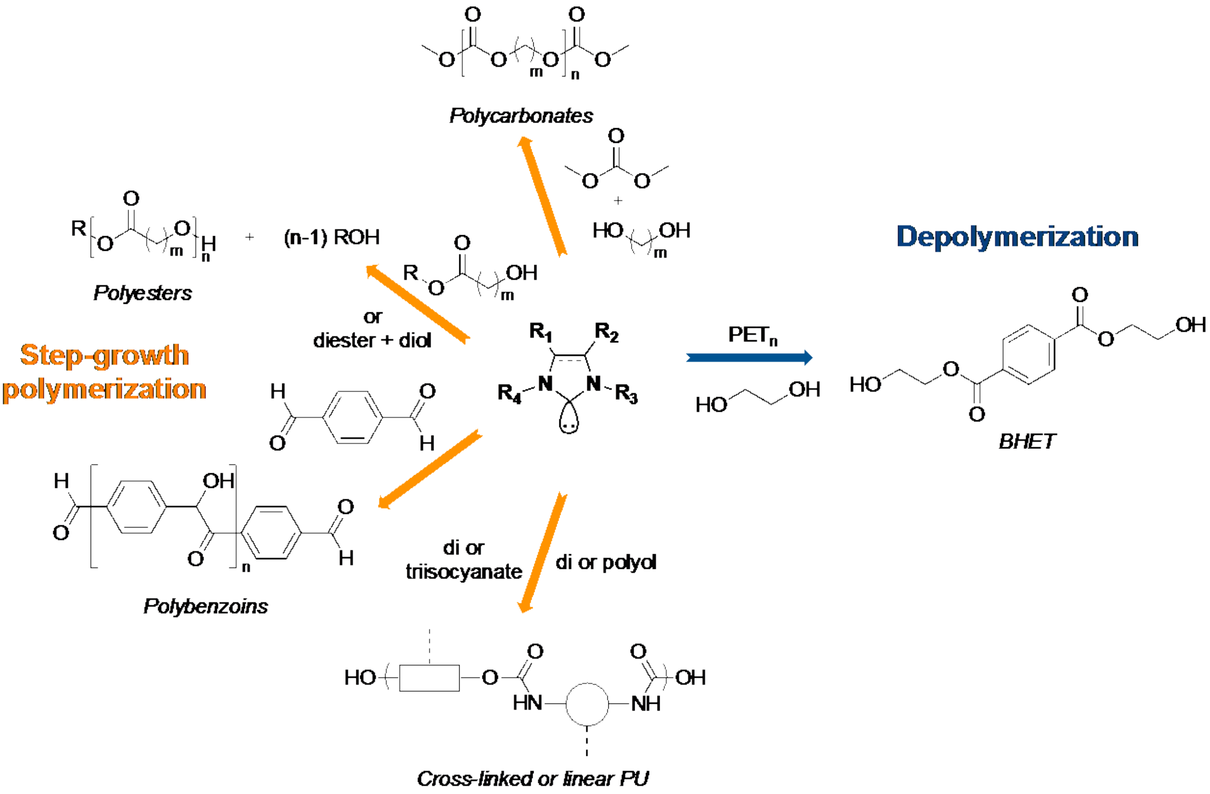


Figure 5. Examples of *N*-heterocyclic carbenes catalyzed step-growth polymerizations and depolymerization.

Cyclic guanidines comprise another large area of organocatalysts for step-growth polymerizations. **Figure 4** depicts a few examples of these popular compounds that found success to access a wide range of polymers, such as polyesters, polyurethanes, and polycarbonates. In the field of polycarbonates, TBD was utilized on multiple occasion (**Figure 6**) [33,34]. This bifunctional transacylation catalyst activates through two proposed mechanisms, amidation or hydrogen bonding stabilization [35]. Convenient preparation of this catalyst transpires from inexpensive and non-toxic chemicals in one-step with high yield [36]. production of polycarbonates with M_n of 33 kg.mol^{-1} occurred at low catalyst loadings (0.5 mol %) and relatively mild conditions (< 150 °C) [33]. Other guanidine bases, such as DBU, and pyridine base derivatives like DMAP also demonstrated success as step-growth polymerization catalysts [34].

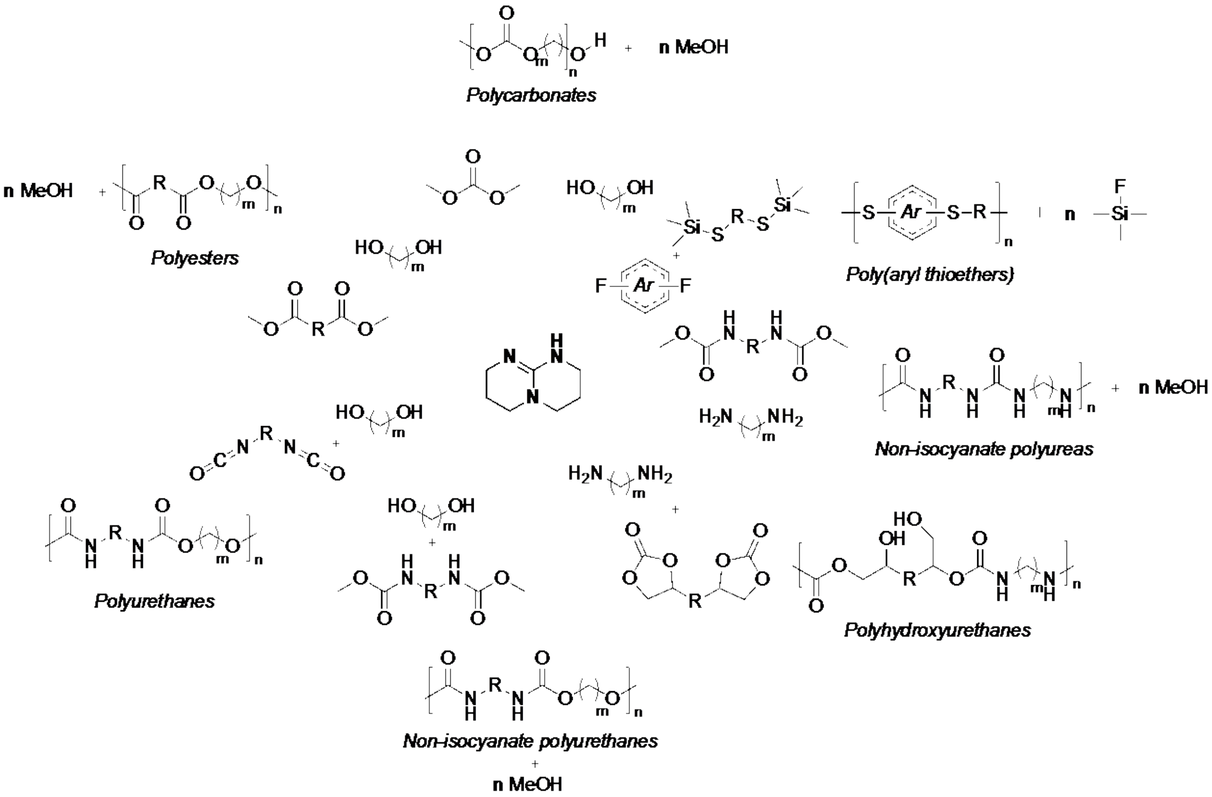


Figure 6. Examples of TBD catalyzed step-growth polymerizations.

While nucleophilic/general base catalyst mechanisms exhibit encouraging results in polyesters and polycarbonates, acid catalysts displayed superior activity in isocyanate-based reactions. Acid catalysts expand the range of monomer options overcoming base sensitivity that limits compounds containing carboxylic acids and amides [37]. Triflic acid (TfOH), *p*-toluenesulfonic acid (PTSA), and bis(trifluoromethanesulfonyl)imide (Tf_2NH), undergo a dual activation mechanism in which the nitrogen of the isocyanate electrophilically activates along with simultaneous nucleophilic activation of the alcohol. Using these acids, high molecular weight PU's were achieved in 6 h unlike the 24 h necessary to achieve > 98% conversion using DBU or the traditional metal catalyst, dibutyltin dilaurate (DBTDL) [38]. Acid catalysts also demonstrate use in dendritic polyacetals and unique ionic liquid with acid moieties act as both catalyst and solvent in the synthesis of polyesters and polyethers (**Figure 7**) [39–41].

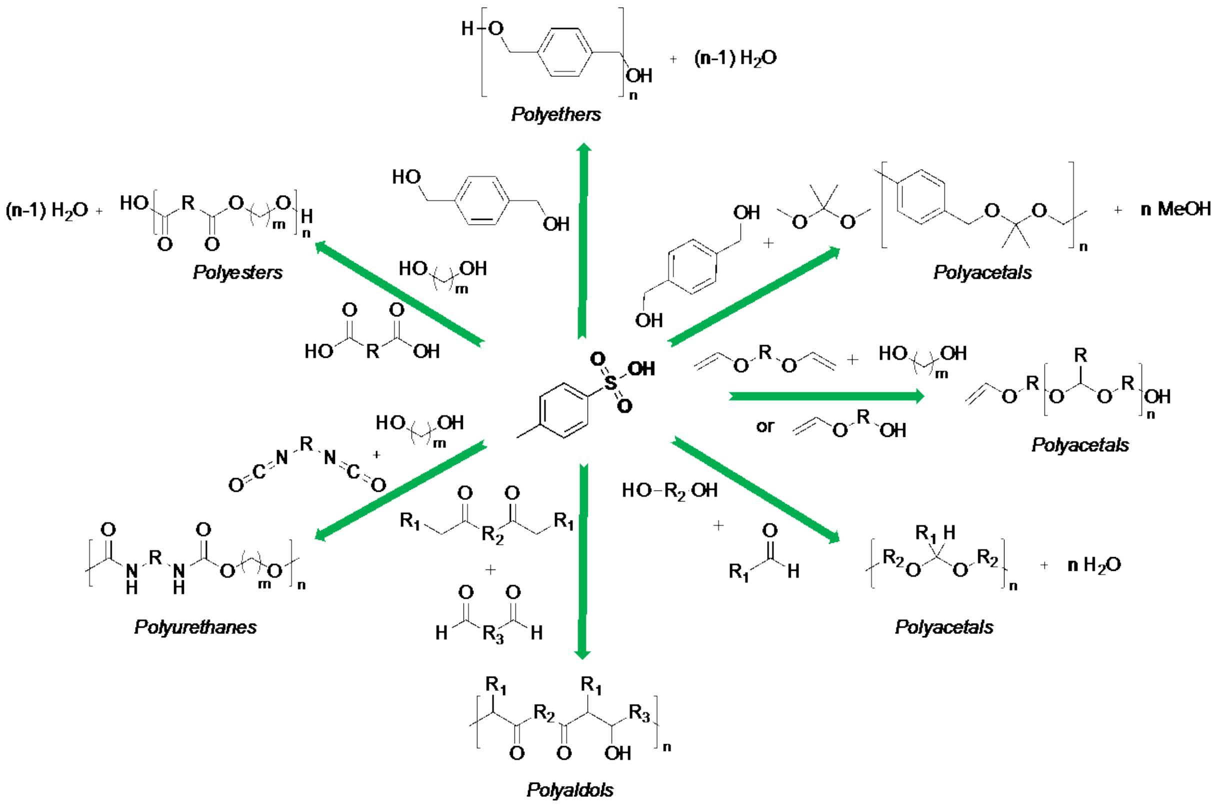


Figure 7. Examples of PTSA catalyzed step-growth polymerizations.

Figure 8 illustrates the field of organocatalysts within step-growth polymerization from 2001 until now as expanded upon in this review. A focus is given on the main step-growth polymers such as polyurethanes, polyureas, polyesters, polycarbonates and polyethers synthesized using organic Lewis or Brønsted bases or Lewis or Brønsted acids. This review will also have a particular focus on comparing the best organic catalysts in each step-growth polymerization in terms of efficacy and selectivity with metal catalysts commonly used in each polymerization. The last section of the review will deal with the limitations and open challenges of organocatalyzed step-growth polymerizations.

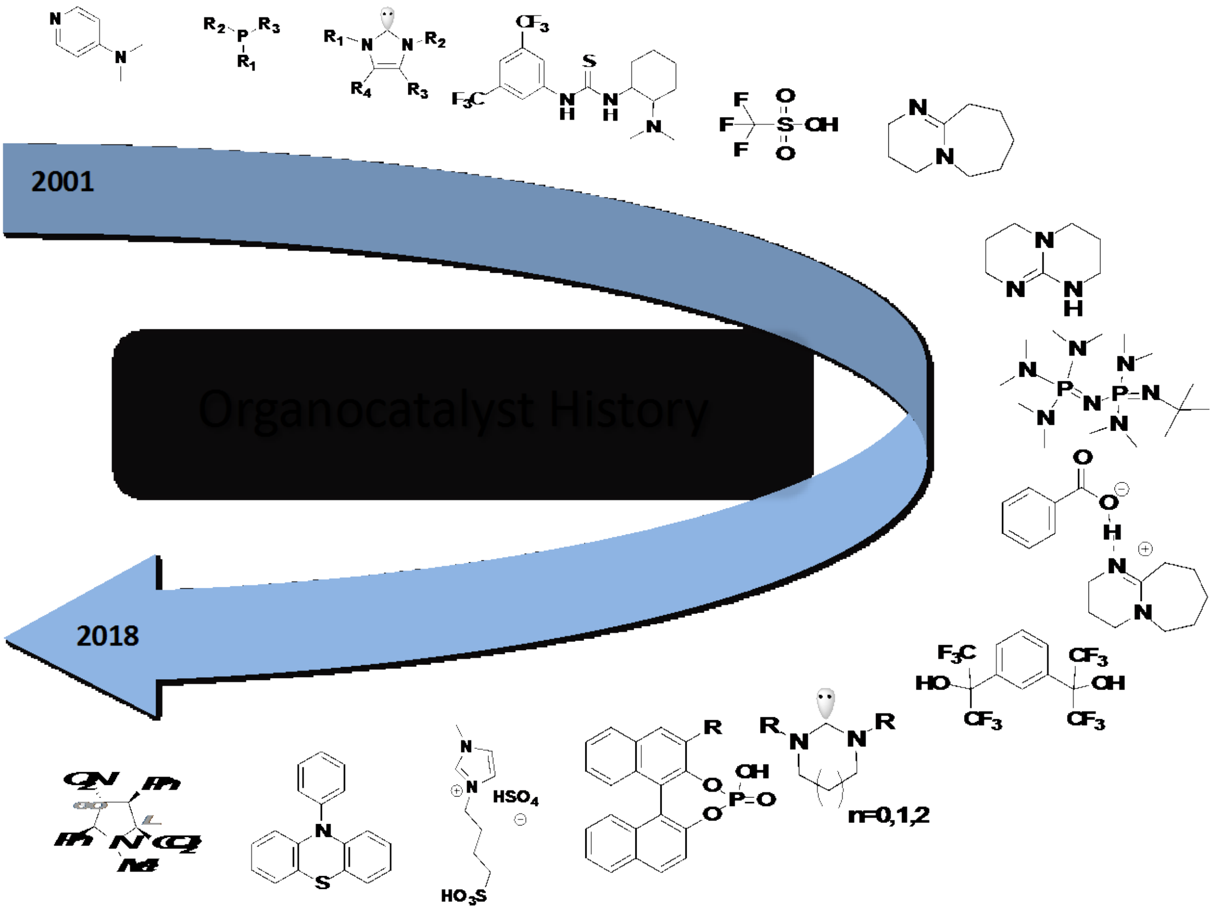


Figure 8. Chronological compilation of organocatalysts utilized in chain growth and step-growth polymerizations.

3. Synthesis of polyurethanes, and poly(urea-urethane)s via step-growth polymerization using organocatalysis

Since their first synthesis by Otto Bayer in 1937, polyurethanes (PUs) provoked interest due to their high versatility, good mechanical and physical properties, and relatively low cost [42]. Polyurethanes constitute the sixth most important class of polymeric materials used worldwide, with a global production that reached 18 Mt in 2016, and a demand in continuous expansion [43,44]. Industrially synthesized from the polyaddition between polyols and polyisocyanates in the presence of a metal-based catalyst (mercury- or tin-based catalysts). These versatile materials find applications in rigid and soft foams, coatings, adhesives, sealant or as biomedical materials [45,46]. Most industrial processes involve the use of a short chain diol or diamine, acting as chain extender in order to attain higher molecular weights. In this case, the polyurethane synthesis is usually performed in two steps with the first step involving the use of a long chain diol to form a PU prepolymer. In the second step, the short chain diols (more reactive) are added to complete the polymerization and to achieve high molar masses.

Catalysts play an enormous role in the process of synthesizing industrially relevant polyurethanes. The most employed catalyst being organotin compounds, such as dibutyltin dilaurate [47]. The success behind this catalyst is related to its high activity at low loading concentration. Nevertheless, the remarkable difficult and costly purification, limits the catalyst removal from the final polymers. This residual catalyst provokes detrimental effects on the ageing of the final polyurethane. In addition, some studies suggested the possibility of tissue function endangerment through slow penetration of the catalyst into the blood circulation system which should be considered when employing tin catalyzed PU in biomedical or food contact applications [48–54]. These issues have led to the implementation of regulations by the European Union to restrict its use [50,55,56].

Recent efforts in polyurethane synthesis were thus oriented toward the design and synthesis of novel organocatalysts that performed as effectively as tin-based catalysts. Several classes of organic compounds including strong and weak Brønsted/Lewis acid or bases, phosphazenes, amines and ammonium derivatives, guanidines and amidines, and thiourea derivatives demonstrated high catalytic activity in PU synthesis, highlighted in the following sections (**Figure 9**) [57].

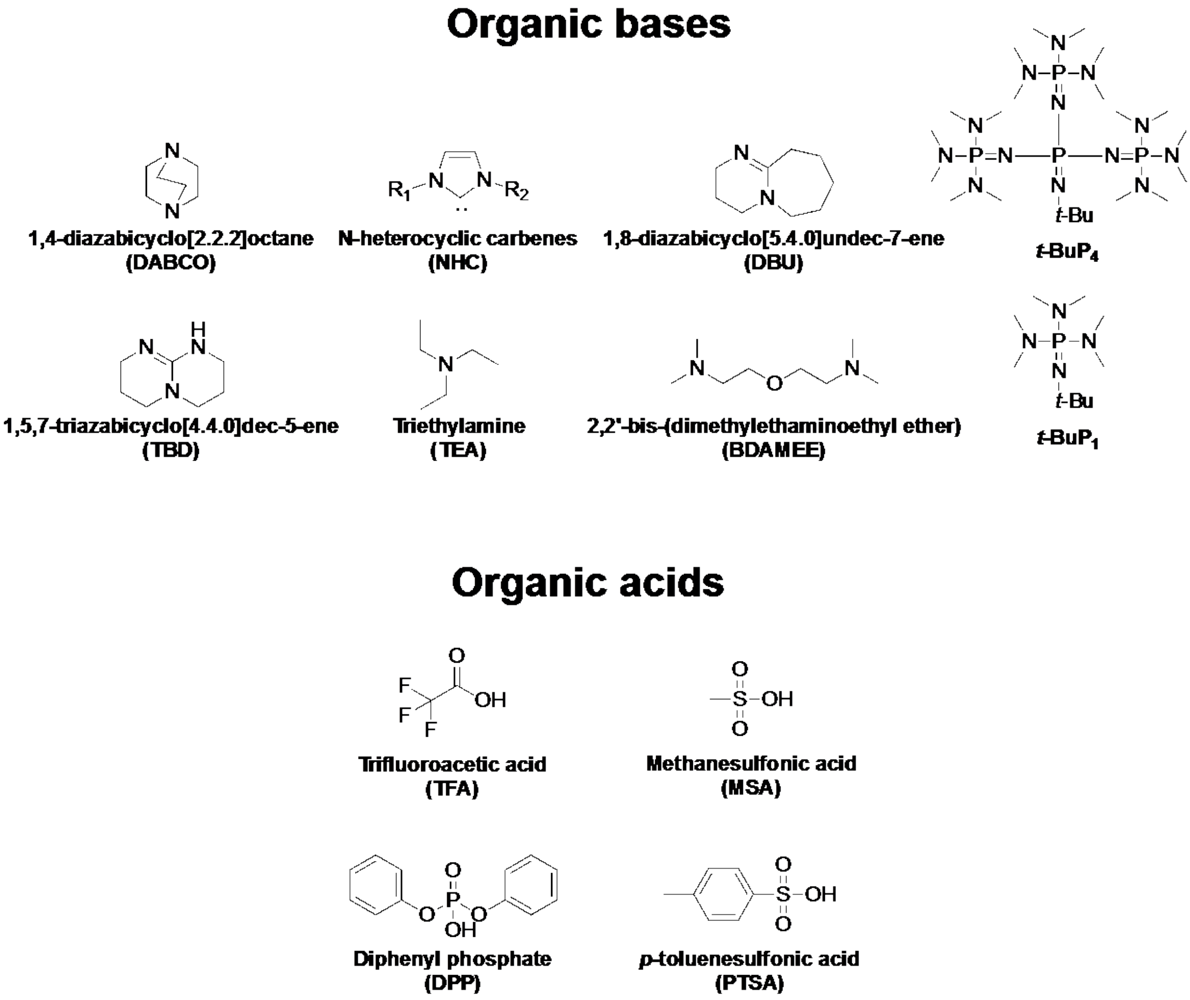
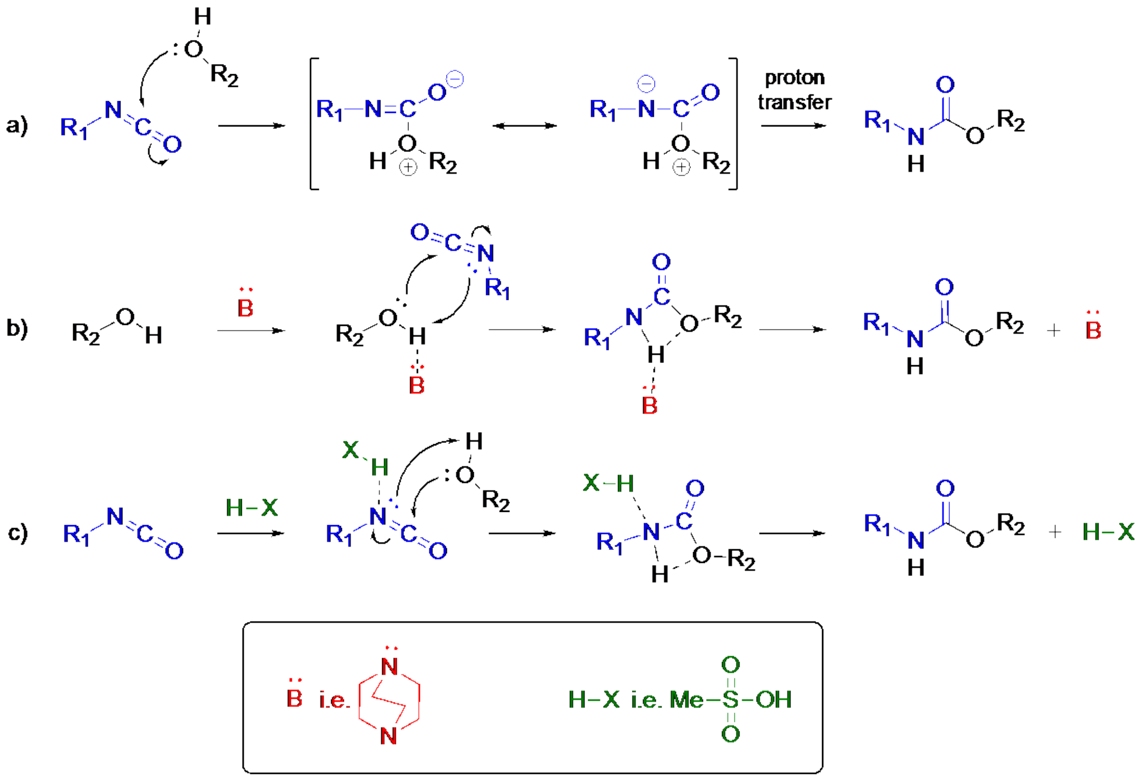


Figure 9. Conventional organic bases and acids used as catalysts for step-growth polymerization of polyurethane. Adapted from ref. [57].

3.1. Use of organic base catalysts.

Although preparation of polyurethanes under catalyst free conditions is possible (**Scheme 1.a**), a catalyst is often required to achieve high molecular weight polymers under milder conditions. These catalysts comprise electrophilic activators, such as Brønsted acids, that activate the isocyanate group (**Scheme 1.c**) and nucleophilic activators, such as amines, that activate the alcohol group (**Scheme 1.b**) [57].



Scheme 1. Mechanism of the reaction between isocyanate and alcohol in the presence of a) no catalyst, b) a base or nucleophilic activator as catalyst or c) an acid or electrophilic activator Adapted from ref. [57].

Tertiary amines.

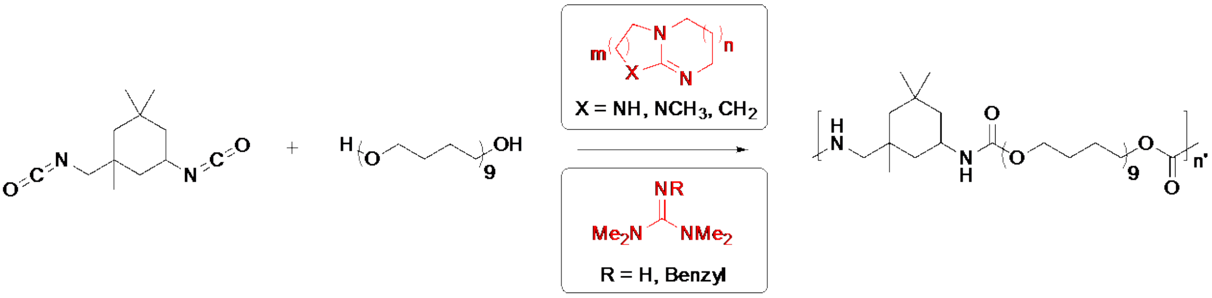
Historically, the most common organic base catalysts employed in urethane polymerization reactions consisted of tertiary amines. Among them, 1,4-diazabicyclo [2,2,2]octane (DABCO) and 2,2′-bis-(dimethylaminoethyl ether) (BDMAEE) represent the most industrially employed catalysts [58]. While the amine activation mechanism during the urethane formation remains unclear, it is well understood that DABCO can catalyze both isocyanate-water and isocyanate-hydroxyl reactions. In the 1940’s, Baker *et al*. researched the base catalysis of urethane formation through a series of kinetic studies indicating that the isocyanate undergoes nucleophilic activation by DABCO [59,60]. Other groups, such as Schwetlick and coworkers, contradicted this original study by demonstrating that the urethane formation involves first protonation of the catalyst, then nucleophilic addition of the alcohol onto the isocyanate, and finally proton transfer from the catalyst to the complex (**Scheme 1.b**) [61][60]. Density functional theory (DFT) calculation recently confirmed this mechanism as the most dominant pathway [62].

Unfortunately, catalysis with DABCO exhibited limit reactivity enhancement relative to non-catalyzed reactions during the synthesis of linear aliphatic isocyanates[63]. Moreover, tin-based catalysts still outperform these systems in terms of reaction rates indicating that organocatalysts require molecules with higher basicity (amidines and guanidines).

Cyclic guanidines and amidines.

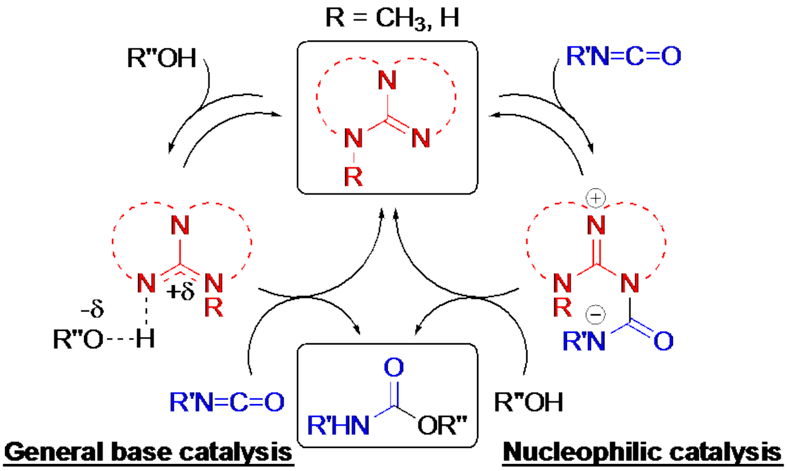
Tetra-alkylated guanidines, for example TBD (MeCN pKa $TBDH^+$ = 26), amidines, such as DBU (MeCN pKa $DBUH^+$=24.3), and penta-alkylated guanidines, such as MTBD (MeCN pKa $MTBDH^+$ = 25.5) have been intensively studied in the ring-opening polymerization (ROP) processes [55]. Recent studies revealed potential in the area of step-growth polymerizations.

In 2012, amidines, acyclic guanidines, and cyclic guanidines were characterized as possible catalysts for polyurethanes based on isophorone diisocyanate (IPDI) and poly(tetramethylene oxide) 650 (PTMO-650) with the results compared to conventional DBTDL. The reaction was performed in bulk at 60 °C using 1 mol % of catalyst (**Scheme 2**) while FTIR monitored conversion [63].



Scheme 2. Synthesis of PTMO 650 and IPDI based polyurethanes utilizing amidine and guanidine catalysts. Adapted from ref. [63].

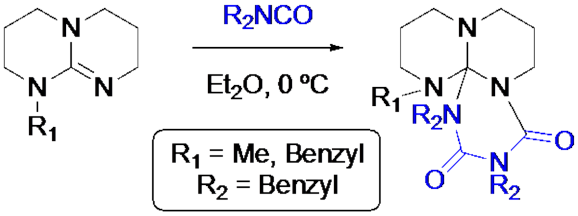
MTBD and DBU catalysts exhibited a significant improvement over DBTDL in the synthesis of PUs decreasing the time to full conversion from 1 h to 15 min. PUs with molecular weights, $M_{w,}$ up to 74 kg.mol^{-1} ($Đ$ = 1.9) were obtained with 1 mol % of DBU. Further study into this area, demonstrate the application of DBU to the room temperature solution polymerizations of polyether-based polyurethanes. Sardon and coworkers achieved molecular weight up to 188 kg.mol^{-1} using trans-1,4-cyclohexylene diisocyanate [64]. A mechanism in which the base activates the alcohol should imply that the higher the basicity of the catalyst the higher the reaction rate. Comparing the results obtained from acyclic and cyclic guanidines which exhibit similar pKa values in acetonitrile (25.4 and 25.43) [65,66], similar activities could be expected. However, kinetic studies showed that cyclic guanidines were much more reactive than their acyclic counterparts. Cramail *et al.* attributed the difference to the ring strain in the cyclic structure. The nitrogen atoms are constrained into a conformation where the lone pairs, being aligned, can be easily delocalized. Furthermore, TBD demonstrated much lower reactivity than MTBD even though it is a stronger base. The evidence indicates that another mechanism might occur in the catalyzed isocyanate-alcohol polymerization process. As shown in the **Scheme 3** below, adducts form through a nucleophilic mechanism between isocyanates and a guanidine catalyst triggering the formation of urethanes.



Scheme 3. Proposed mechanism for the reaction between isocyanates and alcohols catalyzed by guanidines. Adapted from ref. [63].

Using this side reaction, Cramail and coworkers prepared delayed-action catalysts, activated upon heating through blocking the isocyanates moieties [67]. Preparation of the catalysts occurred through reacting one equivalent of different cyclic and acyclic guanidines (TBD, MTDB, TMG, etc.) or amidines (1,5-diazabicyclo[4.3.0]non-5-ene (DBN), DBU) with two equivalents of the desired isocyanate. The research confirmed through X-ray diffraction that MTDB reacting with benzylisocyanate formed a heterocyclic compound. (**Scheme 4**). The catalytic activity of the compounds was tested on the reaction between IPDI and PTMO 650 with a catalyst loading of 1 mol %. Activity was not found at 20 °C, however upon heating at

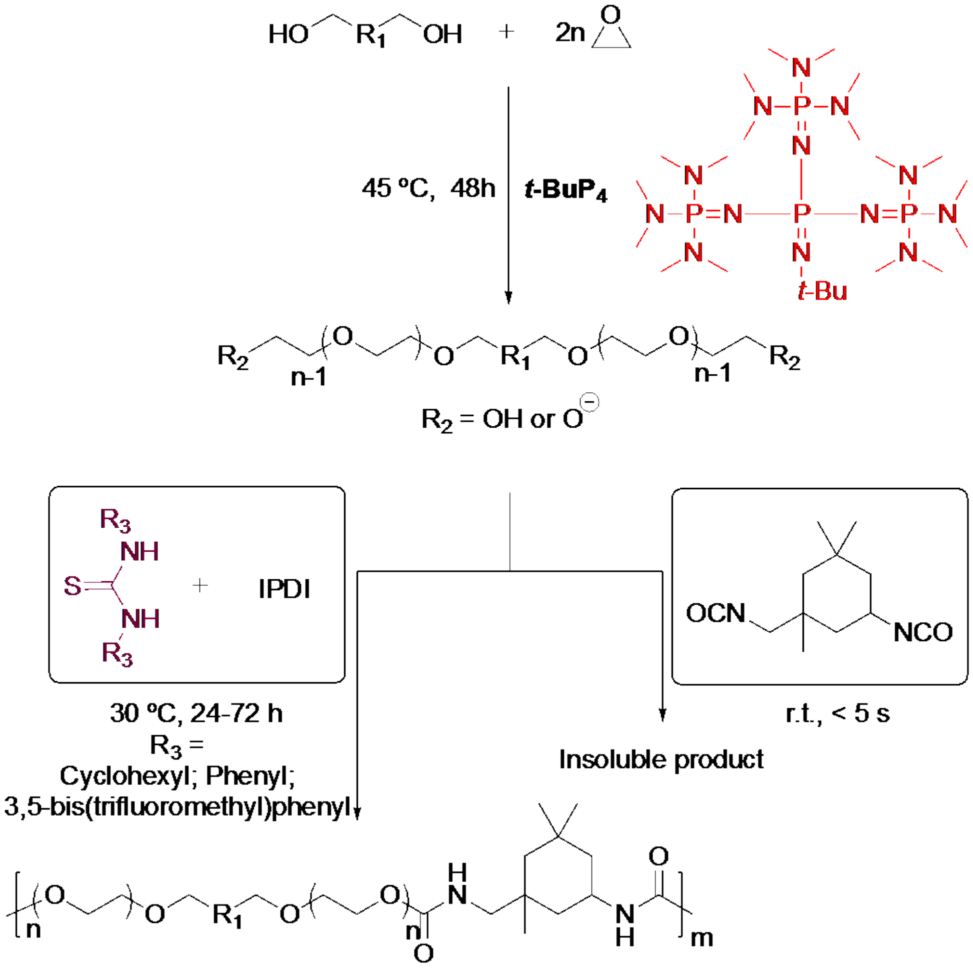
60 °C, polymerization occurred. Employing MTBD-based latent catalyst, full conversion was achieved within 18 h and PUs with relative high molecular weight (M_w = 57.6 kg.mol^{-1}, $Đ$ = 1.6) were obtained. The authors explained this latent activity by suggesting that decomposition of the heterocycle might occur upon heating. The alcohol functionality of the diol reacted with the isocyanurate functional group in the catalyst to form urethanes and regenerating the guanidine precursor. This latent catalyst also exhibited excellent selectivity with both aliphatic and aromatic isocyanates, producing PU without traces of cyclodimers and cyclotrimers. The key characteristic of latent or delayed action catalyst arises from their storage abilities and enables on-demand polymerizations.



Scheme 4. Delayed-action catalyst based on guanidine. Adapted from ref. [67].

Phosphazenes.

Phosphazene-containing compounds function as extremely strong non-nucleophilic Brønsted bases. First introduced in 1987 by Schwesinger *et al.*, they were used as effective catalysts for the ring-opening polymerizations of heterocycles or vinyl monomers [68,69]. Xia *et al.*, in 2016, investigated the use of *t*-BuP$_4$ (MeCN pKa BH$^+$= 42.7) [69] to generate polyurethanes based on poly(ethylene oxide) (PEO) and IPDI [70]. They found that fast gel formation occurred upon addition of IPDI to a solution of PEO suggesting crosslinking of the isocyanate groups to form a polyamide structure under these basic conditions. In order to mediate this reaction, the addition of different thioureas as a cocatalyst with the phosphazene was studied. Employing 1,3-diphenylthiourea, they avoided the formation of polyamide side-products, and after 72 h obtained high molecular weight polyurethanes (M_n = 67.8 kg.mol^{-1}, $Đ$ = 1.6) (**Scheme 5**).

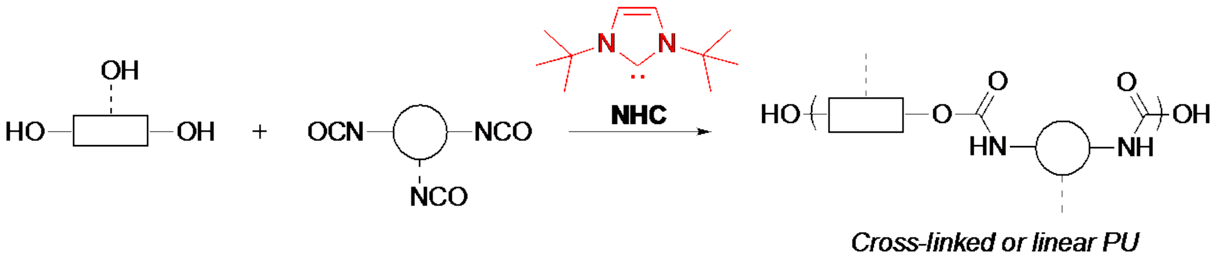


Scheme 5. Synthesis of PUs with PEO soft segments utilizing phosphazene/thiourea co-catalyst systems in a one-pot sequential manner. Adapted from ref. [70].

The group later investigated the application of a phosphazene catalyst with lower basicity, (*tert*-butylimino-tris(dimethylamino)phosphorene, *t*-BuP$_1$, MeCN pKa BH$^+$= 26.9) [71,72]. A macro-diol, poly(3,4-dihydrocoumarin-alt-ethylene oxide), was synthesized using *t*-BuP$_1$ in toluene prior to the addition of hexamethylene diisocyanate (HMDI) which was allowed to react at room temperature for 24 h. Under these conditions, the authors obtained polyurethane with a molecular weight of M_n = 43.9 kg.mol^{-1} ($Đ$ = 2.1).

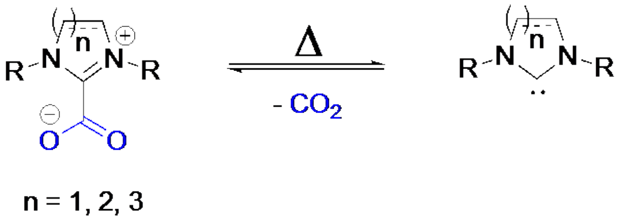
N-Heterocyclic carbenes.

The σ-donor characteristic of the *N*-heterocyclic carbenes (NHCs) enables these molecules to act as either Brønsted bases (pKa= 15-30 in H_2O) or as nucleophiles [73]. Coutlier *et al*. recently demonstrated the synthesis of aliphatic diols and diisocyanates through catalytic activation with NHCs [74]. This study utilized low catalyst loading (1 mol % 1,3-bis(ditertiobutyl)imidazol-2-ylidene) and low temperatures (30-50 °C) to achieve PUs [29]. The authors found that the order of addition of reactants was crucial to achieve linear polyurethanes. The addition of the diisocyanate to the reaction prior to the diol resulted in deactivation of the NHC, while the reverse order resulted in rapid polymerization. This suggests that a hydrogen-bonding mechanism dominates.



Scheme 6. Synthesis of crosslinked or linear polyurethanes catalyzed by NHCs.

One of the advantages of carbenes, in comparison to other catalysts, relies on their potential to prepare carbene adducts that can be further used as latent catalysts. Buchmeiser *et al*. reported in 2009 the first NHC-catalyzed synthesis of crosslinked polyurethanes (**Scheme 6**) [75,76]. NHC-CO_2 adducts were used as latent catalysts for that purpose. The reactions were performed at 60-70 °C in dichloromethane, and the free carbene forms via thermal activation with subsequent release of CO_2 (**Scheme 7**).

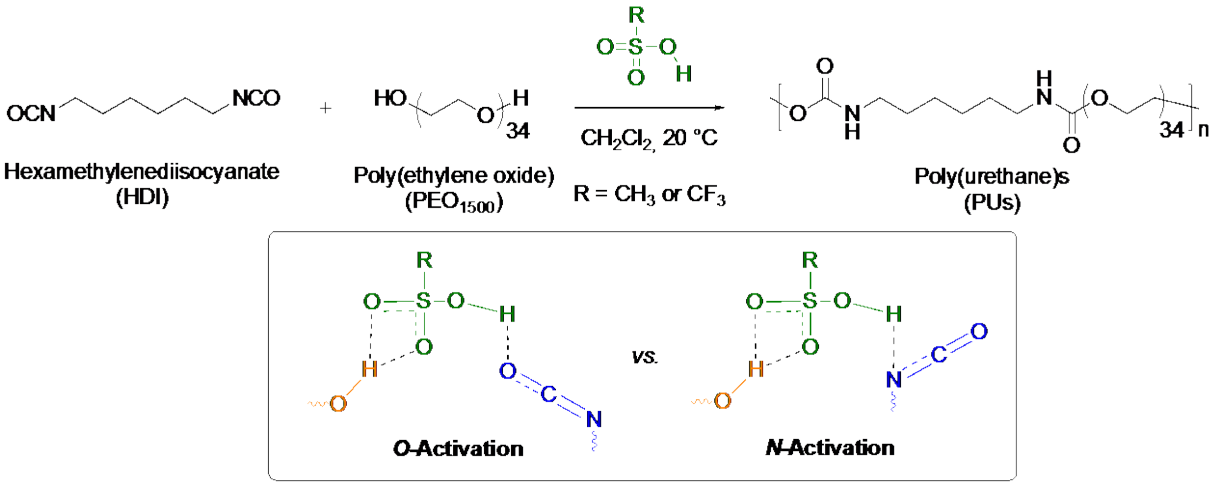


Scheme 7. NHC-CO_2 delayed-action catalyst. Adapted from ref. [75,76].

On demand activation resulted in significant interest towards this particular NHC catalyst to replace commonly used, but toxic, mercury derivatives.

3.2. Use of organic acid catalysts.

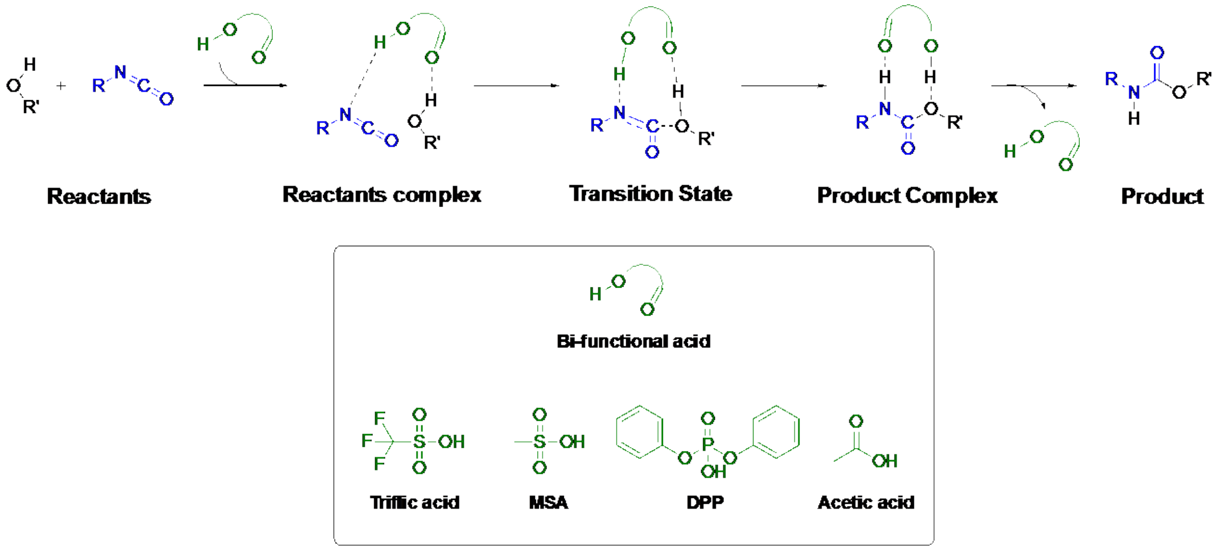
Similarly to organic bases, strong organic acids proved to effectively catalyze the traditional isocyanate based polymerization of polyurethanes [38,77,78]. Until 2013, few studies reported on the synthesis of PUs using organic acid catalysts and those that did reported poor activities relative to traditional tin catalysts [78]. In 2013, Sardon and coworkers analyzed the potential of a range of organic acids to catalyze the solution polymerization of a poly(ethylene glycol) oligomer and HMDI at room temperature, as illustrated in **Scheme 8** [38].



Scheme 8. O-activation *vs.* N-activation mechanism for the step-growth polymerization of hexamethylene diisocyanate and poly(ethylene glycol) 1500 in dichloromethane at room temperature. Adapted from ref. [38].

In this study, the researchers found that reactions without the presence of a catalyst resulted in negligible conversions. Alternatively, the addition of 5 mol % of “super strong” acids, such as bis(trifluoromethanesulfonyl)imide (Tf_2NH, pKa = -18 [79]) and triflic acid (TfOH, pKa = -13 [37]) afforded high molecular weight PUs (M_w= 24 kg.mol^{-1}, $Đ$ = 1.5) within 6 h. The catalytic capabilities of these acids outperformed the tin and DBU catalyzed reactions which only achieved complete conversion after 24 h. MSA and PTSA catalysts (sulfonic acids) afforded slower reaction rates relative to the “super strong” acids, but achieved higher molecular weights (M_w = 10.1 kg.mol^{-1}, $Đ$ = 1.7 and 18.5 kg.mol^{-1}, $Đ$ = 1.9, respectively) than the tin-catalyzed reaction (M_w = 7.4 kg.mol^{-1}, $Đ$ = 1.7). Apart from sulfonic acids, the authors also studied diphenylphosphate (DPP, pKa = 1.1), but 48 h were needed to reach full conversion, and PUs with low molecular weights were obtained after 6 h in comparison to the other acid catalysts (M_w = 4.3 kg.mol^{-1}, $Đ$ = 1.4). Moving to even weaker acid catalysts, such as trifluoroacetic acid

(TFA) and acetic acid (AcOH), proved completely ineffective. DFT calculations indicated that catalysis follows a dual hydrogen-bonding mechanism. This involves an electrophilic activation of the isocyanate prior to nucleophilic activation of the alcohol (**Scheme 9**). The activation of the nitrogen exhibits a preference over the possible oxygen activation pathway suggesting that both acid strength and conjugate base nucleophility are important characteristics in the catalysis of polyurethanes.



Scheme 9. The proposed formation of a urethane functionality through organic acid catalysis following an N-activation pathway. Adapted from ref. [38].

Recently, Fukushima and coworkers evaluated different organocatalysts for the synthesis of antithrombotic poly(carbonate-urethane) *via* one-pot sequential ring-opening polymerization and polyaddition process [80]. Among the used catalysts, triflic acid and diphenylphosphate were found to be the most active for the polyaddition of the polycarbonate-diol with HDI. TfOH enabled the synthesis of poly(carbonate-urethane) with a molecular weight of M_n = 17.2 kg.mol^{-1} ($Đ$ = 1.7). However, to monitor quantitatively the number of hydroxyl group formed in the early stage of the reaction, a weak acid such as DPP was preferred because of its capability of providing prepolymers with narrower dispersities without promoting side reactions. On the other hand, the mixtures TU/DBU and TU/SP were not suitable for the polyaddition as high monomer conversion could not be achieved.

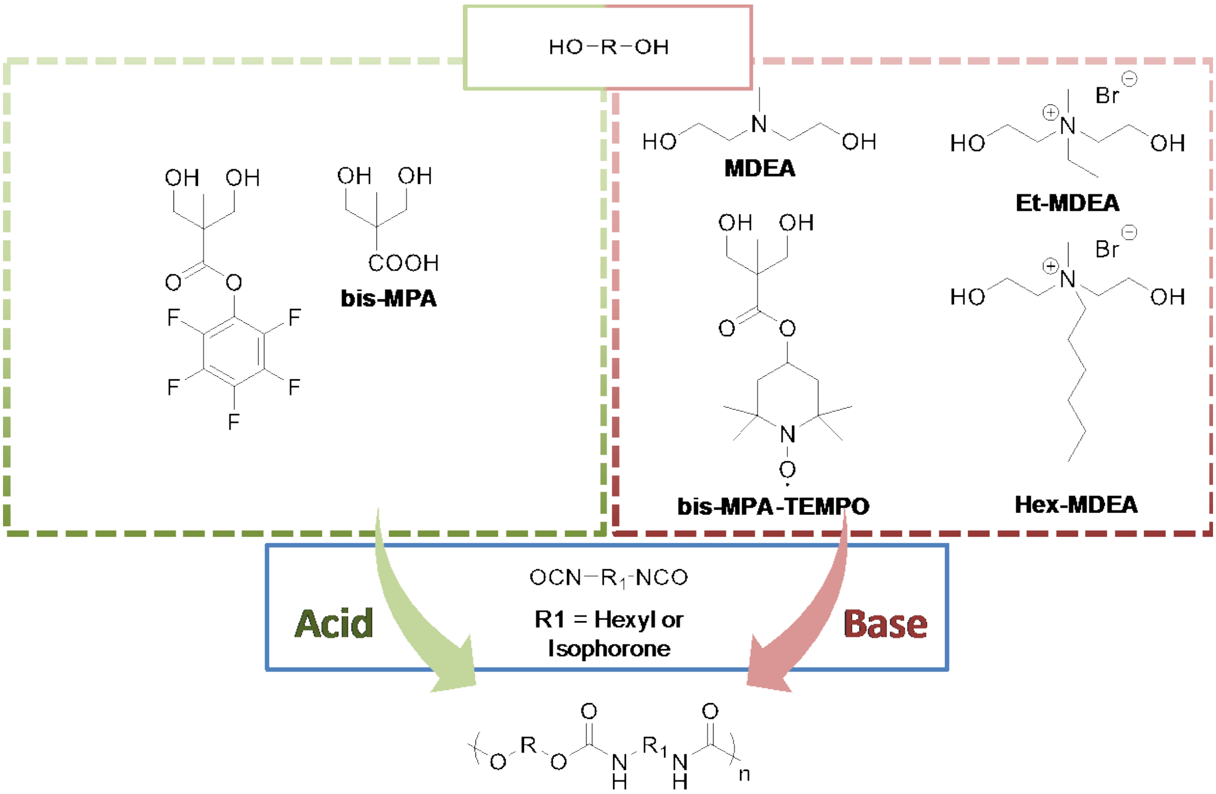
3.3. Catalyst selection for the synthesis of functional polyurethanes

While both organic base and organic acid catalysts demonstrated activation of the step-growth polymerization of isocyanates and alcohols to some extent, catalyst choice is key when employing monomers featuring functional groups, as the latter may deactivate the catalyst.

Sardon and coworkers described the acid-catalyzed synthesis and post-polymerization modification of PUs containing pendant activated pentafluorophenyl esters (**Scheme 10**). These systems cannot polymerize in the presence of a base catalyst as they interact with the pendant ester group [77]. In order to prevent this interaction, polymerizations were performed in dichloromethane at room temperature using 5 mol % triflic acid. This enabled the synthesis of high molecular weight polyurethanes ranging from M_n = 25 to 37 kg.mol^{-1} ($Đ$ = 1.4). Moreover, ^{19}F NMR spectroscopy confirmed that the pentafuorophenyl esters remained intact after the polymerization. Interestingly, this method allowed a broad range of functionality to be incorporated in polyurethanes with pendant pentafluorophenyl through post-polymerization nucleophilic substitution (alcoholysis and aminolysis).

The same group recently prepared thermally-responsive polyurethanes synthesized from PEG-diols of varying molecular weight (M_n = 600, 1000 and 1500 kg.mol-1), IPDI, and 2,2-bis(hydroxymethyl)-propionic acid (bis-MPA) (**Scheme 10**) [81]. The reaction was performed in presence of 5 mol % methane sulfonic acid (MSA) catalyst. The authors argued that the catalyst choice was logical based on the mutual compatibility of the sulfonic acid and the carboxylic acid groups. Increasing the PEG content in the poly(ether urethanes) afforded a tunable LCST in aqueous media ranging from 30 to 70 °C. In order to access a wide range of thermoresponsive polyurethanes, Sardon *et al.* replaced bis-MPA with *N*-methyldiethanolamine (MDEA) and quaternary amine-containing diols based on *N*-methyldiethanolamine (*i.e.* Et-MDEA and Hex-MDEA) (**Scheme 10**). Polycations are attractive materials for biomedical applications in DNA or protein delivery, due to their temperature-responsiveness. In the case of cationic diols, the authors employed DBU as nucleophilic activator based on the mutual incompatibility between tertiary and quaternary amines with acid catalysts.

Organic bases were found optimal for the polymerization of monomers bearing nitroxides [82]. Nitroxides contain oxygen-centered free radicals with a single unpaired electron, and are extensively employed in batteries, catalysis or nitroxide mediated polymerization; they also recently emerged as molecular magnetic resonance imaging (MRI) probes. One potential issue when using organocatalysts in the presence of nitroxide functionalities is that they can interact with strong acids, disproportionating the nitroxide and diminishing the catalytic activity. Garmendia and coworkers concluded that, in order to polymerize monomers bearing nitroxide functionality, organic bases, *e.g*. DBU, were the most suitable catalysts (**Scheme 10**).



Scheme 10. Adequate choice of catalyst for the synthesis of PUs employing monomers featuring functional groups.

In summary, both organic bases and acids have proven suitable catalysts for the step-growth polymerization of isocyanates and alcohols. Under specific conditions they exhibit comparable catalytic activities to commonly used tin-based catalysts. While strong acids may appear as an attractive choice, they can react with moisture potentially reducing their catalytic activity [83]. Strong bases can overcome this issue by catalyzing step-growth polymerizations even in the presence of moisture. However, as reported by Smith *et al*., formation of urethane groups in supercritical CO_2 using DBU as catalyst provided lower activities compared to the reactions in conventional media as a result of its reaction with CO_2 [84]. These findings suggest that in order to compete with tin-based catalyst organocatalyzed polymerization should be performed under dry and inert atmospheric conditions, which can be challenging for industrial applications.

4. Synthesis of non-isocyanate polyhydroxyurethane, polyurethanes and polyureas) via step-growth polymerization using organocatalysis

The use of isocyanate based starting material in PU synthesis raises severe health concerns [85]. Common isocyanates are synthesized using phosgene, a highly reactive and toxic gas, used during World War I as chemical weapon. In the context of the new REACH regulation - implying the restriction on the use of substances containing free isocyanate - and taking into account the need to guarantee the users' safety, it is important to find alternative and greener routes to PUs, involving non-toxic reagents [56]. In the last decade, alternative and environmentally friendly approaches have been developed to synthesize non-isocyanate polyurethanes (NIPUs) (**Figure 10**).

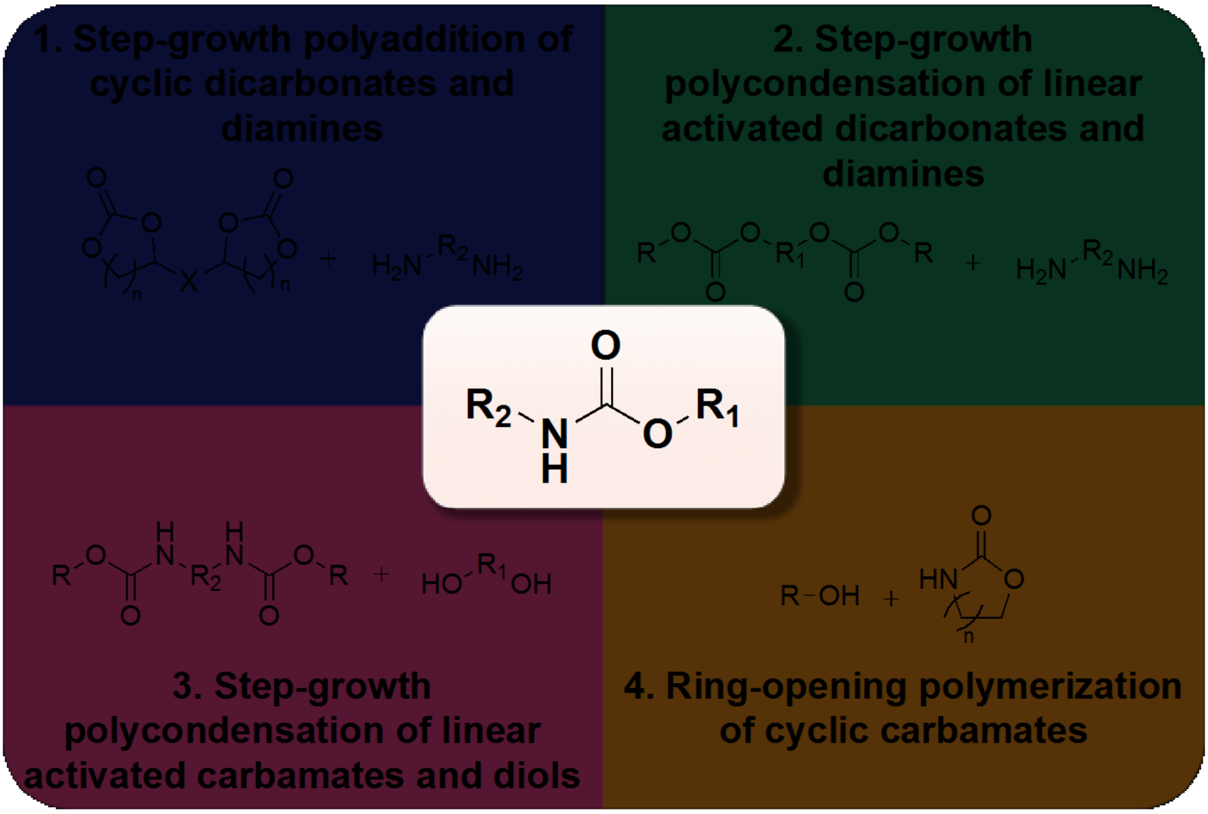
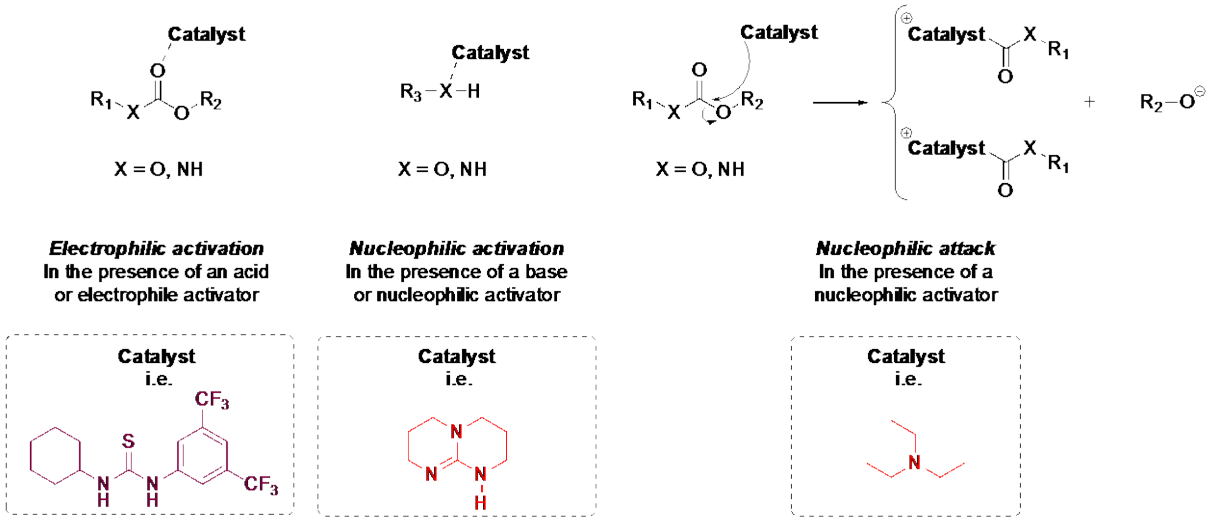


Figure 10. Most employed synthetic routes toward non-isocyanate polyurethanes (NIPUs). Adapted from ref. [57]

The step-growth polyaddition of five-membered cyclic carbonates and diamines for the formation of polyhydroxyruethanes (PHU)s were reported as early as 1957 [86]. These polymers possess an important number of hydroxyl groups in their backbone, which confers them specific features compared to regular PUs discussed above.

A catalyst is generally required to promote the reaction between the nucleophilic moiety of the monomer (alcohol or amine type) and the electrophilic center of the comonomer (carbonate or carbamate). There are evantually three ways to activate the reaction and facilitating the polymerization: a) increase the electrophilicity of the carbonate/carbamate center; b) increase the nucleophilicity of the amine/alcohol and c) a nucleophilic activation of the carbonate/carbamate (**Scheme 11**) [44].

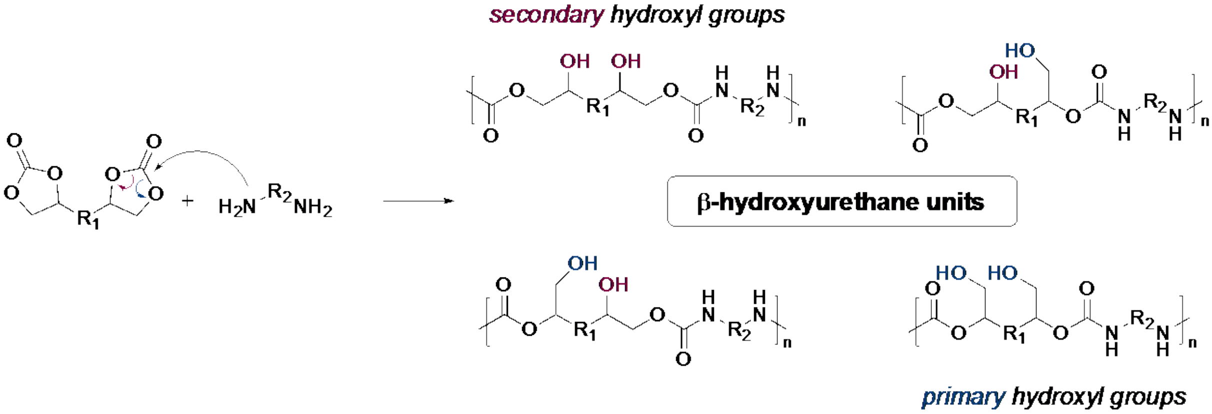
Several types of organic molecules have thus been employed as nucleophilic catalysts, such as tertiary amines, cyclic guanidines and amidines, Brønsted and Lewis bases/acids or phosphazenes.



Scheme 11. General activation mechanism for the organocatalyzed isocyanate-free synthesis of polyurethanes. Adapted from ref. [44].

4.1. Organocatalyzed step-growth polyaddition of cyclic dicarbonates and diamines

The most popular synthetic pathway toward NIPUs is based on the reaction between cyclic dicarbonates and diamines (**Figure 10.1**). In this context, 5-, 6-, 7 and 8-membered dicyclic carbonate monomers have been the most studied [87–98]. While 6, 7 and 8-membered carbonates prove more reactive than their 5-membered counterparts, and facilitate catalyst-free polymerization, their synthesis generally requires the use of toxic chlorinated carbonylating agents. On the contrary, synthesis of 5-membered cyclic carbonates can easily be performed from coupling CO_2 into epoxides [99]. In all these cases, the resulting polyurethanes structurally differ from conventional PUs by the presence in the β-position of the urethane bond of primary and/or secondary alcohols (**Scheme 12**) [100].



Scheme 12. Synthesis of polyhydroxyurethane from 5-membered cyclic carbonates and diamines. Adapted from ref. [100]

This section focuses on the organocatalysts employed in the polymerization of 5-membered cyclic carbonates.

Two reaction mechanisms have been proposed for the formation of urethanes by the aminolysis of cyclic carbonates. Tomita *et al.* and Garipov *et al.* suggested a mechanism through an amphoteric tetrahedral intermediate (**Figure 11**) [101,102]. Contrary to this work, Zabalov and Sardon *et al.* established with DFT calculations that hydroxyurethane formation may progress notably through a six-center ring intermediate based on the 5-membered cyclic carbonate and two amine molecules, one acting as catalyst and the other performing the nucleophilic attack (**Figure 11**) [98,103]. In this sense, the ring-opening reaction of cyclic carbonates may be accelerated through activation of the monomers. To this purpose, addition of Lewis acid catalysts may increase the electrophilicity of the cyclic carbonate group, while base catalysts may increase the nucleophilicity of the amine.

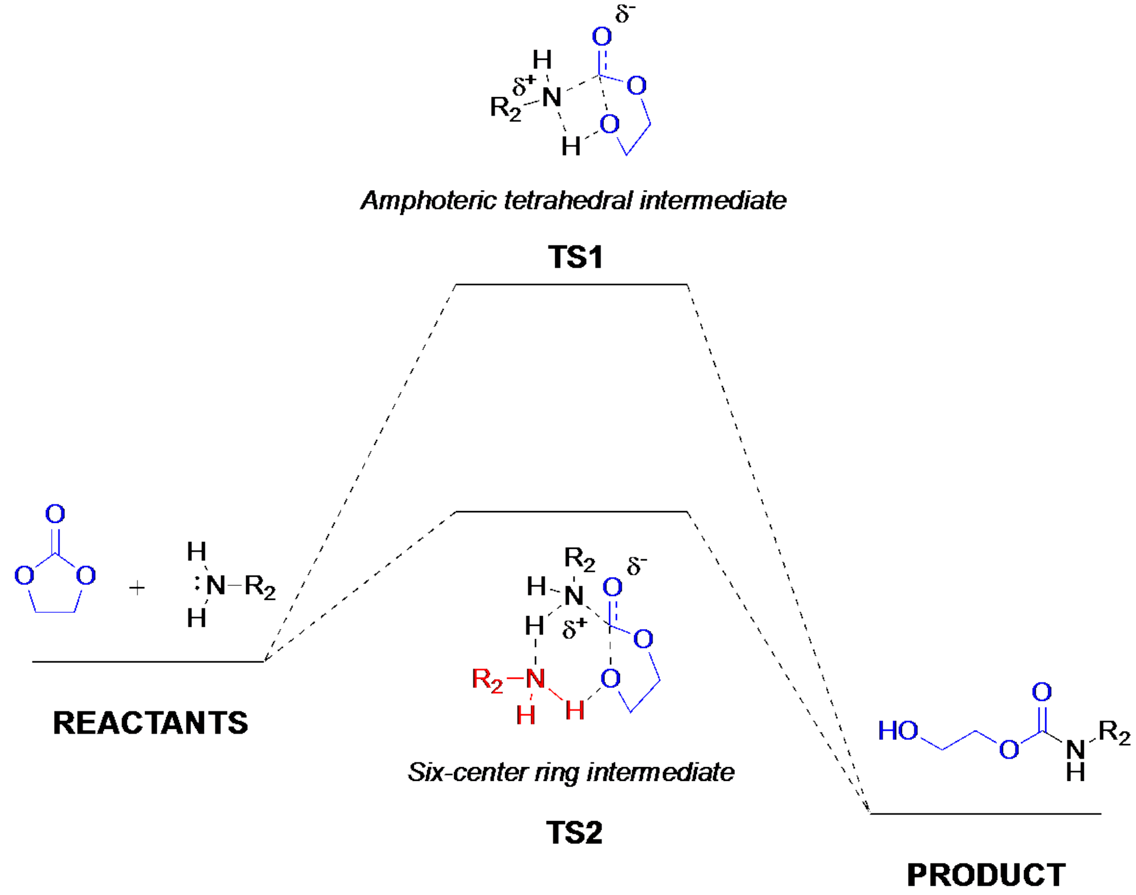
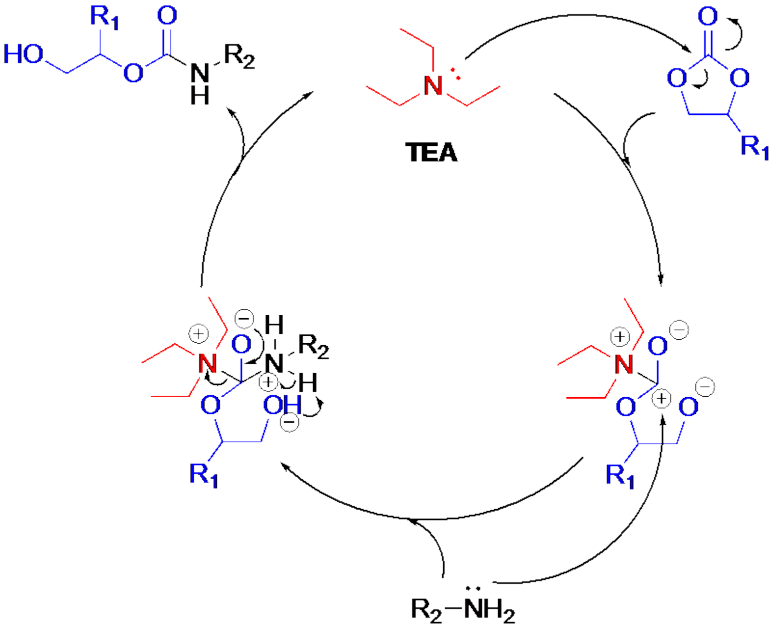


Figure 11. Proposed mechanism of the activation of cyclic carbonates with amines via an amphoteric tetrahedral intermediate (TS1) or via a six-center ring intermediate (TS2). Adapted from ref. [103].

Tertiary amines

In 2004, Diakoumakos and Kotzev presented the first examples of the use of organocatalysis for step-growth polymerization of cyclic carbonates and diamines through the addition of piperazin or TEA [104]. The polymerizations were performed using aromatic and aliphatic diamines in conjuction with a cyclocarbonate resin reacted in bulk at 25 and 60 °C. The addition of TEA (1 wt %) to the polymerization afforded a decrease in the activation energy by 17.5 % (5.23 kJ/mol), in comparison with the non-catalyzed reaction (6.33 kJ/mol), and the reactions reached full conversion faster at both temperatures. According to the authors, the mechanism of catalyst activation using TEA involves the nucleophilic activation of the carbonate moiety prior to nucleophilic addition of the monomeric amine (**Scheme 13**).



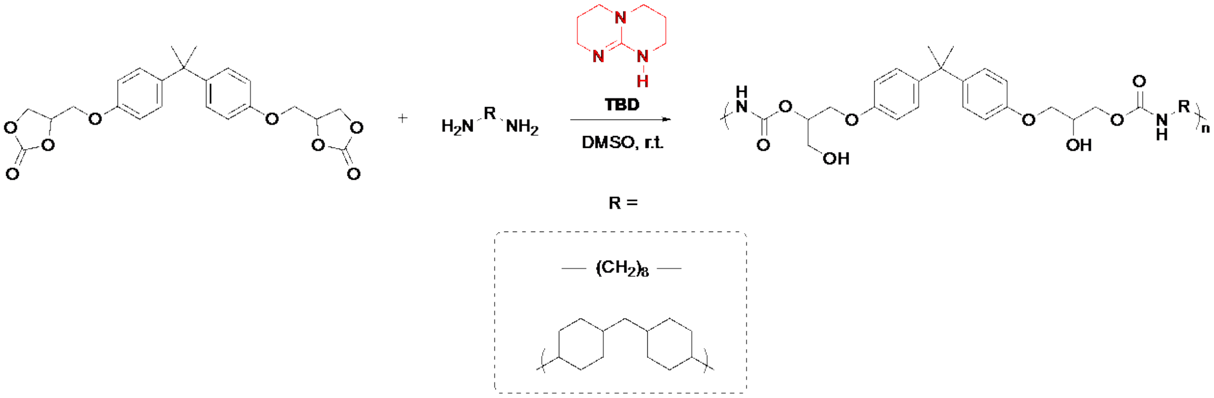
Scheme 13. Proposed catalytic activation of cyclic carbonates utilizing triethylamine. Adapted from ref. [104].

D'Mello *et al*. further characterized the catalytic capabilities of TEA upon application to the polymerization of naturally derived cyclic carbonates with 1,6-hexamethylenediamine and/or isophorone diamine [105]. The two diamines reacted with equimolar amount of cyclic carbonate in bulk at 120 and 150 °C. The authors discovered that the addition of TEA in conjuction with the higher temperatures afforded faster rates of polymerization with M_n ranging from 2.7 to 4.6 kg.mol^{-1} ($2.7 \leq Đ \leq 6.8$).

Cyclic guanidines and amidines.

Amidines and cyclic guanidines, such as DBU and TBD, are also powerful catalysts for the ring-opening polymerization of cyclic esters and carbonates [55]. In particular, TBD which is the most studied bicyclic guanidines, has been reported to act as a bifunctional activator via H-bonding in a cooperative fashion. Moreover, and as discussed in the previous section, amidines and guanidines have shown efficient activation of the reaction between isocyanate and alcohol.

Similarly, some authors reported the synthesis of polyhydroxyurethanes employing amidines and cyclic guanidines as catalysts. In particular, TBD proved efficient for the aminolysis reaction of cyclic carbonates with amines [106]. Lambeth and Henderson conducted the aminolysis model reaction of two different 5-membered cyclic carbonates, i.e. 4-phenyl-1,3-dioxolan-2-one (5CC1) and hexahydrobenzo[d][1,3]dioxol-2-one (5CC2) with hexylamine using TEA, TBD and DBU [87]. Carrying out the reactions in DMSO at room temperature, DBU and TBD improved the reaction rate in comparison to TEA. Specifically, while employing 5CC1 the reaction barely reached 20 % conversion after 15 h, but with 10 mol % of TBD full conversion was achieved within 2.5 hours. Applied to difunctional materials, the authors reported the achievement of PHUs with molecular weights up to M_n = 53.4 kg.mol^{-1} ($Đ$ = 1.4) (**Scheme 14**). In comparison, the non-catalyzed polyaddition yielded PHUs with much lower molecular weight (M_n = 5.43 kg.mol^{-1}, $Đ$ = 1.4).



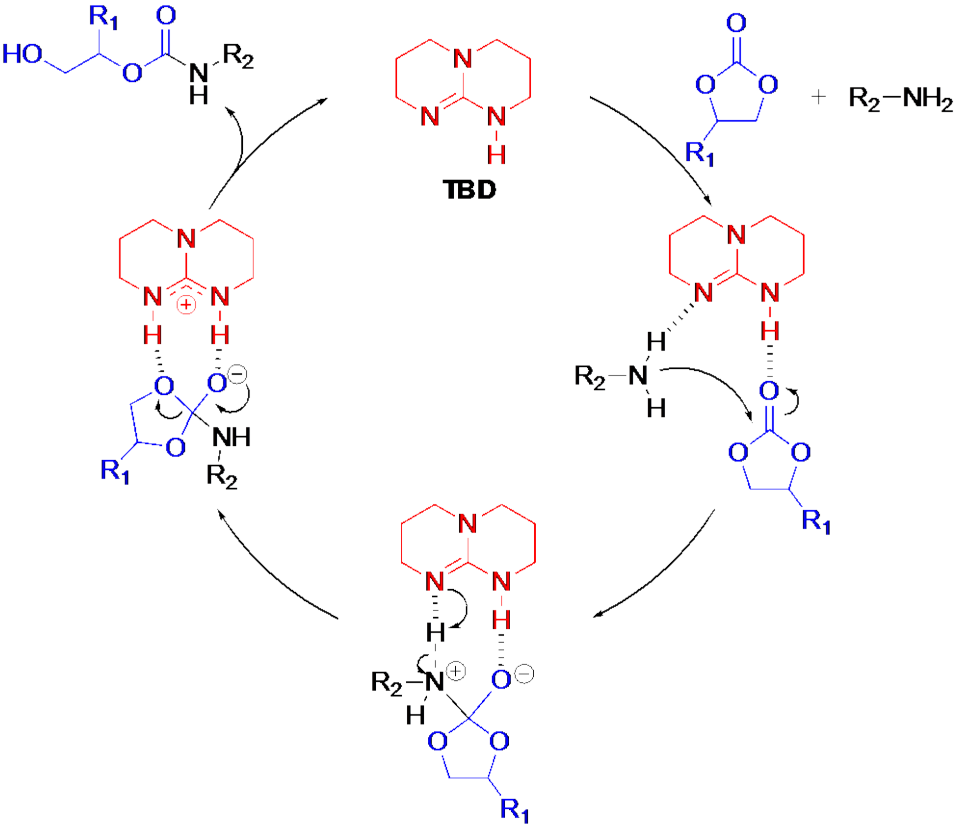
Scheme 14. TBD catalyzed solution polymerizations of diaminooctane or bis-(4-aminocyclohexyl) methane with a 5-membered cyclic dicarbonate at room temperature. Adapted from ref. [87].

Chen and coworkers investigated further these reactions by performing polymerizations at room temperature with or without TBD using three commercially available diamines [107]. In the case of hexamethylenediamine, high molecular weight PHUs (M_n = 30 kg.mol^{-1}, $Đ$ = 1.7) with close to 100 % conversion were achieved after 24 h through the addition of 5 mol % TBD. Slightly lower molecular weights (M_n= 23 kg.mol^{-1}, $Đ$ = 1.7) and lower percent conversions (93 %) were obtained upon removal of the catalyst. The results also demonstrated that the reaction rate improved using hexamethylenediamine rather than isophorone diamine probably due to the steric hindrance of isophorone diamine.

Caillol and coworkers further exploited the TBD catalyst to prepare NIPU-type foams. This study characterized the step-growth polymerization of diamines (Priamine1073 or

Jeffamine EDR148) with 5-membered cyclic carbonates (trimethylolpropane tris-carbonate or polypropyleneoxide bis-carbonate) [108]. Poly(methylhydrogenosiloxane) was used as blowing agent, which reacted with the diamines releasing dihydrogen that expanded the NIPU materials in the presence of 5 mol % catalyst.

A H-bonding mechanism for catalytic activation using TBD has been hypothesized based on previous ROP literature for cyclic carbonates (**Scheme 15**). However, recent studies indicated that a nucleophilic activation mechanism may dominate instead [63].



Scheme 15. Proposed hydrogen bonding activation mechanism of TBD-catalyzed step-growth polymerization of cyclic carbonates.

Phosphines and phosphazenes

Andrioletti and coworkers investigated the use of stronger bases, such as different phosphine and phosphazene derivatives (triphenylphosphine and *t*-BuP$_2$), for the aminolysis of propylene carbonate with cyclohexylamine at room temperature [106]. While these organo-compounds proved to effectively activate the conventional reaction between diisocyanate and diols, they appeared ineffective for NIPU formation. For example, 5 mol % of 2-tert-

Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) catalyst, only achieved a maximum conversion of 24 % within 1 hour.

Thiourea

Urea and thiourea derivatives represent another popular class of hydrogen-bonding catalysts that have been utilized successfully in a large variety of organocatalytic transformations in molecular chemistry, as well as in organocatalyzed ring-opening polymerization processes [109,110]. Especially, these Brønsted acids form hydrogen-bonded complexes with Lewis basic substrates, such as carbonate moieties, *via* bidentate binding interactions (**Figure 12**) [109,111].

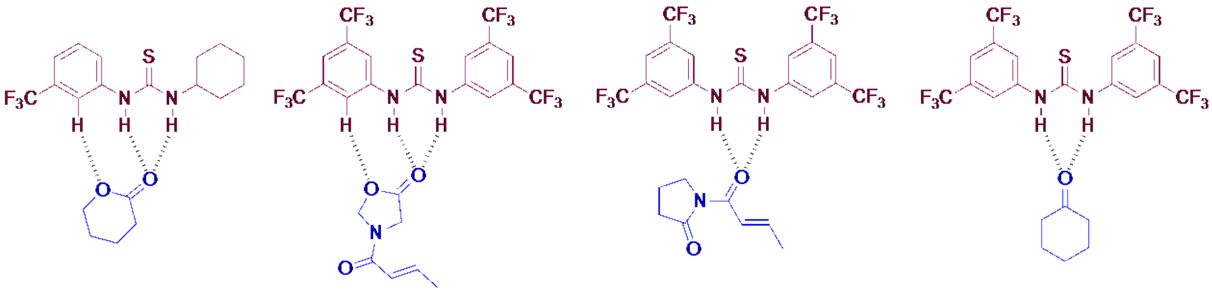


Figure 12. Examples of bidentate hydrogen bonds for different thiourea-carbonyl substrates complex as determined by NMR and computational results. Adapted from ref. [111].

In particular, ureas and thioureas bearing 3,5-bis(trifluoromethyl)phenyl rings were extensively studied due to the high acidity that results in these double H-bonding molecules. This acidity results from the strong σ-electron withdrawing properties. Overall, the urea derivatives exhibit lower acidity relative to the thioureas, as indicated by the pKa values in **Figure 13** [112]. Moreover, these compounds possess the advantage of being easily prepared from the reaction between iso(thio)cyanate derivatives and amines.

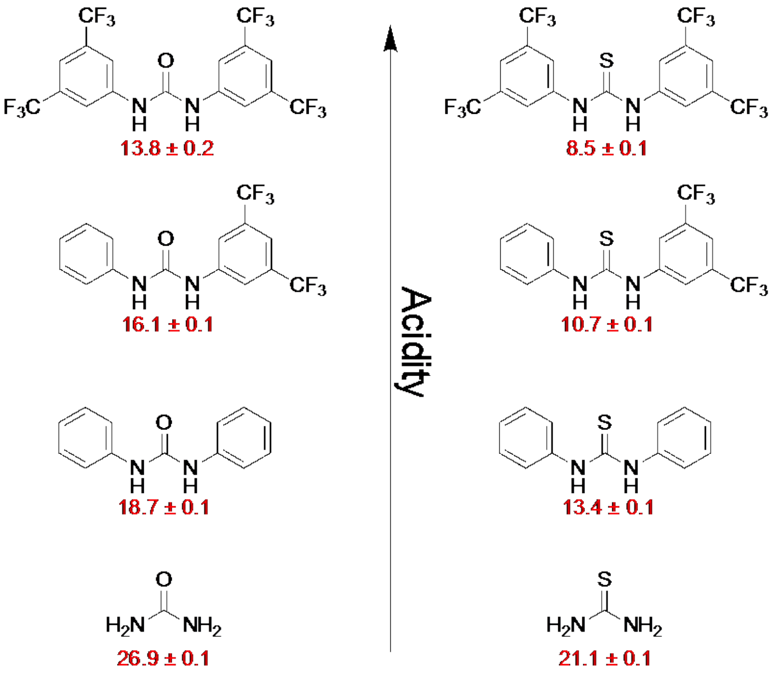


Figure 13. The effect of the 3,5-bis(trifluoromethyl)phenyl rings on the acidity of various ureas and thioureas. pKa values determined in DMSO. Adapted from ref. [112].

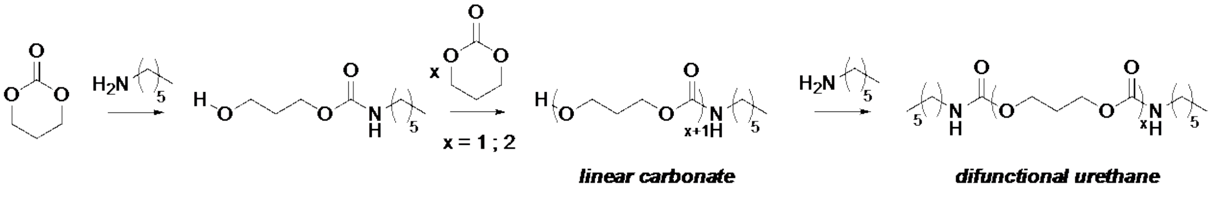
In 2014, Blain *et al*. examined the catalysis of aminolysis reactions between a range of amines and different cyclic carbonates with thioureas. They reported the use of two different thioureas as organocatalysts, namely, 1-(3,5-bis(trifluoromethyl)phenyl)-3-butylthiourea and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea [106]. Employing propylene carbonate and cyclohexylamine as model compounds, the authors found that the thioureas exhibited activities equivalent to TBD at a catalyst loading of 5 mol %. Both catalysts achieved > 60 % conversions after only 1 h when reacting at room temperature. Interestingly, the cyclohexylphenyl-based thiourea outperformed TBD at low catalyst loading.

The same group investigated a wide variety of urea and thiourea derivatives as organocatalysts for the aminolysis reaction of propylene carbonate with cyclohexylamine [113]. The reaction was performed in bulk at room temperature for 10 h. They discovered that the catalytic activity of the different thio(urea)s were mainly governed by their acidity (**Figure 13**). In the case of thioureas, deprotonation occured when utilizing catalysts with high acidity inhibiting activation and resulting in low monomer conversions. Alternatively, catalysts with low acidity were not a strong enough activating agent to promote nucleophilic attack. Contrary to the difficulties of thioureas, higher conversions were achieved when utilizing aromatic urea derivatives. The lower acidity of these catalysts limited the deactivation mechanism that inhibited thiourea use.

These limitations did not prevent Caillol *et al.* from utilizing thioureas in the room temperature synthesis of isocyanate-free polyurethane foams [114]. These foams were synthesized through copolymerization of polypropylene oxide bis-carbonate, trimethylolpropane tris-carbonate, and Jeffamine EDR148 with 1 mol % catalyst (cyclohexylphenyl-based thiourea).

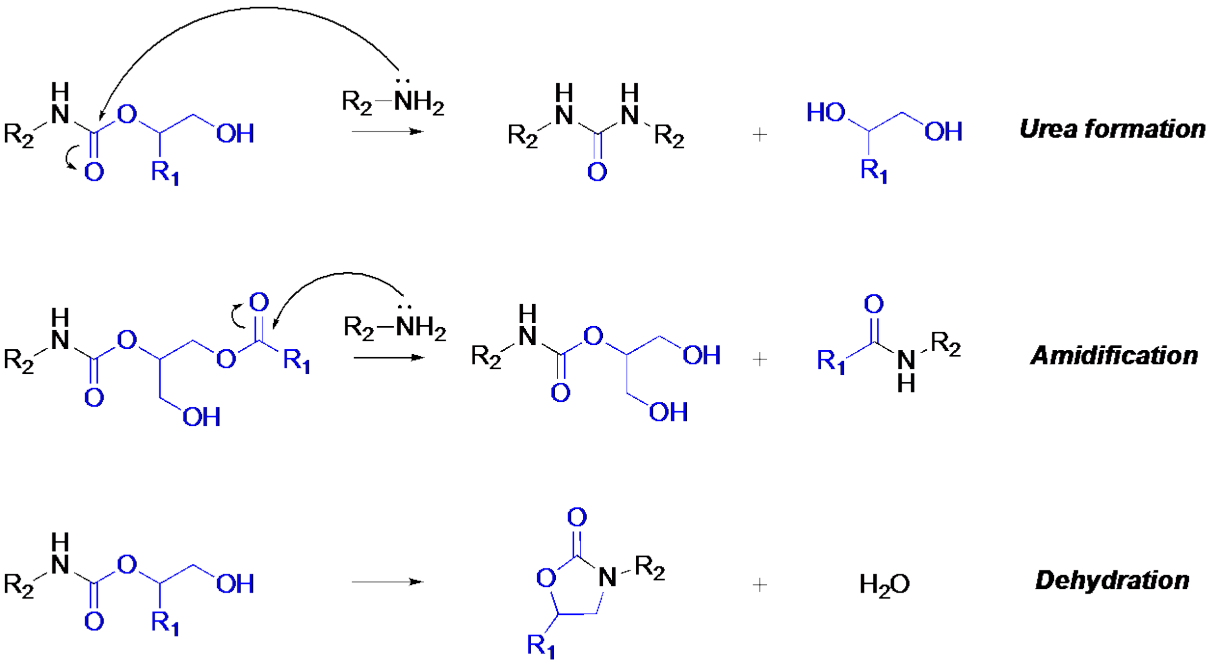
Even if thioureas act successfully as organocatalysts for PU synthesis, they suffer from a lack of commercial availability and their synthesis could raise some health concerns. Currently these molecules require the use of isothiocyanate or isocyanate starting materials that are generally produced from thiophosgene or phosgene.

Despite the successful synthesis at room temperature of PHU (or NIPUs) using TBD or thiourea catalysts, a few authors employed cyclic carbonates with more than 5-membered rings. For instance, Lambeth and coworkers conducted a detailed study of the aminolysis model reaction of trimethylene carbonate (TMC) and hexylamine using 10 mol % of different organocatalysts, namely TBD, DBU, 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea) and phenolic derivative [115]. Overall only thiourea and TBD enabled a dramatic increase of the reaction rate, compared to the phenolic compounds and non-catalyzed reaction. Polymerization between a carbonate derivative of di(trimethylolpropane) and diaminopentane yielded a NIPU with M_n up to 42.9 kg.mol^{-1} ($Đ$ = 2.1) in presence of thiourea catalyst at 50°C. Although the reaction rate could be significantly enhanced, molecular weights were limited due to side reactions, especially gelation resulting from the ring-opening reaction of TMC with pendant hydroxyl group, occurring during the reaction (**Scheme 16**).



Scheme 16. Side reactions occurring during the aminolysis of TMC with hexylamine explaining the gelation occurring in polymerization as determined by ^{1}H NMR and mass spectroscopy. Adapted from ref. [115].

As described in previous studies by Besse *et al*. and Lamarzelle *et al*., the use of organocatalyst in harsh polymerization conditions for enhancing the reactivity of 5-membered cyclic carbonates usually implies the formation of secondary reactions [93,116]. In the presence of primary amines, urethane groups are indeed prone to urea formation. Moreover, ester-containing monomer can be subjected to amidification. It has been shown that oxazolidinones resulting from the dehydration of hydroxyurethanes can also be formed (**Scheme 17**).



Scheme 17. Possible side reactions between 5-membered cyclic carbonate and amine: a) urea formation, b) amidification and c) dehydration. Adapted from ref. [93].

Sardon and coworkers recently took advantages of the urea side reactions occurring during the organocatalyzed polymerization of five-membered dicyclic carbonates and diamines, to access a range of poly(hydroxyurea−urethane)s (PHUUs) with precise urethane to urea ratio in a one-pot process. The as-formed PHUUs exhibited improved mechanical properties in comparison with the corresponding PHUs [117].

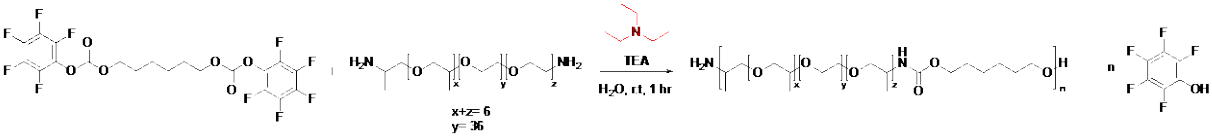
Although the step-growth polyaddition of cyclic dicarbonates and diamines represents an attractive alternative to isocyanate-free polyurethanes, more work is needed to obtain good control over the polymerization and limitation of side products. Most authors agree on the fact that temperature, initial concentration of the reactants, and solvent play a pivotal role in this polymerization together with the catalyst. The increase of the reaction temperature leads to a higher reaction rate and much better conversions but alternatively high temperatures (100 °C) yield side products. Still there is a need to search a selective molecule, *e.g.* a Lewis acid or a Lewis base, capable of catalyzing the aminolysis of cyclic carbonates without favoring the side reaction between the pending alcohol of polyhydroxyurethanes and cyclic carbonates.

4.2. Other isocyanate-free methods to obtain polyurethanes by step-growth polymerizations using organocatalysis

Organocatalyzed step-growth polycondensation of linear activated dicarbonates and diamines

Another synthetic pathway described in the literature to access NIPUs involves the polycondensation reaction between linear activated dicarbonates and diamines (**Figure 10.2**).

In 2013, Hedrick *et al.* reported an efficient method to prepare PEG-based NIPUs in water using polycondensation of a highly reactive linear pentafluorophenyl dicarbonate and Jeffamine (**Scheme 18**) [118]. The polymerization was carried out at room temperature for 1 hour in presence of TEA catalyst. This polymerization achieved NIPUs with molecular weight in the range of M_n = 15-16.5 kg.mol^{-1} ($Đ$ = 1.9). The authors suggested that, due to the high reactivity of the employed carbonate, the urethane formation occurred before decomposition of the carbonate in water. One drawback of this process is the release of toxic pentafluorophenol as side-product in the reaction mixture, requiring dialysis to purify the polymer prior to its final application.



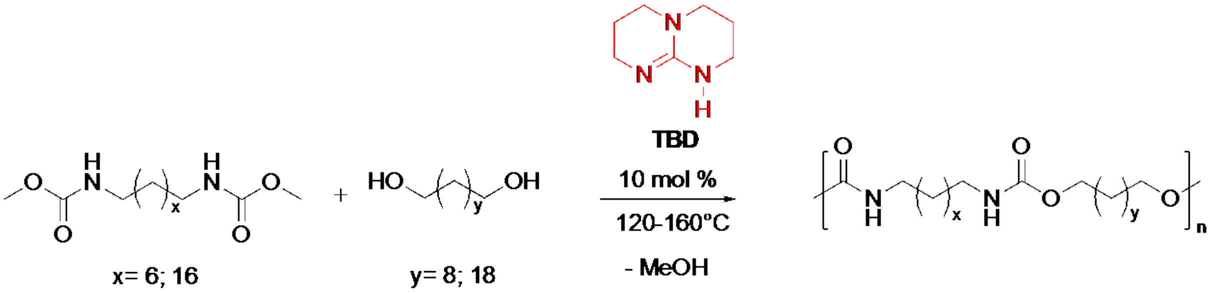
Scheme 18. Synthesis of a linear pentafluorophenyl dicarbonate and Jeffamine based polyurethane utilizing TEA. Adapted from ref. [118].

Following the same concept, Sardon and coworkers developed a one-pot process for the preparation of NIPU nanoparticles based on linear activated dicarbonates and diamines, using surfactant-assisted interfacial polymerization [119]. Activated pentafluorophenyl dicarbonates were polymerized with poly(oxyethylene) (bis)amine by interfacial polymerization (H_2O/DCM mixture) in the presence of sodium dodecyl sulfate as anionic emulsifier. This afforded NIPUs with M_n = 27 kg.mol^{-1} which enabled the formation of a range of nanoparticles with sizes from 200−300 nm. Nucleophilic attack on the dicarbonate was enabled through the TEA facilitated deprotonation of the diamine. Although this represents a unique strategy that can be implemented in water, the utilization of pentafluorophenol derivatives limits its industrial implementation, not only because of their prohibitive price of but also due to the tedious purification process.

Organocatalyzed step-growth polycondensation of linear activated dicarbamates and diols

Another isocyanate-free approach to PUs involves the reaction between linear activated dicarbamates and diols (**Figure 10.3**). Due to the low reactivity of diols compared to diamines, this reaction has been less studied in the literature. In addition, weak tertiary amines, such as TEA or DABCO, are not strong enough to obtain decent molecular weights.

Unverferth and coworkers utilized TBD as a catalyst in the polymerization of the main fatty acid of castor oil, ricinoleic acid derived dimethyl dicarbamates, and diols as illustrated in **Scheme 19** [120]. The authors noted that degradation of the catalyst and monomers occurred when utilizing high reaction temperatures (160 °C) but lower temperatures (110 °C) inhibited conversion resulting in low molecular weight. In order to circumvent this, the authors decided to add 0.1 equivalent of TBD in three increments, while increasing gradually the temperature from 120-160 °C. The reactions were performed under continuous vacuum to remove the methanol condensate pushing the equilibrium toward the formation of polyurethanes. This optimized procedure achieved PHUs with molecular weights of up to M_n = 24.6 kg.mol^{-1} ($Đ$ = 2.0).



Scheme 19. Polymerization of diols and ricinoleic acid derived linear dicarbamates utilizing TBD catalyst. Adapted from ref. [120].

Similarly in 2014, Firdaus and Meier performed the step-growth polycondensation of limonene based linear dicarbamates with various diols in bulk at 120 °C, using 5 mol % of TBD [121]. Once again, the group applied continuous vacuum to efficiently remove methanol. Using limonene derived diols, NIPUs with molecular weight around $M_n = 7.9$ kg.mol^{-1} ($Đ = 1.9$) were obtained after 16 hours of reaction. No further molecular weight increase was observed over longer reaction times. According to the authors, the steric hindrance of these diols, due to the presence of the cycloaliphatic group, could account for the limited molecular weight. This was verified by obtaining slightly higher molecular weight PHUs ($M_n = 8.7$-12.6 kg.mol^{-1}, $Đ = 1.8$-2.1) after employing less hindered long chain diols.

Using the same transurethanization process, Duval *et al.* synthesized novel renewable NIPUs based on dimethyl carbonate [122]. Dicarbamate monomers were first prepared from the reaction between dimethyl carbonate and different diamines using TBD as catalyst. Then, the transurethanization reactions between the carbamate monomers and different linear and branched diols were performed in bulk and under continuous flow of nitrogen with 10 mol % of TBD or 5 mol % of potassium carbonate (K_2CO_3). As described by Unverferth, the polymerization temperature was increased gradually from 120-160 °C to avoid monomer degradation [120]. Due to solubility issues, only the molecular weight of the branched PUs could be assessed by GPC. PUs synthesized from carbamate based on 1,10-diaminodecane and methyl ricinoleate-based diol in the presence of TBD, exhibited molecular weights up to $M_n = 6.6$ kg.mol^{-1} ($Đ = 1.3$). Thanks to the higher thermal stability of K_2CO_3, the same polymerization performed at 200 °C using 5 mol % of K_2CO_3 led to PUs with higher molecular weight ($M_n = 13.9$ kg.mol^{-1}, $Đ = 1.9$). As further example, PUs with molecular weight of $M_n = 10$ kg.mol^{-1} ($Đ = 2.7$) were achieved employing priamine-based carbamate and 1,10-

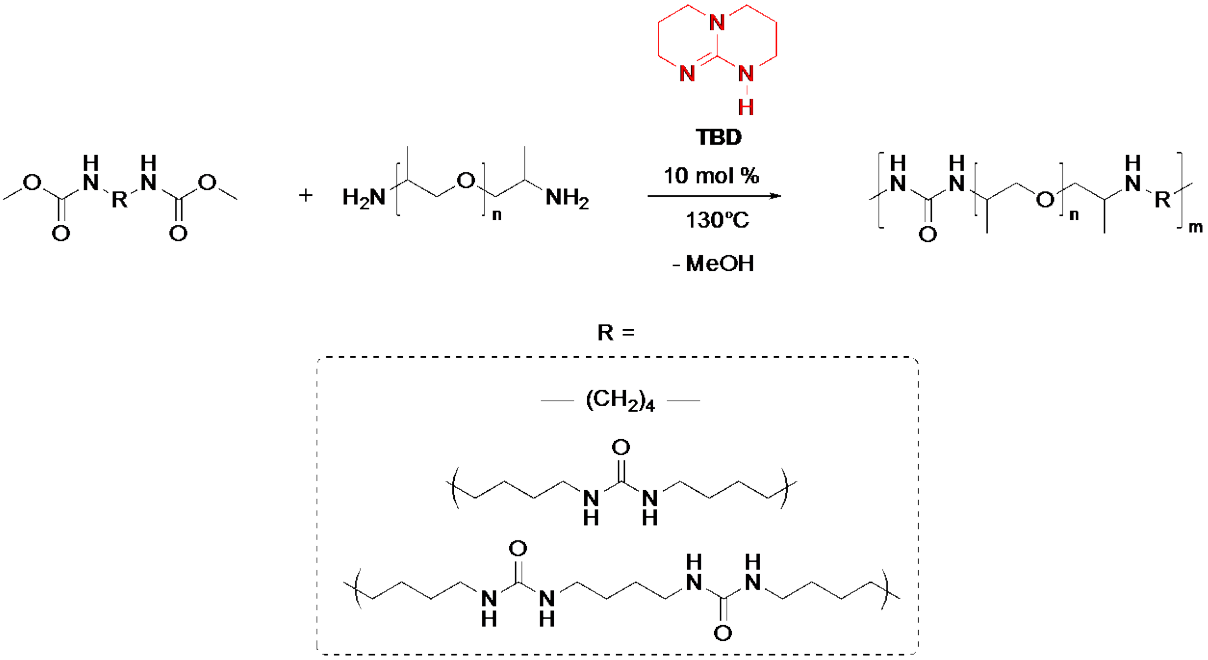
decanediol, with TBD. These results revealed that both K_2CO_3 and TBD were efficient catalysts for transurethanization reactions.

The same group also prepared photo-crosslinkable materials from allyl terminated renewable NIPUs and polyureas. Dicarbamates were first synthesized by transurethanization of diamines with dimethyl carbonate and subsequently reacted with excess diamines or diols to provide the corresponding methyl carbamate-terminated NIPUs and amine-terminated polyureas. Reaction with 9-decen-1-ol and 10-undecenoic acid led to the allyl-functionalized polymers. All reactions were performed in bulk at 140 °C for 6 h with 10 mol % of TBD [123].

In summary, among all nitrogen-containing bases tested, TBD proved to be an efficient catalyst, not only for the well-studied step-growth polyaddition of cyclic carbonates with diamines, but also for the transurethanization between dicarbamates and diols. In contrast, tertiary amines, such as TEA, appeared to provide minimal enhancement to polymerization rates, presumably due to its lower basicity when compared to amidines or guanidines. Thanks to the wide variety of commercially available guanidine and amidine-based catalysts, as well as their ability to promote the polymerization under mild conditions, such molecules are attractive organocatalysts for the synthesis of non-isocyanate polyurethanes.

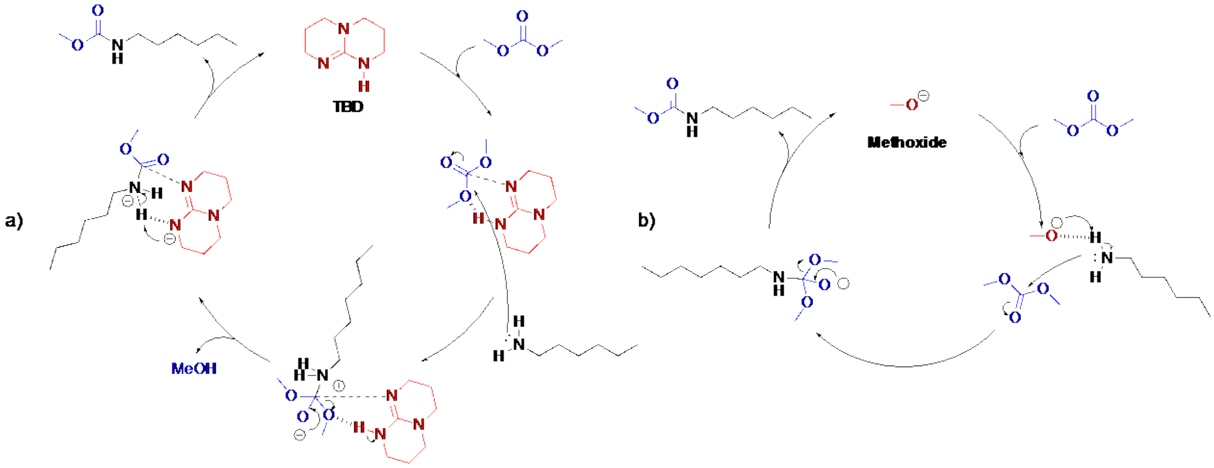
Organocatalyzed step-growth polymerization of non-isocyanate polyureas

The substitution of isocyanates with greener alternatives also comprises a substantial area of research in polyureas[57]. For example, in 2011, Koning and coworkers prepared a series of segmented polyureas starting from different dicarbamates and poly(propylene glycol)-based diamines (PPGda-400, M_n = 400 kg.mol-1 and PPGda-2000 M_n = 2 kg.mol^{-1}) using TBD as catalyst (**Scheme 20**) [124]. The authors first prepared three dicarbamate monomers using 1,4-diaminobutane and dimethyl carbonate as starting materials. Polycondensation reactions were performed at 130 °C in different solvents depending on the dicarbamates, with 10 mol % TBD. Overall, the results showed that all monomers led to polyureas and the molecular weights obtained were in the range of M_n = 27-36 kg.mol^{-1} ($Đ$ = 1.4-1.9).



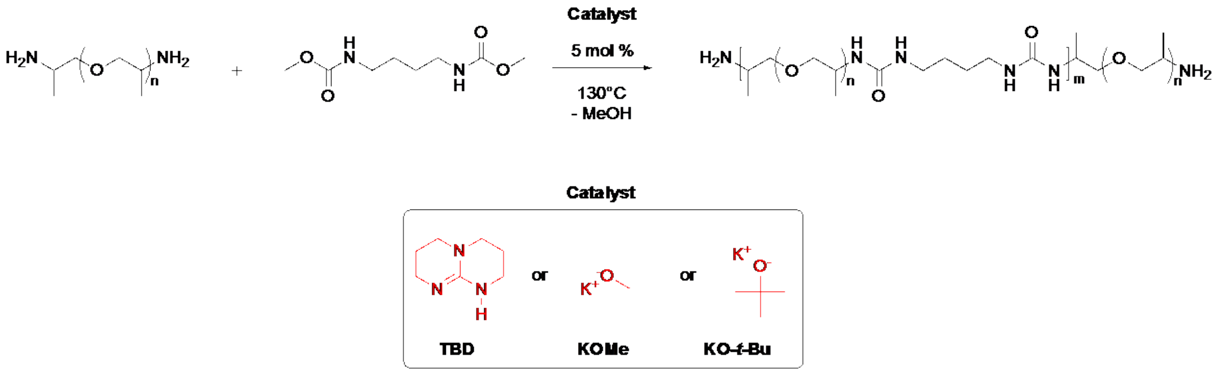
Scheme 20. Polymerization of segmented polyureas utilizing TBD catalyst and non-isocyanate based monomers, dicarbamates and poly(propylene glycol) diamines. Adapted from ref. [124].

Recently, the same group conducted a study to assess the catalytic activity of different organocompounds, such as guanidines (TBD, MTBD, TMG), amidine (DBU) phosphazene (P_2-Et), alkoxy-alkyl molecules (KOMe, KO-*t*-Bu), organo-alkyl-metal compound (KHMDS) along with transition-metal derivatives for the formation of polyurea at different temperatures starting from hexylamine and dimethylcarbonate [125]. Among all tested catalysts, KOMe, KO-*t*-Bu and KHMDS showed the best results, explained by the generation of an alkoxide anion RO^- upon reaction with the alcohol ROH condensate which exhibits much more efficient activation than TBD. A proposed mechanism for the alkoxy-alkyl catalyzed model reaction was presented (**Scheme 21**). The higher basicity of KO-*t*-Bu (pKa = 19) and KHMDS (pKa = 26) compared to KOMe (pKa = 15.5), resulted in the bases reacting easily with the methanol condensate during the reaction to produce methoxide anions. Computational calculations by DFT with MeO^- as active species revealed an activation energy for the reaction between *N*-hexyl methylcarbamate and hexylamine of 75 kJ/mol, comparable to the experimental value calculated from the Arrhenius plot (73.2 kJ/mol). In comparison, the activation energies obtained without catalyst or with TBD are much higher (126 kJ/mol and 94.8 kJ/mol respectively). As expected, an increase in the temperature resulted in an increase in the reaction rate for the most active catalyst (KOMe – 70 °C – ~60 % conversion; KOMe – 100 °C – ~85 % conversion).



Scheme 21. Catalytic mechanism for the formation of urethane linkage from dimethyl carbonate and *n*-hexylamine using a) TBD and b) KOMe as organocatalysts. Adapted from ref. [125].

The activity of these catalysts was also tested in the polycondensation of poly(propylene glycol)-based diamine (M_n = 2 kg.mol^{-1}) with butylene biscarbamate (**Scheme 22**). Reactions were performed at 130 °C in the presence of 5 mol% TBD, KOMe, or KO-*t*-Bu catalysts. The authors found that the results agreed with observations made in the model reaction, in which the most active species is MeO^-. In this system, under argon, both KOMe and KO-*t*-Bu performed similarly to each other and better than TBD with molecular weights, M_n, reaching more than 90 kg.mol^{-1} and 15 kg.mol^{-1} respectively after 30 h of reaction. Under air however, these catalysts were less active than TBD due to the formation of KOH upon reaction with H_2O, which is completely inactive toward amine-carbamate reactions. Thus, TBD demonstrated much less sensitivity toward water than these alkali-based catalysts.



Scheme 22. Polycondensation reaction of poly(propylene glycol)-based diamine with butylene biscarbamate using organocatalysis. Adapted from ref. [125].

5. Other polymer families obtained via organocatalyzed step growth polymerization

Organocatalysts like TEA, TBD, DMAP or PTSA, have also been applied to the synthesis of less explored polymers, such as polyethers, polycarbonates and polyacetals. This section will focus on the development of these polymer families.

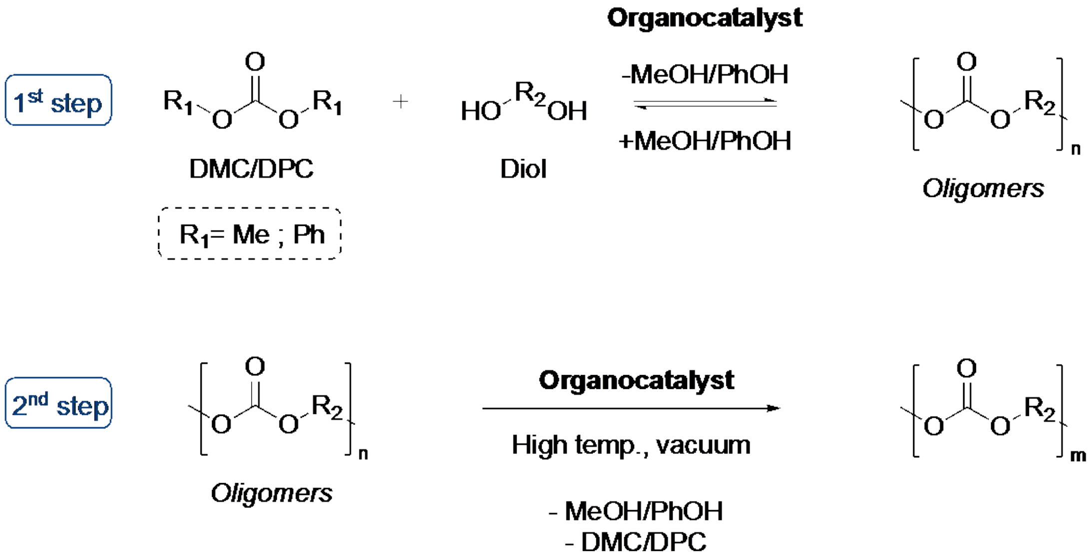
5.1. Polycarbonates

Regarding the literature, polycarbonate synthesis comprises two main polymerization techniques: (i) the ring-opening polymerization of cyclic carbonates and (ii) the polycondensation between dicarbonates and diols. In this section the focus will be placed on polycarbonates obtained by the polycondensation route. The discovery of polycarbonates dates to 1898, when Einhorn disclosed the transformation of hydroquinone and resorcinol derivatives into polymeric materials [126]. However, at the beginning of the 20th century the limited solubility of this polymer and its difficult processing restricted its study.

In 1953, the first aromatic polycarbonates were commercialized by Bayer and were widely used as engineering plastics, owing to their outstanding high impact, low scratch- and temperature-resistance [127]. Traditionally, polycarbonates were synthesized by interfacial polycondensation, between phosgene and sodium salts of bisphenol-A at 20-40 °C and atmospheric pressure. Weak organic bases, such as trimethylamine, were employed to accelerate the polycondensation reaction and achieved high molecular weights. The catalyst was hypothesized to act as a weak base activating the alcohol or as neutralizing agent to avoid the delivery of HCl to the environment. Continuous restriction on the use of phosgene derivatives, have pushed both industry and academia to develop phosgene derivative-free synthesis of polycarbonates. In this sense, phosgene has been replaced by dimethyl carbonate and diphenyl carbonate. In addition, some carbonylation agents, such as dimethyl carbonate can be synthesized using CO_2 as building block.

Thus, polycarbonate synthesis can be successfully performed through the polycondensation of dimethyl carbonate (DMC) or diphenyl carbonate (DPC) with a diol in a two-step process (**Scheme 23**). During the first reaction step consisting of the initial condensation, the temperature is maintained at 100-130 °C over a period of 1-24 hours until the equilibrium is reached. In this stage, hydroxyl and carbonate end groups react eliminating methanol, leading to low molecular weight oligomers ($< 1{,}000$ g.mol^{-1}). In the second step, the chain growth takes place by transesterification between hydroxyl and methyl/phenyl carbonate end groups in the presence of transesterification catalyst. High temperatures (150-350 °C) and high vacuum are normally required to remove all unreacted monomers and condensates. The mole ratio of this polymerization is crucial to enhance the conversion of the first step and to obtain high molecular weight polycarbonates during the second step. The aim is to increase the number of methyl/phenyl carbonate groups for the transesterification reaction, which are more reactive compared to hydroxyl groups. This can be achieved with an excess of dimethyl/diphenyl carbonate leading to higher molecular weight [128].

This methodology not only avoids the use of chlorinated reagents but is also performed in bulk avoiding the employment of organic solvents and hindering the formation of cyclic carbonates side products. Nevertheless, the reactivity of these two linear carbonates is much lower and the reaction must take place at higher temperature (150-350 °C), reduced pressure usually with the required addition of catalysts. Metal and alkali metals, such as NaH or NaOH, have dominated the field of polycarbonates obtained by step growth polymerizations [129–131].



Scheme 23. General route for the synthesis of polycarbonates via step-growth polymerization. Adapted from ref. [34,128].

New efforts in polycarbonate synthesis were oriented toward the design of novel organocatalysts that achieved high molecular weights. As in the case of non-isocyanate polyurethanes, there are three ways to activate the reaction: a) increasing the electrophilicity of the carbonate b) increasing the nucleophilicity of the alcohol and c) a nucleophilic activation of the carbonate [44]. Several classes of organic compounds, including tertiary amines, strong bases such as guanidines and amidines, *N*-heterocyclic carbenes and thiourea derivatives have been investigated in polycarbonate synthesis, as described in the following sections (**Figure 14**).

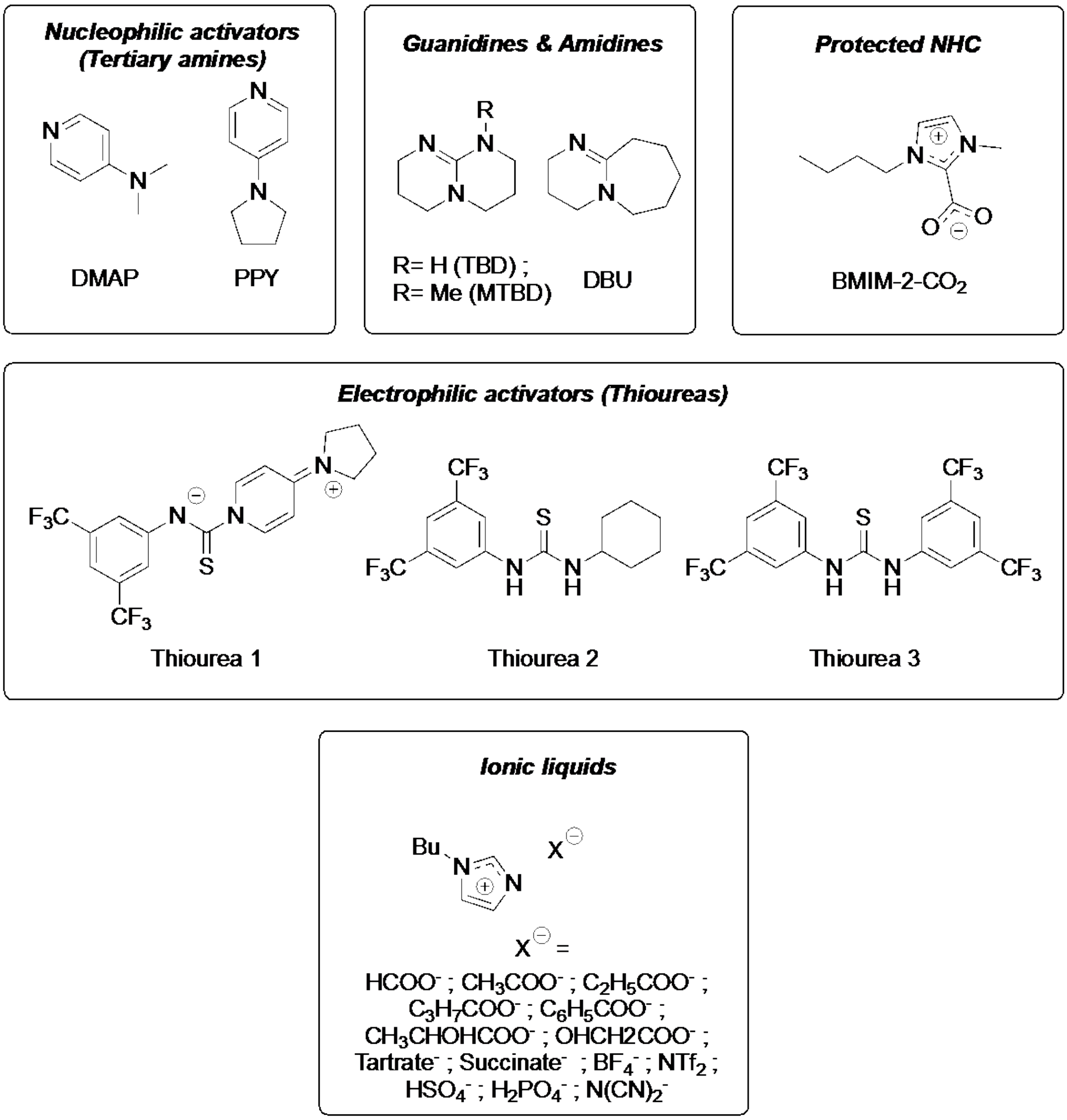
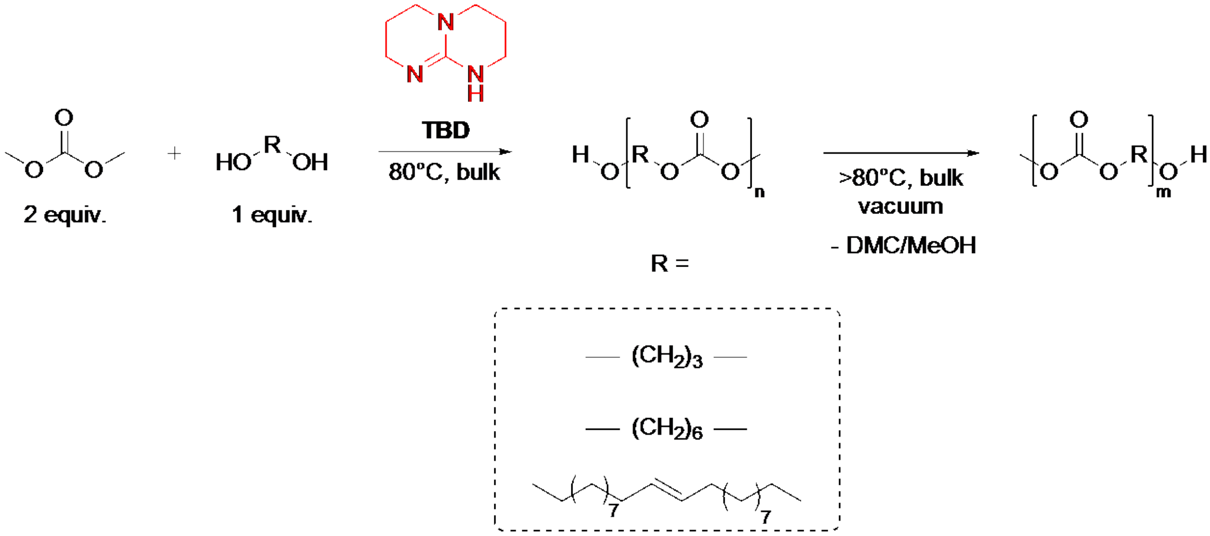


Figure 14. Conventional organic bases used as catalysts for step-growth polymerization of polycarbonates.

Cyclic guanidines and amidines

In spite of the success of weak organic bases, such as TEA, to mediate the synthesis of polycarbonates using phosgene or phosgene derivatives, the weak basicity of tertiary amines leads to limited molecular weights in presence of dimethyl carbonate and diphenyl carbonate. Stronger bases, such as guanidines and amidines, in particular, TBD, MTBD, and DBU have thus been investigated as potential catalysts. [33,34,132].

Meier *et al*. investigated the step-growth polymerization in bulk of 1,6-hexanediol and dimethyl carbonate in presence of TBD (**Scheme 24**) [33]. When using 0.5 mol % of catalyst, a polymer with M_n of 33 kg.mol^{-1} could be prepared. Increasing the TBD concentration to 1 mol % decreased the molecular weights. Studies by NMR spectroscopy demonstrated that at high TBD loadings, the terminal methyl carbonates were cleaved, forming terminal allyl carbonate groups. This study resulted in significant improvements toward the polymerization with regards to previously reported results for similar polymer, which obtained M_n of 11 kg.mol^{-1} from the polymerization of diethyl carbonate with 1,6-hexanediol catalyzed by immobilized Candida antarctica Lipase B.23.



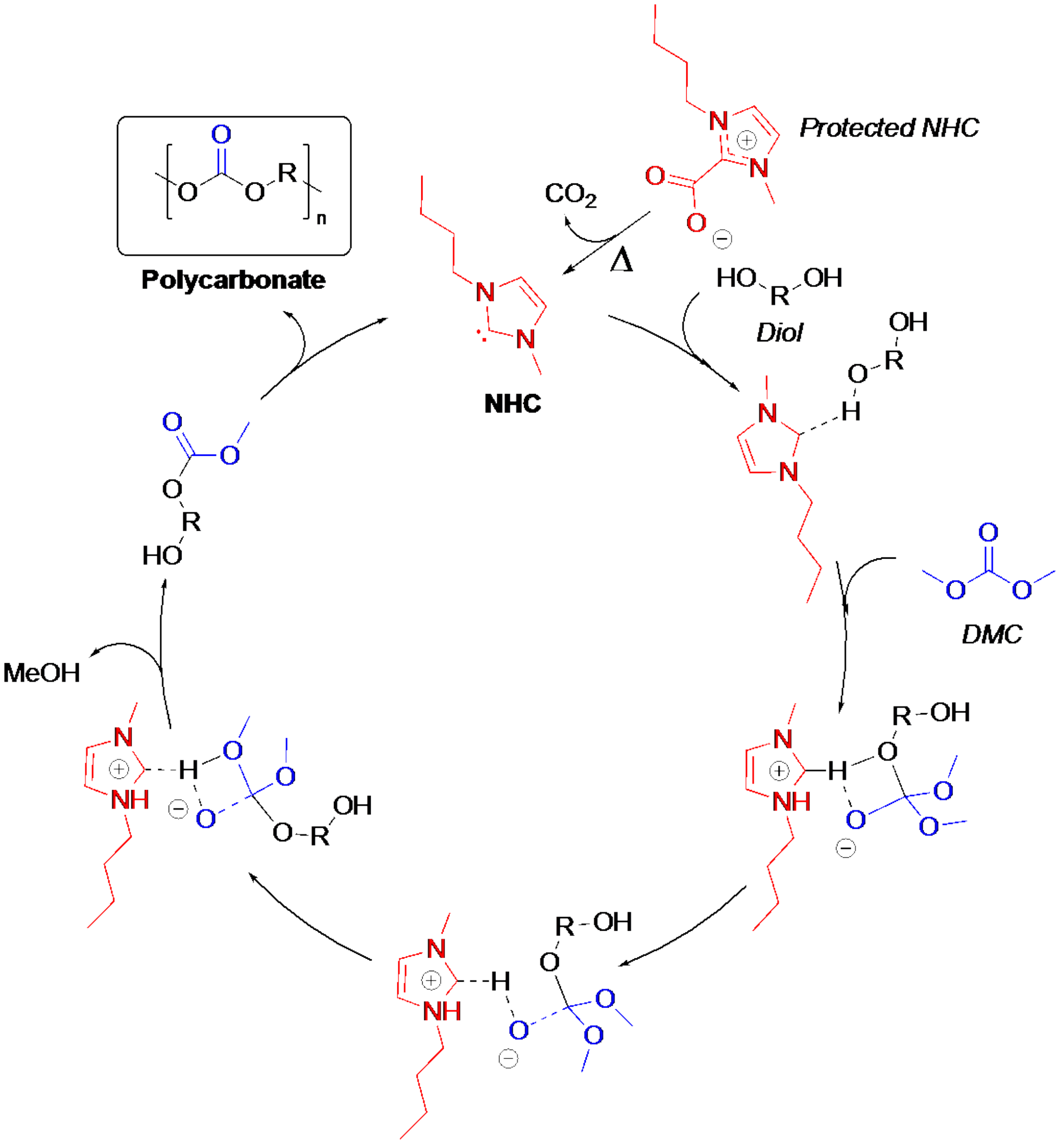
Scheme 24. Synthesis of polycarbonates utilizing TBD as catalyst and 1,6-hexanediol and dimethyl carbonate as monomers. Adapted from ref. [33].

More recently, Sun *et al*. investigated the effects of different organocatalysts on the synthesis of polycarbonates [34]. Comparing MTBD and TBD catalysts, polymers exhibited significantly higher molecular weight with MTBD. The MTBD catalyzed melt-polycondensation achieved M_n = 17 kg.mol^{-1}, whereas with TBD, molecular weights of 6.2 kg.mol^{-1} were obtained. While no explanation was provided, this behavior could be related to the formation of allyl carbonate groups in presence of TBD or to the dual character of TBD which plays a detrimental role such as in the case of polyurethanes.

In order to perform the polymerization at lower temperatures in solution, Malkoch *et al*. designed activated carbonates functionalized with carbonylimidazolide moieties [133]. This strategy allowed the preparation of a unique library of polycarbonates including (i) rigid, flexible and reactive polycarbonate backbones, (ii) molecular weights 5–20 kg.mol^{-1}, (iii) dispersities of 1.3–2.9 and (iv) a wide span of glass transition temperatures from −45 to 169 °C. DBU was found to be an excellent organocatalyst to mediate this polymerization. Sugar-derived polycarbonates from isosorbide and dihydroxyacetone were also prepared using 1 mol % of DBU. In all cases, polycarbonates exhibited quite similar molecular weights (M_n = 5 – 9 kg.mol^{-1}, $Đ$ = 1.5-2.0) [132].

N-Heterocyclic carbenes

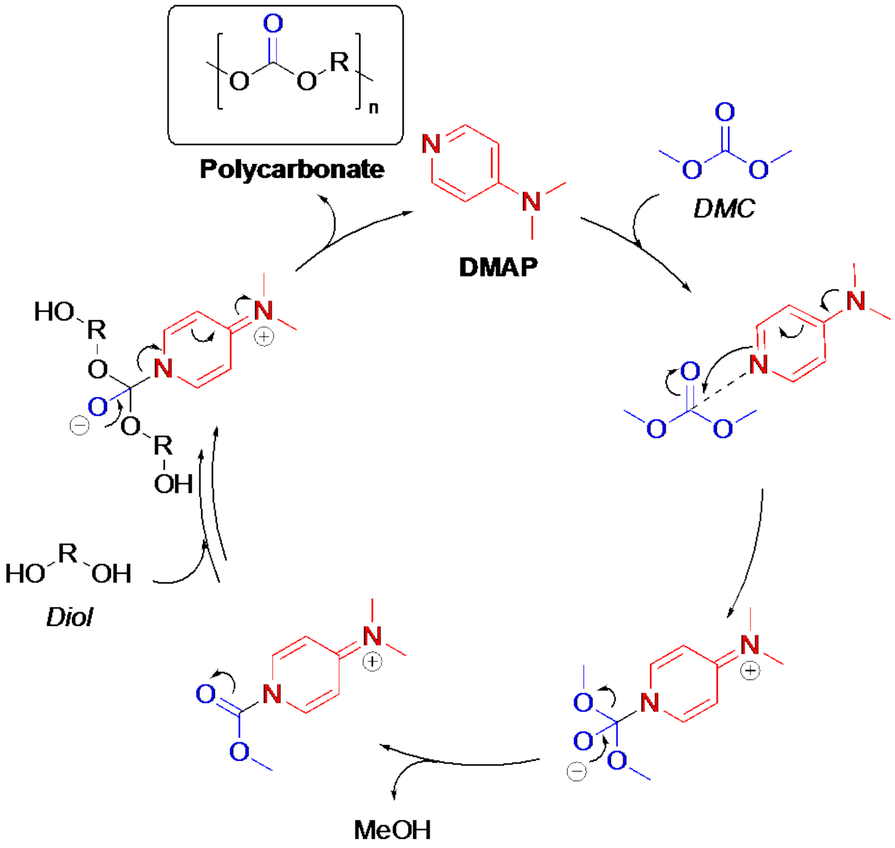
N-heterocyclic carbenes have attracted attention as versatile ligands and ligand-precursors for several sustainable routes, including ring-opening polymerization of cyclic carbonates. In this regard, Naik *et al*. and Bigot *et al*. investigated the synthesis of aliphatic polycarbonates in bulk using 1-n-butyl-3-methylimidazol-2-carboxylate protected carbenes in the presence of dimethyl carbonate and several diols [30,134]. The efficiency of the carbene was studied in different syntheses, with a loading of 1 mol % in respect to the monomer [30]. Polymers with M_n up to 7,400 g.mol^{-1} were obtained within 1 h 15 min. The polymerization was performed first by heating at 100 ºC for 15 min, and then at 150ºC for 1 h under reduced pressure. The authors hypothesized that the catalytic mechanism of the NHC occurred through decarboxylation to generate the carbene *in situ* which promoted hydrogen-bonding activation of the alcohol by the NHC to enable the formation of a polycarbonate (**Scheme 25**).



Scheme 25. Hypothesized mechanism for the *in situ* deprotection and catalytic activation of 1-n-butyl-3-methylimidazol-2-carboxylate protected carbenes in the polymerization of polycarbonates. Adapted from ref. [30].

Nucleophilic activator

Nucleophic activation of cyclic monomers for ROP has been demonstrated with the use of catalysts, such as 4-pyrrolidinopyridine (PPY) and 4-dimethylaminopyridine (DMAP) [135,136].

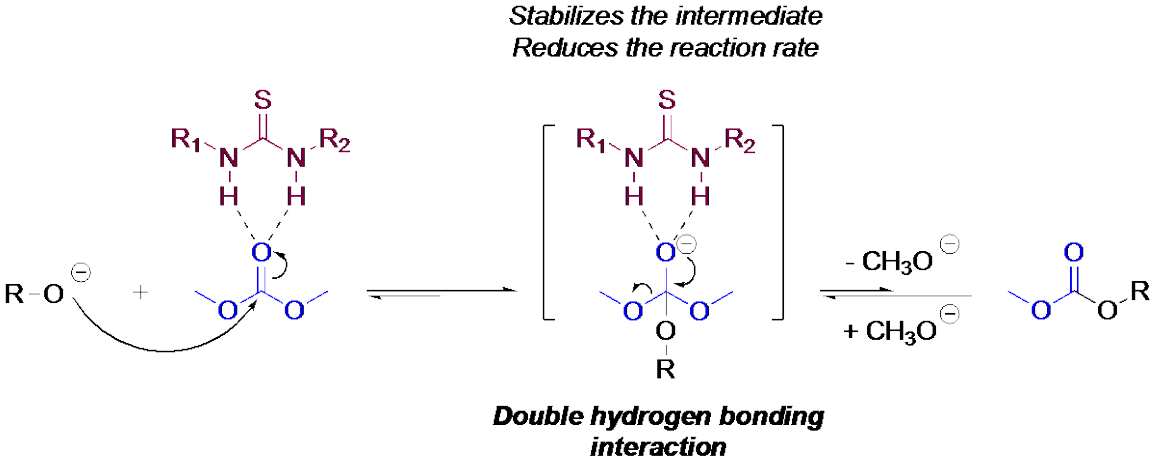


Scheme 26. Proposed nucleophilic activation mechanism of DMAP in the polymerization of polycarbonates. Adapted from ref. [135].

The application of DMAP to step-growth polymerizations has been demonstrated by different authors in the case of polycarbonates (**Scheme 26**) [34,137,138]. Sun *et al*. screened different catalysts and found that DMAP was the most active towards the promotion of polycarbonate synthesis [34]. This polymerization achieved high molecular weights (M_n = 52 kg.mol^{-1}) using a two-step synthesis at 170 °C and a catalyst molar ratio of 2:1:0.01 DMC:diol:DMAP. Similarly, Meabe and co-workers explored different parameters to optimize the polymerization [128]. This group demonstrated that polymerizations with longer diol oligomers required a higher mol % of DMC in the reaction. The authors further investigated the potential of these polycarbonates as polymer solid electrolytes for lithium batteries, and as alternatives to prepare biodegrable PEG-based polycarbonates. DMAP has also been investigated as catalyst for the reaction between aromatic diols and diphenyl carbonates. Haba and coworkers utilized 1 mol % DMAP in a high temperature reaction (up to 215 °C) between bisphenol-A and diphenyl carbonate. Unfortunately, these conditions did not afford high conversions in the polymerization [129]. Other nucleophilic activators, *e.g.* PPY, were also studied and only catalyzed the step-growth process in a modest fashion [34].

Electrophilic activators

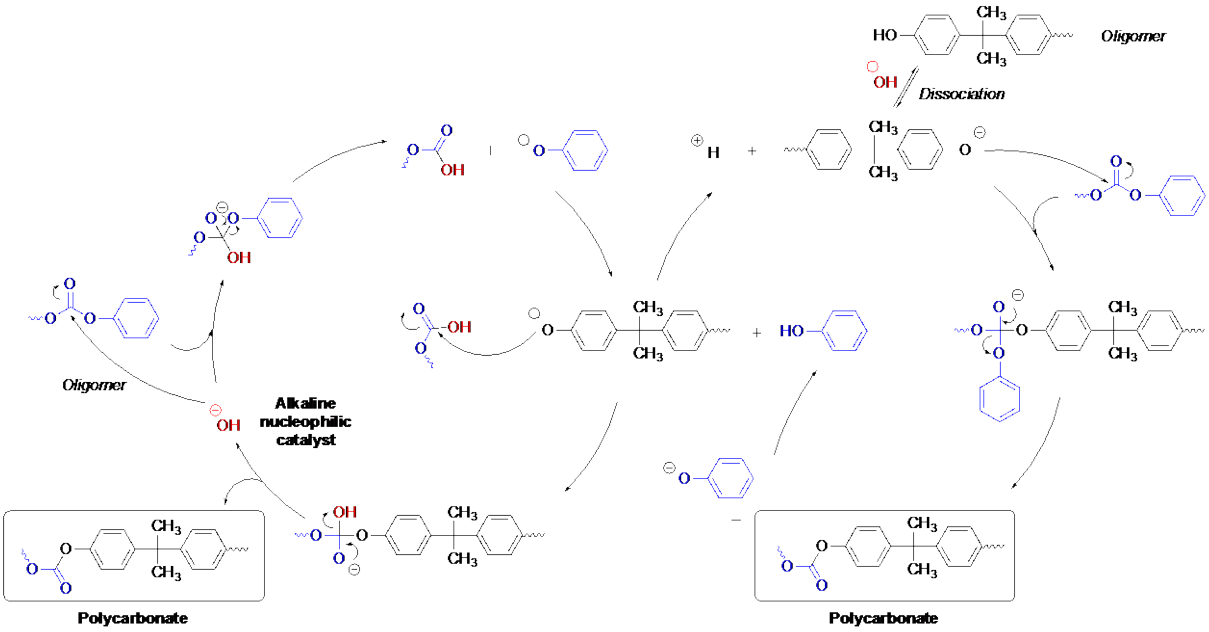
Thioureas have demonstrated considerable success in the catalysis of ROP of cyclic carbonates. This work drove Sun *et al.* to study a variety of thioureas as catalytic systems in the step-growth polymerization of polycarbonates based on 1,4-butanediol and DMC [34]. These polymerizations only achieved lower molecular weights when using DMAP or MTBD (16 and 17 kg.mol^{-1}, respectively). In an attempt to increase the molecular weight and the polymerization kinetics, the authors studied the novel use of a co-catalyst system combining thioureas with other base catalysts, such as MTBD. Unfortunately, polymerizations with these co-catalysts were largely unsuccessful and inhibited molecular weight growth. The authors proposed that stable intermediates were formed during the activation of the carbonyl with the thiourea catalyst reducing the propensity of the reaction to move forward (**Scheme 27**).



Scheme 27. Proposed stabilized intermediate formation in the catalysis of dimethyl carbonate with thiourea. Adapted from ref. [34].

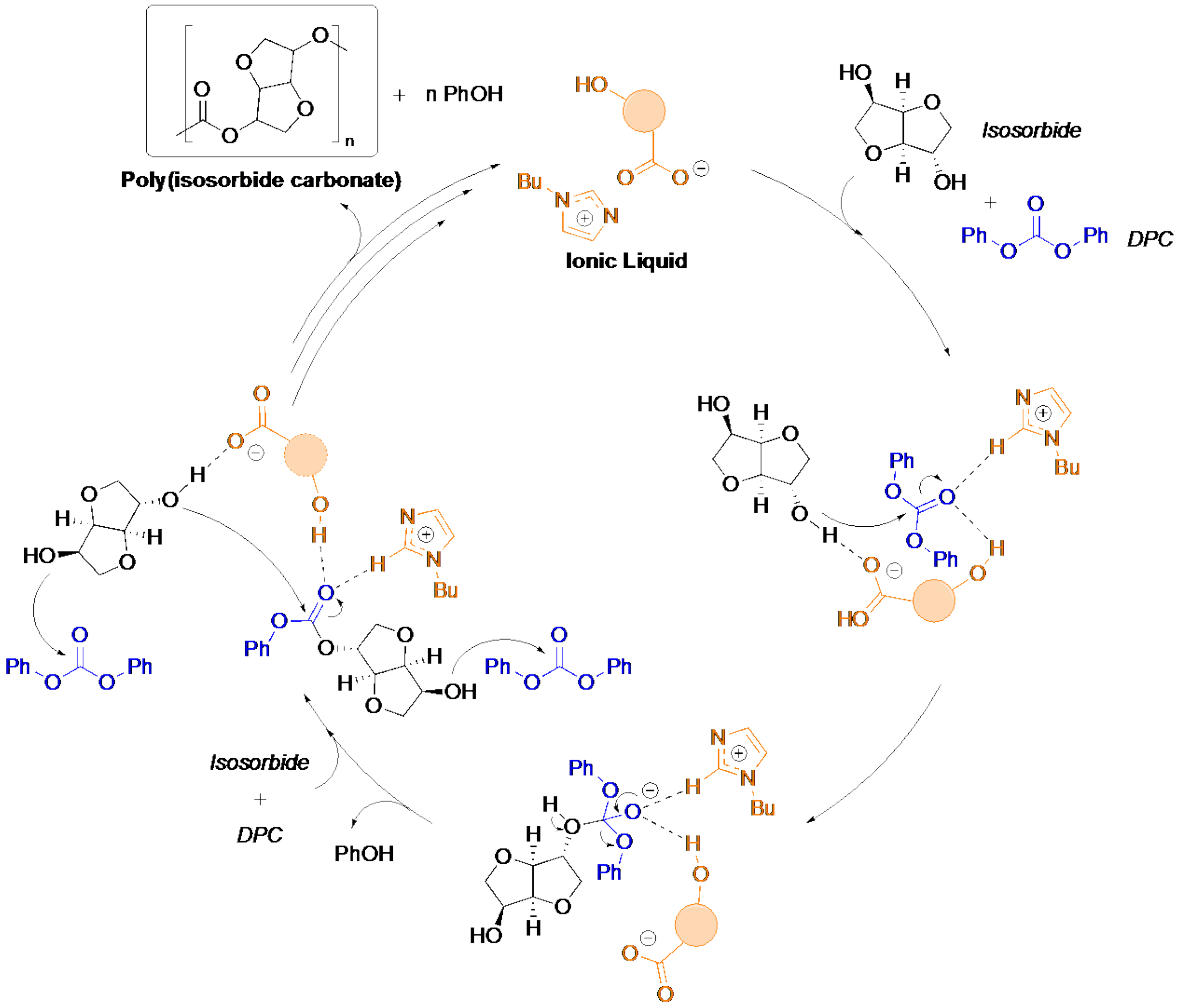
Dual catalyst based on ionic compounds

The high temperatures required to achieve high molecular weights is one main issue of this reaction. As recently reported by Flores *et al.*, use of DMAP at high temperatures resulted in coloured polymers [139]. In order to overcome this limitation, an alternative might be to use of ionic compounds possessing a superior thermal stability. Bi *et al.* thus studied the mechanism and kinetics of a model melt polycondensation between bisphenol-A and diphenyl carbonate, catalyzed by tetraethyl ammonium hydroxide [140]. This reaction can only take place at high temperature (150-350 °C) under reduced pressure to remove the phenol by-product. The catalyst acts as a base deprotonating the bisphenol-A alcohol to increase its nucleophilicity. The authors performed DFT calculations to demonstrate that the polymerization was favoured in presence of a base than without catalyst (**Scheme 28**).



Scheme 28. Proposed mechanism for the step-growth polymerization of diphenyl carbonate and Bisphenol-A using a base as catalyst. Adapted from ref. [140].

In order to obtain more sustainable polycarbonates, besides exploring non-metallic catalysts, polycarbonates based on naturally occurring synthons have been also prepared by step-growth polymerization. Diphenyl carbonate and isosorbide were thus polymerized using imidazolium-based ionic liquids as organocatalysts. [141] The reaction was performed in two steps, *i.e.* at 100 and 240 °C first, then under vacuum (<5 kPa) to obtain high molecular weight polymers (M_n = 34-75 kg.mol^{-1} and T_g 174 °C) [142]. The screening of different ionic liquids based on imidazolium demonstrated that to achieve high molecular weight poly(isosorbide carbonate)s, it was necessary to employ anions with stronger electronegativity which are able to hydrogen bond. Ma *et al.* proposed a cooperative nucleophilic-electrophilic mechanism for this reaction. The authors claimed the possibility of rapid electrophilic activation of diphenyl carbonate through a hydrogen bond of the imidazolium cation's hydrogen **(Scheme 29**).



Scheme 29. Proposed mechanism for the step-growth polymerization of diphenyl carbonate and isosorbide using imidazolium-based ionic liquids as organocatalysts. Adapted from ref. [142].

Organocatalysts thus appear as promising alternatives of organometallic catalysts, though achievement of high molecular weight polycarbonates by organocatalyzed step-growth polymerization remains an issue. While metal-based catalyzed polymerization leads to molecular weights higher than 100 kg.mol^{-1} (M_n = 150 kg.mol^{-1} using NaH) [130], it is indeed more problematic to reach molecular weights higher than 80 kg.mol^{-1} from organocatalysts. Imidazolium-based ionic liquids and DMAP prove the most attractive compounds in this context. The use of activated carbonates, as proposed by Malkoch *et al.*, might represent another opportunity to produce polycarbonates by organocatalysis, as it requires lower reaction temperatures. One drawback of this reaction, however, is the use of toxic imidazole that is produced as a side product; hence, polymers must be processed before the final application [133].

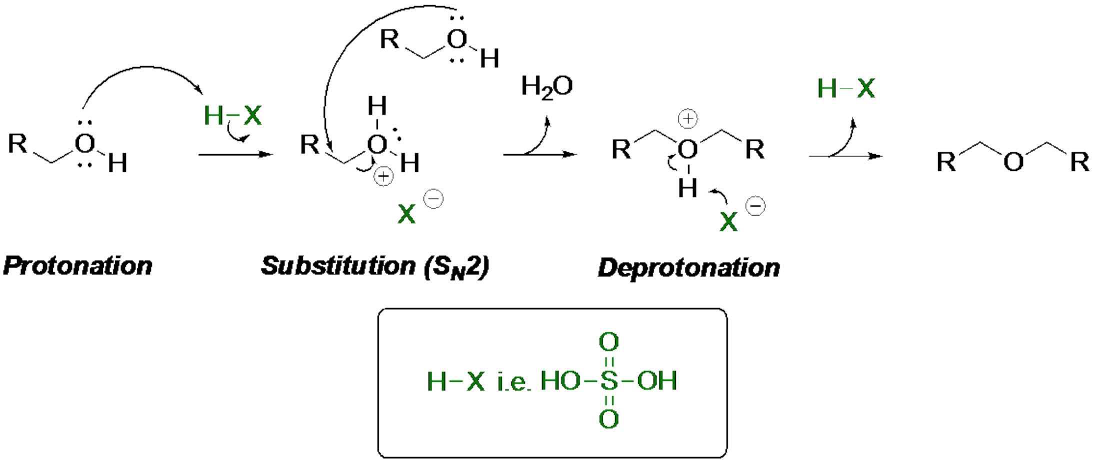
5.2. Polyethers

Ethers or oxyalkylenes are chemical compounds that contain R-O-R' bond, where R and R' comprise any alkyl or aryl moieties. Since their first synthesis by Wurtz in the 1860s, polyethers received tremendous attention due to their versatile synthesis, thermal and chemical stability, and multiple possible structural modifications. The properties of these materials range from liquid and amorphous to highly crystalline, depending on the polymer nature. Therefore, the range of applications for polyethers is broad and range from water-soluble surfactants and drug delivery vehicles to high engineering applications, such as solid polymer electrolytes in battery applications.

Among the different aliphatic polyethers, the most employed are poly(epoxide)s, poly(oxetane)s, and poly(tetrahydrofuran) prepared by means of the ring-opening polymerization of the corresponding cyclic ethers. However, using this method, larger size polyethers (containing 6 or more methylene units) cannot be obtained because the cyclic ethers are extremely stable. In these cases, the production of longer methylene unit polyethers can be achieved using step-growth polymerization methods [143,144].

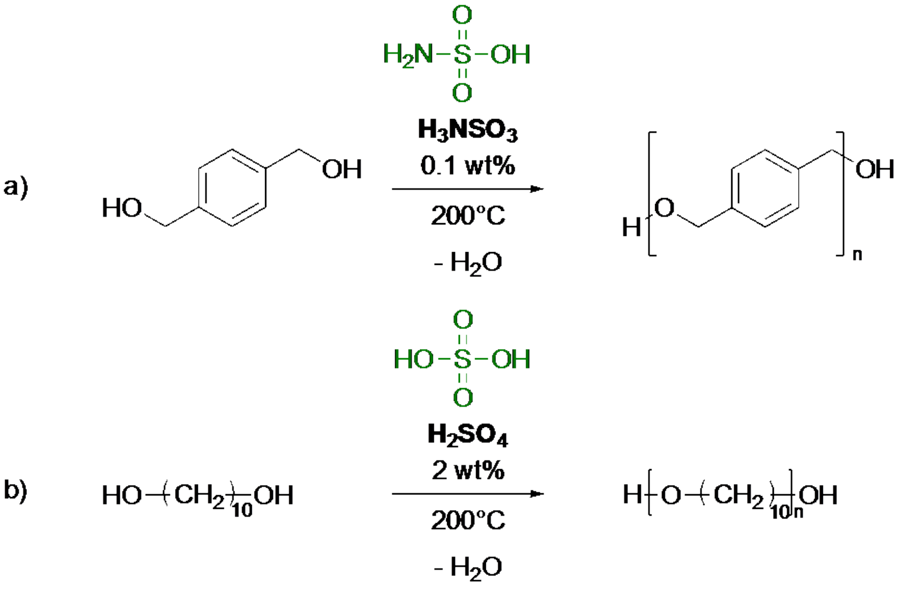
There are eventually two main routes to access polyethers by step-growth polymerization. The first pathway was reported in 1850 by Williamson who showed that the ether linkage could be generated by a nucleophilic substitution of an alkali alkoxide on an alkylating reagent (typically a haloalkane). Although this method is highly efficient, choline is generated as a side product during the polymerization, limiting its industrial implementation. The second route is based on the acid-catalyzed condensation of two alcohols, resulting in an ether bond. Rhoad and Flory described, in 1950, the synthesis of polyethers by self-condensation at high temperature (≥ 200 °C) from aromatic and aliphatic diols, such as *p*-xylylene glycol or dimethyloldurene and 1,10-decanediol [145].

Alcohols generally need to be activated in this reaction, and typically acid catalysts are employed in polyether synthesis. The reaction proceeds in three-steps: the first one consists in the protonation of the alcohol group, forming its conjugated acid that is a better leaving group. This facilitates the second step, where nucleophilic attack of another alcohol onto the adjacent carbon via a S_N2 mechanism takes place. Finally, ether is formed via subsequent deprotonation (**Scheme 30)**.



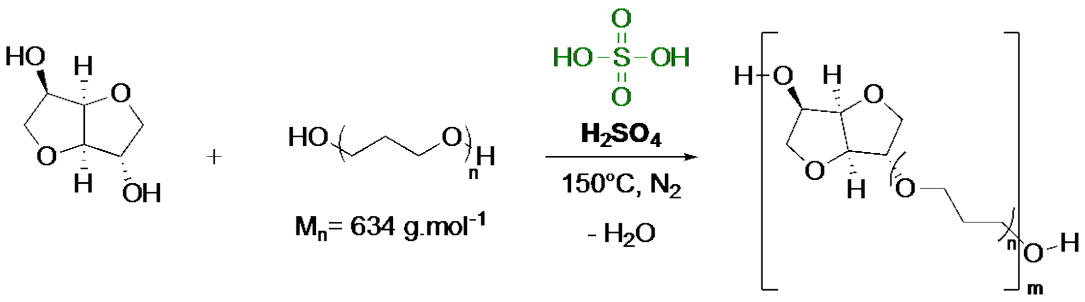
Scheme 30. General mechanism for the condensation of alcohols in the presence of acid as catalyst.

Different acids, such as PTSA, sulfamic acid, and sulfuric acid (H_2SO_4), along with other metal-halides were tested as potential catalysts. Among all catalysts investigated, sulfamic acid and H_2SO_4 produced the best results. For example, *p*-xylylene glycol was found to undergo self-condensation at high temperature (200 °C) with 0.1 wt % of sulfamic acid catalyst. Similarly, 1,10-decanediol was polymerized in bulk at 200 °C using 2 wt % of H_2SO_4 (**Scheme 31**).



Scheme 31. Self-polycondensation of a) *p*-xylylene glycol and b) 1,10-decanediol at 200°C using acids as catalysts. Adapted from ref. [145].

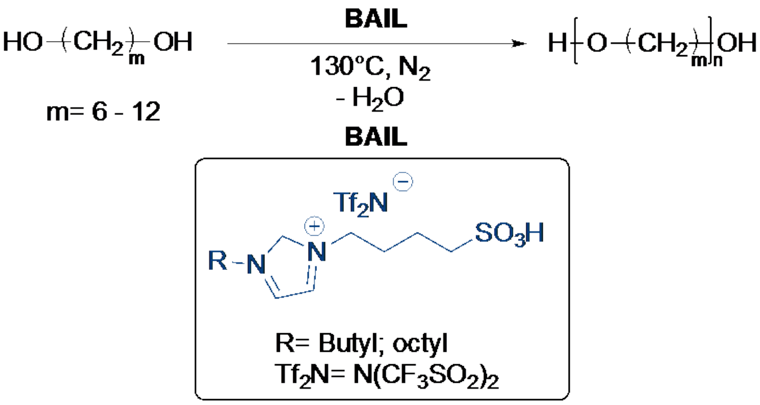
On the same basis, Lal and Trick, as well as Kobayashi and coworkers, later synthesized linear polyethers from aliphatic diols HO-$(CH_2)_m$-OH (m = 6, 7, 8, 9, 10 and 12) at 160 to 210 °C, in presence of concentrated H_2SO_4 and boron trifluoride-diethyl ether complex $(C_2H_5)_2O{\cdot}BF_3$ as catalysts [146,147]. However, the molecular weights of the final polymers were not mentioned. Recently, Fleury and coworkers investigated the homopolymerization of secondary alcohols such as isoborbide [148]. Although homopolymers could not be obtained from isoborbide, oligomers (M_n = 1.2 kg.mol^{-1}; $Đ$ = 18.6) could be achieved when copolymerizing with polytrimethylene ether glycol (PTEG, M = 634 g.mol^{-1}) in the presence of H_2SO_4 at 150 °C (**Scheme 32**).



Scheme 32. Polycondensation of isosorbide and polytrimethylene ether glycol at 150°C using H_2SO_4 as catalyst. Adapted from ref. [148].

Obviously, water must be removed to achieve high molecular weights, which requires high temperatures. These conditions are not recommended for acid catalysts as they are volatile and they can be decomposed at elevated temperatures. Recently, Fradet *et al* showed how to minimize these drawbacks by using Brønsted Acid Ionic Liquids (BAILs) as reaction media and catalysts [41]. Acidic ionic liquids combine the catalytic activity of Brønsted acid with the high thermal stability and low vapour pressure of ionic liquids. They reported for the first time the use of BAILs, such as 4-(3'-butyl-1'-imidazolio)-1-butanesulfonic acid bis(trifluoromethylsulfonyl)imidide ([BBSIm]Tf_2N) and 4-(3'-octyl-1'-imidazolio)-1-butane-sulfonic acid bis(trifluoromethylsulfonyl)imidide ([OBSIm]Tf_2N), as solvent/catalyst for the synthesis of polyethers from aliphatic diols (**Scheme 33**). The polymerization was peformed using the corresponding diol HO-$(CH_2)_m$-OH (m = 6-12) and the acidic ionic liquid in 2:1 molar ratio under N_2. Performing the polymerization at 130°C, good yields were achieved in all cases.

The authors reported the ability to obtain high molecular weights ($M_w \geq 20$ kg.mol^{-1}). For instance using 1,8-octanediol and [BBSIm]Tf_2N they were able to reach a molecular weight of M_w = 42 kg.mol^{-1} ($Đ$ = 2.2). Attempts to homopolymerize 1,4-butanediol and 1,6-hexanediol under the same conditions resulted in the formation of tetrahydrofuran and oxepane.



Scheme 33. Schematic representation of the preparation of polyethers from diols using BAILs as reaction media and catalysts. Adapted from ref. [41].

5.3. Polyesters

Polyesters represent another important class of polymeric materials finding applications in food packaging, biomedical, or electronic devices. They are defined by the R-COO-R' linkage in their structure, where R and R' represent any aliphatic or aromatic moieties. A wide range of polymerization synthetic routes to polyesters are known, including the step-growth polymerization of diacids and diols (and derivatives), the self-polycondensation of hydroxy acid, or the ring-opening polymerization of cyclic esters (**Figure 15**) [149,150].

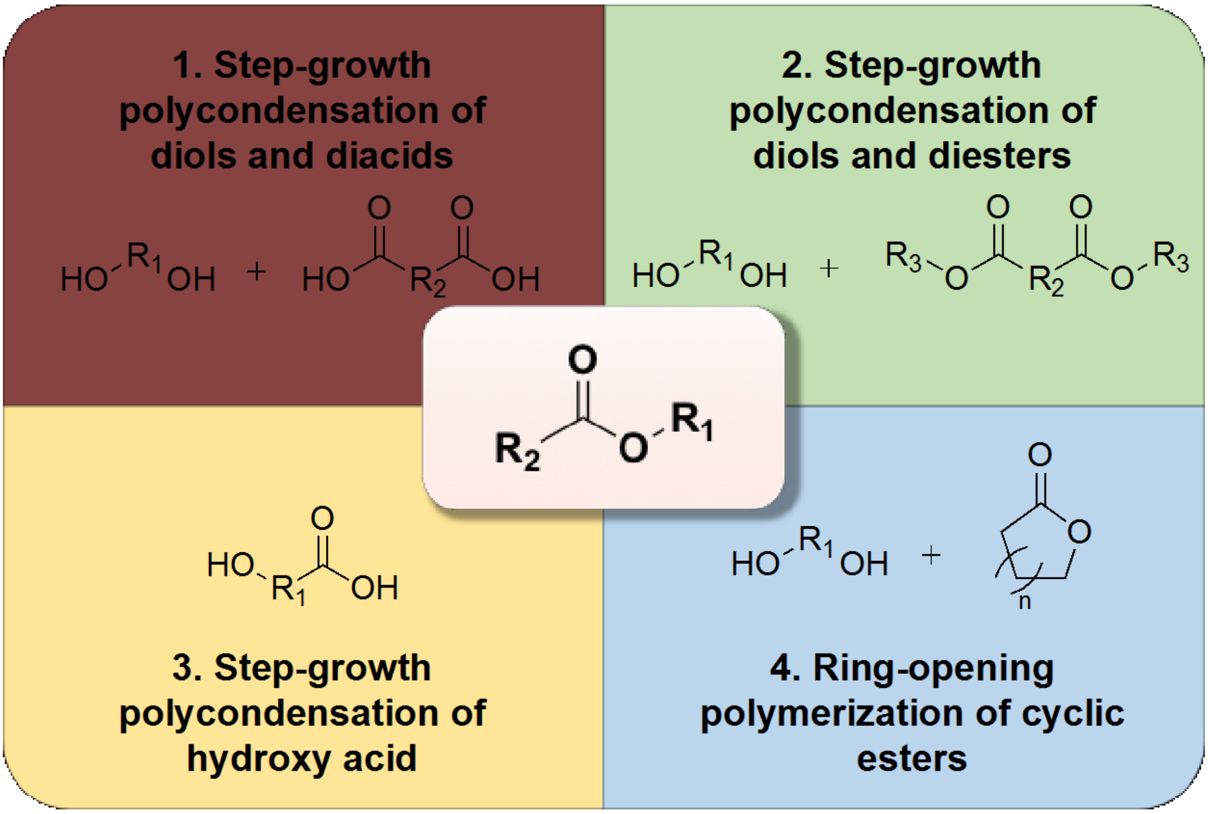
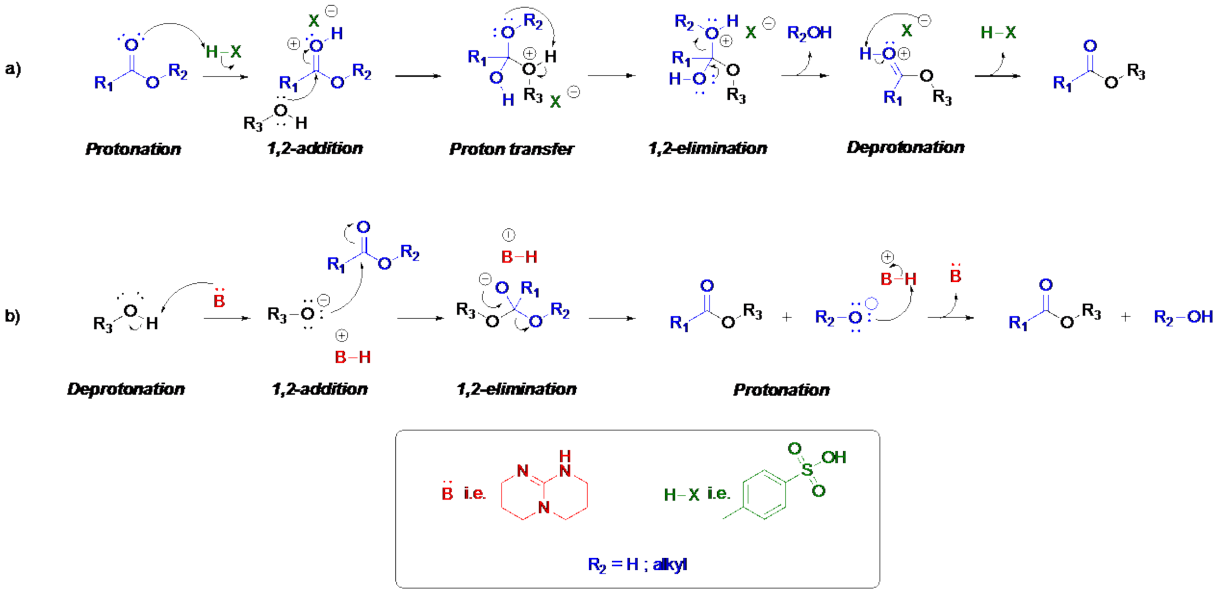


Figure 15. Most employed synthetic routes toward polyesters.

Ring-opening polymerization allows for precise control over molecular weights and dispersity and gives access to complex structure, such as block copolymers. Even so, the polycondensation of diacids or diesters with diols represents the most studied and industrially applicable routes to polyester. However, this process often requires harsh polymerization conditions, such as high temperatures, long reaction time, vacuum to remove condensate by-products, and catalysts to achieve high molecular weights. Among the common metallic salts used, such as titanium alkoxides, tin alkoxides, and zinc or magnesium carboxylates, the antimony-based catalysts represent the most successful. Despite of the excellent performance of antimony-based catalyst in polyesterification reactions, intensive research has been devoted to develop greener catalysts, considering the high potential of such materials in the biomedical and packaging industries [151]. Different types of organocatalysts have already demonstrated success in step-growth polymerization process to polyesters, including strong Brønsted acids, strong Brønsted bases, amines, and *N*-heterocyclic carbenes (**Scheme 34**). In the last decade, ionic mixtures, such as Brønsted acids ionic liquids or protic ionic salts showing a superior thermal stability have also been considered.

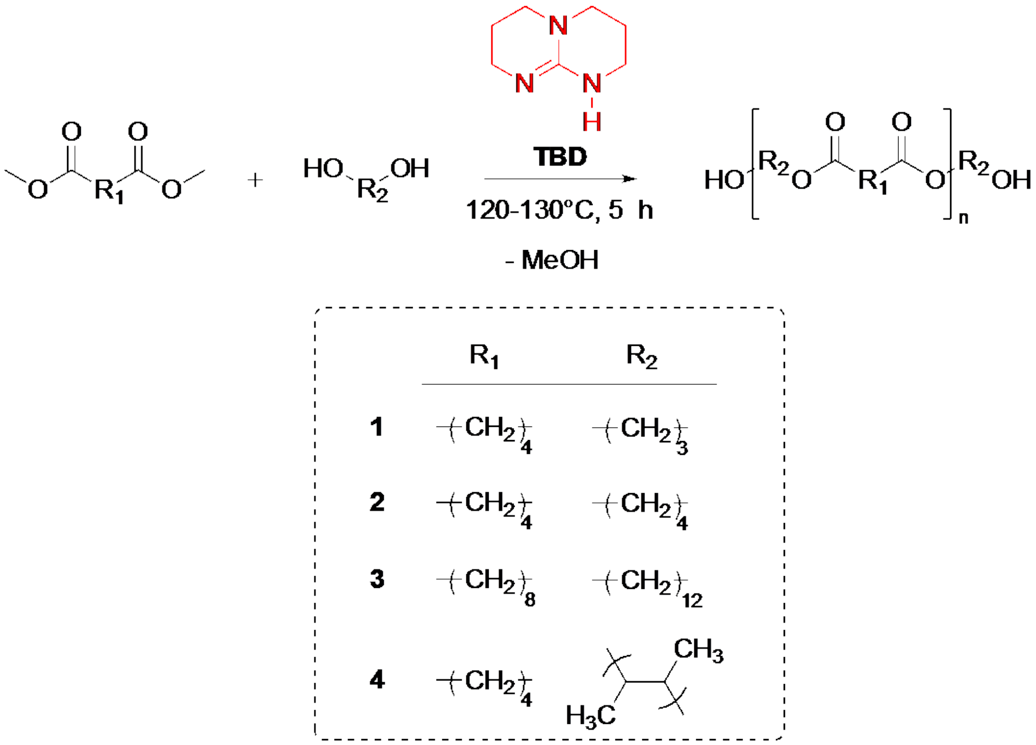


Scheme 34. General mechanism of alcohol/carboxylic acid (or derivatives) reaction in the presence of a) acid or b) base as catalysts.

5.3.1. Use of organic base catalysts

Amidines, guanidines and DMAP

Due to the harsh polymerization conditions needed, tertiary amines, such as triethylamine, have been ineffective for this polymerization and stronger bases deemed necessary. For instance, Cramail *et al* investigated the synthesis of bio-based hyperbranched polyesters from AB_n-type monomers (n=2,3), in presence of various organocatalysts at 120 ºC in bulk [152]. They compared the behavior of different amidines and guanidines, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), *N*-methyl 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), the amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO), with sodium methoxide (NaOMe), a widely used transesterification catalyst in oleochemistry. However, only TBD exhibited a comparable activity to the metal catalyst. It was hypothesized that the dual catalytic behavior of TBD was beneficial for this polymerization. Similarly, Tang *et al*. reported the use of TBD for the formation of hydroxyl-terminated polyesters via polycondensation of bifunctional esters such as dimethyl adipate and sebacate in the presence of slight excess of different diols at about 120 °C (**Scheme 35**) [152]. For instance, the polyesterification of 1,3-propanediol and dimethyl adipate reached full conversion within 5 h in presence of 5 mol % of TBD. In contrast, using titanium(IV) butoxide (TiBut) only achieved 30 % conversion after 24 h. In these conditions, poly(1,3-propylene adipate) (M_n = 1.7 kg.mol^{-1}, $Đ$ = 1.3), poly(1,4-butylene adipate) (M_n =1.2 kg.mol^{-1}, $Đ$ = 1.7), poly(1,12-dodecylene sebacate) (M_n = 2.1 kg.mol^{-1}, $Đ$ = 1.6), and poly(1,2-dimethylethylene adipate) (M_n = 1.2 kg.mol^{-1}, $Đ$ = 1.6) were obtained with catalytic amount of TBD. The polyester-based macro-diols were further reacted with hexamethylene diisocyanate and chain-extended with hexamethylene diamine to yield thermoplastic poly(ester urethane urea)s.



Scheme 35. Polymerization between diesters and diols in the presence of TBD catalyst Adapted from ref. [153].

TBD was also used for the synthesis of polyesters from the polycondensation of α, ω-bifunctional fatty acids [154]. First, α,ω-bifunctional fatty acids and polymerization of the resulting monomer occurred at 120 °C using 5 mol % of TBD catalyst. Linear and hyperbranched polyesters containing thio-ether moieties were obtained without formation of side products, and molecular weights ranged from M_n = 3.9 kg.mol^{-1} ($Đ$ = 1.9) to M_n = 9.4 kg.mol^{-1} ($Đ$ = 3.4).

Until 2018, only TBD proved effective catalyst towards step-growth polymerization forming polyesters. In 2018, Flores *et al.* demonstrated that at high temperature (200 °C), DBU and DMAP were effective to promote the synthesis of poly(ethylene terephtalate) (PET) by step-growth polymerization of dimethyl terephthalate and ethylene glycol [139]. In this work, the authors screened both organocatalysts and more conventional metal-based catalysts such as titanium butoxide. They found that the reaction proceeded with second order kinetics with respect to the monomers $-\,d[M]/dt = k\,[DMT][EG]$, as confirmed by the linear relationship between time, t, and $1/(1-p)$, where p is the fraction of monomer converted to polymer. Rate constants k_0 were obtained for each catalyst (**Figure 16**). DBU was thus found twice less reactive than TBD. In contrast, the catalytic activity of DMAP was 4 times higher than that of TBD, making it a viable option for transesterification reactions.

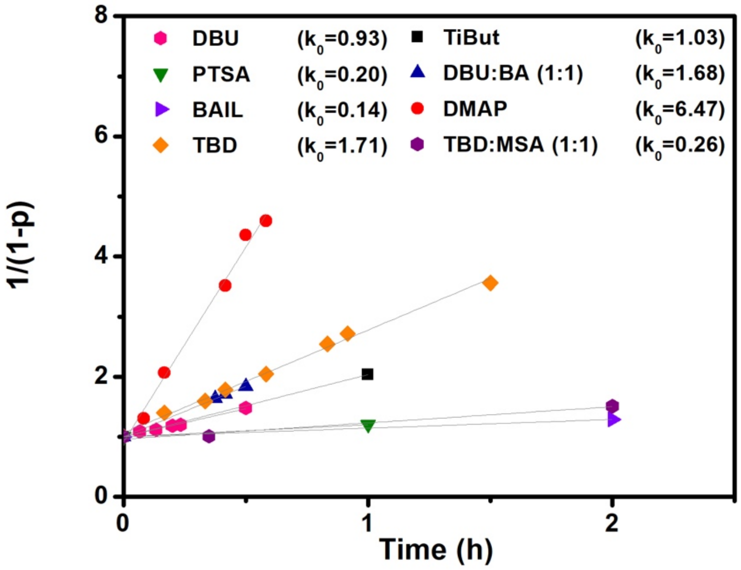
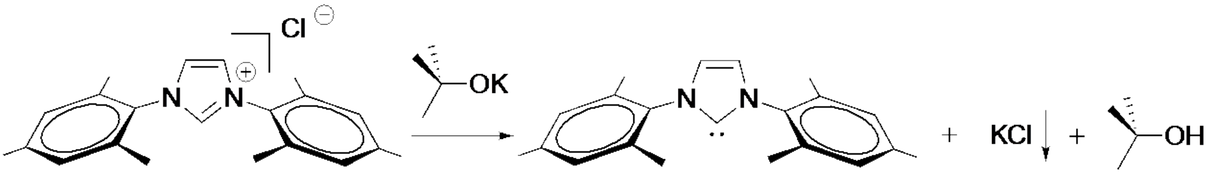


Figure 16. Second order kinetics plot with respect to the monomers for the step-growth polymerization of dimethyl terephthalate and ethylene glycol in the presence of different catalysts. Adapted from ref. [139].

N-heterocyclic carbenes

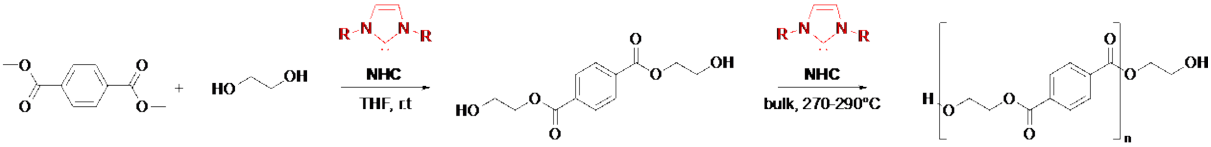
Carbenes have been extensively investigated as transesterification agents in the ROP polymerization of cyclic esters. Nevertheless, their use in step-growth polyesterificataion reactions is far behind. Thus, only one example has demonstrated that NHCs are able to catalyze the preparation of polyesters via step-growth process [28]. Due to the high air and moisture sensitivity of NHCs, the carbene catalyst must be generated *in situ* using the imidazolium chloride salt as starting source (**Scheme 36**).



Scheme 36. Preparation of NHCs using imidazolium chloride salt as carbene source. Adapted from ref. [28].

For instance, polytransesterification of ethyl 6-hydroxyhexanoate and ethyl glycolate in presence of 1,3-dimethylimidazol-2-ylidene at 60 °C under reduced pressure produced poly(caprolactone) and poly(glycolate) with M_n ranging from 8 to 21 kg.mol^{-1}. The polycondensation of dimethyl adipate with ethylene glycol was performed under similar conditions, and 95 % monomer conversion was reported with molecular weight approaching M_n = 10 kg.mol^{-1}.

The synthesis of PET by NHC organocatalysis has also been described. The reaction was performed in two steps, in the first one, bis(2-hydroxyethyl) terephtalate (BHET) was prepared from dimethlyl terephthalate and ethylene glycol. In the second one, the successful polycondensation of BHET was carried out at high temperature (270-290 °C) (**Scheme 37**).

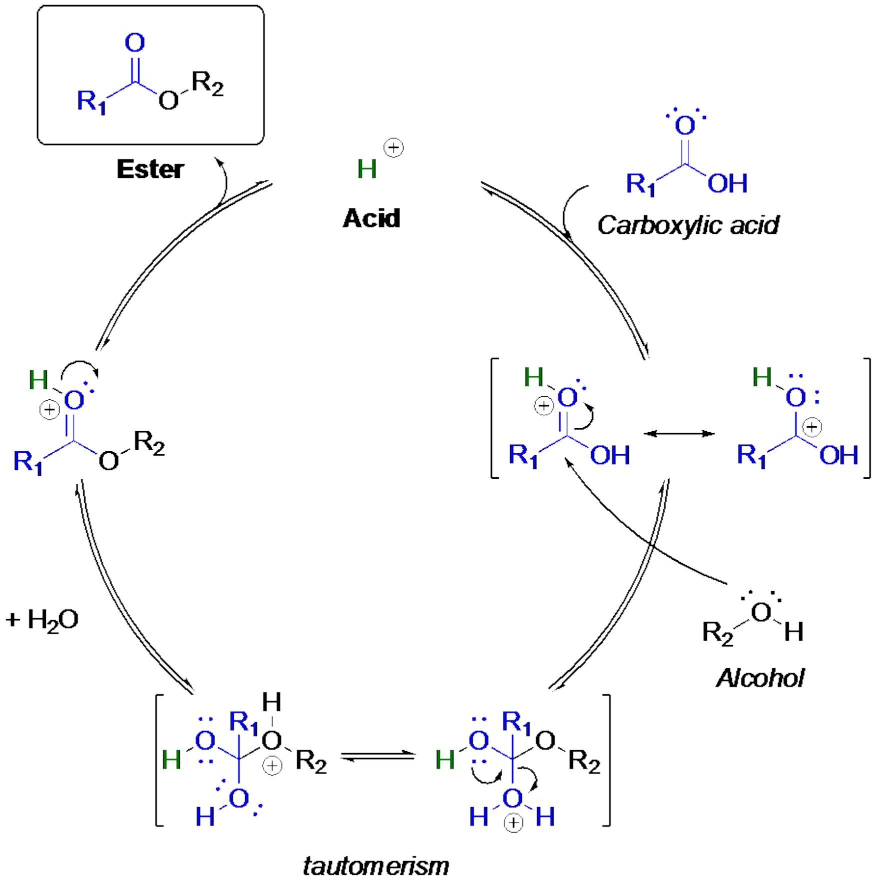


Scheme 37. Two-step preparation of PET using NHCs as catalyst. Adapted from ref. [28].

5.3.2. Use of organic acid catalysts.

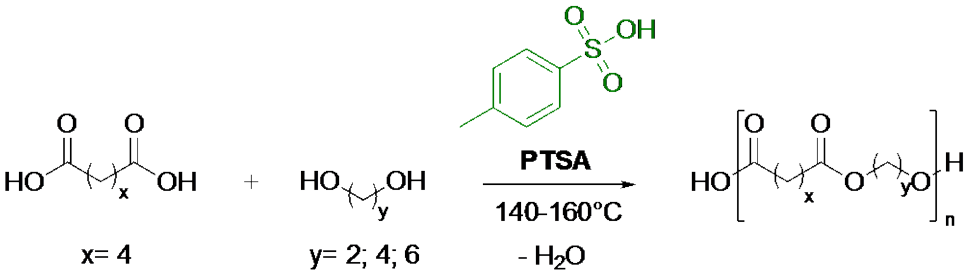
Sulfonic and sulfonimide acids

The esterification of a carboxylic acid and alcohol in the presence of a strong organic acid was first described by Emil Fischer and Arthur Speier in 1895 (**Scheme 38**) [155]. The mechanism involves the protonation of a carboxylic acid with either a Brønsted or Lewis acid to render it more electrophilic. Then, nucleophilic attack of the alcohol leads to the formation of a tetrahedral intermediate that dehydrates after a proton shift (tautomerism) to give water and the corresponding ester.



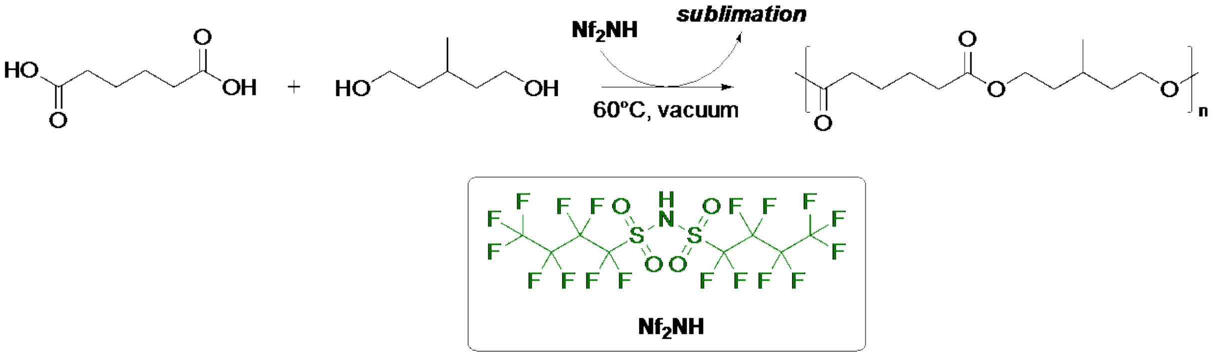
Scheme 38. General mechanism of the Fischer esterification.

In the late 1980's, the PTSA catalyzed polymerization between different adipic acids and different diols was investigated by Kuo and Chen, among others (**Scheme 39**) [156–158]. Performing the kinetic study at 140-160 °C, they found that in the presence of PTSA, the activation energy was lower that without catalyst and decreased in the presence of long chain diols. However, the presence of the catalyst significantly decreased the differences between each adipic acid/diol pairs. Nevertheless, when the catalytic ability of PTSA was compared to other organocatalysts, such as TBD, DMAP or DBU, for the step-growth polymerization of PET from dimethyl terephthalate and ethylene glycol at 200 ºC, it was found that the reaction rate was much inferior than the organic bases [139]. These results seemed to indicate that acid catalysis is preferred when preparing polyesters from carboxylic acids and alcohols.



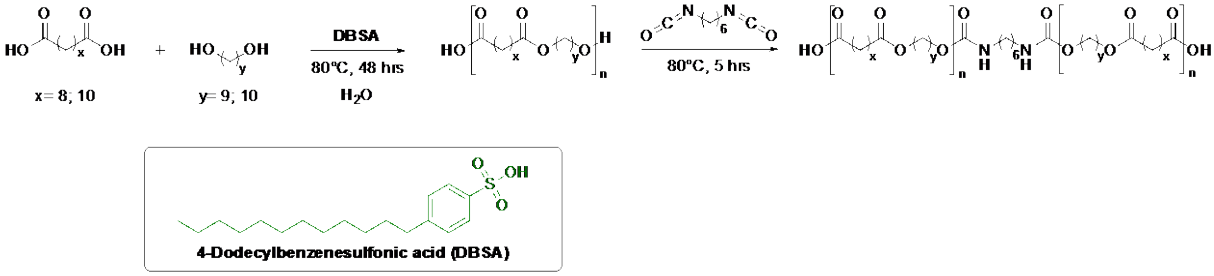
Scheme 39. Schematic representation of the polymerization between diacids and diols to obtain polyesters in the presente of PTSA catalyst Adapted from ref. [158].

Moyori and coworkers investigated the use of different Brønsted acids, such as bis(trifluoromethanesulfonyl)-imide (Tf_2NH), bis(1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl)imide (Nf_2NH), 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonic acid (NfOH), and TfOH as potential catalysts for the bulk polycondensation of diacids and diols (**Scheme 40**) [159]. With 0.1 mol% of Nf_2NH as catalyst, molecular weights up to M_n = 19.1 kg.mol^{-1} (*Đ* = 2.2) were attained using temperatures as low as 60 ºC and vacuum. Under the same conditions, other acids (Tf_2NH, NfOH, TfOH) afforded lower molecular weights (M_n = 12.3-14.3 kg.mol^{-1}, *Đ* = 2.1-2.2). M_n values obtained with these catalysts were higher than those determined when using PTSA or rare-earth acid, such as scandium bis(nonafluorobutanesulfonyl)imide (M_n = 5.8 kg.mol^{-1}, *Đ* = 2.1 and M_n = 10.3 kg.mol^{-1}, *Đ* = 2.5 respectively). Interestingly, bis(1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl)imide strong Brønsted acids could be recycled without loosing the catalytic activity by simple sublimation of the catalyst.



Scheme 40. Polyesterification of adipic acid with 3-methyl-1,5-pentanediol in the presence of bis(1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl)imide strong Brønsted acids. Adapted from ref. [159].

One of the biggest challenge in the preparation of polyesters is the need to remove the generated water or alcohol in order to push the equilibrium and to obtain decent molecular weights. In this regard, Kobayashi *et al.* developed a novel method which eliminates the necessity of water removal from the media. They employed a Brønsted acid catalyst, dodecylbenzenesulfonic acid (DBSA), that at the same time can act as emulsifier. Using this catalyst, they were able to promote the reaction between alcohols and acids by emulsion polymerization. The main advantage of this process is that as the reaction mainly occurs at the monomer droplet, consequently the generated water moves to the aqueous phase, driving the conversion upward. Thanks to this process, the reaction can be performed at low temperatures and using atmospheric pressure [160,161]. Takasu and coworkes further apply this process using difunctional monomers. They investigated the synthesis of polyesters using 16 wt % of DBSA catalyst at 80° C. (**Scheme 41**) [162]. For example, using 1,9-nonanediol and 1,12-dodecanedioic acid, the corresponding polyester was obtained in good yield (95 %) with a molecular weight of M_w = 10.1 kg.mol^{-1} ($Đ$ = 2.0). In comparison, the use of scandium tris(dodesyl sulfate) as surfactant-type Lewis acid led to lower molecular weight (M_w = 4 kg.mol^{-1}, $Đ$ = 1.5), while in absence of catalyst, no polymerization occurred. The authors also reported the feasibility of chain-extending the polyesters with hexamethylene diisocyanate directly in the emulsion to yield higher molecular weights.



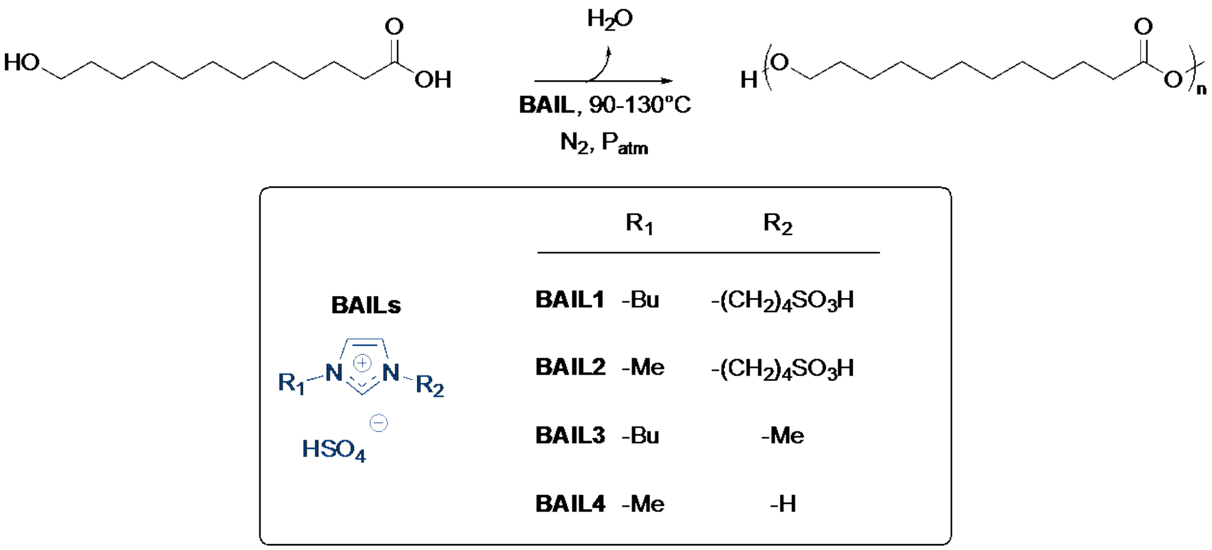
Scheme 41. Emulsion polymerization of diacids and diols in the presence of DBSA catalyst and subsequent chain extension with HMDI. Adapted from ref. [162].

Phosphoric acids

Sokolsky-Papkov *et al.* employed phosphoric (H_3PO_4) and sulfuric (H_2SO_4) acids as catalyst for the polycondensation of adipic acid and sebacic acid with 1,4-butanediol, ethylene glycol, and propylene glycol [163]. Performing the reaction in bulk at 190 °C under vacuum, a small excess of diol was required to achieve higher molecular weight. For example, poly(butylene adipate) and poly(butylene sebacate) were obtained at molecular weights of M_w = 23 kg.mol^{-1} ($Đ$ = 1.4) and M_w = 85 kg.mol^{-1} ($Đ$ = 1.5), respectively using 0.5 wt % of H_3PO_4 and a diacid to diol molar ratio of 1:1.25. In contrast, the molecular weight of poly(butylene adipate) obtained in the non-catalyzed reaction only reached M_w = 8.5 kg.mol^{-1} ($Đ$ = 1.4).

5.3.3. Other type of catalysts: BAILs, ionic salts and chiral catalysts

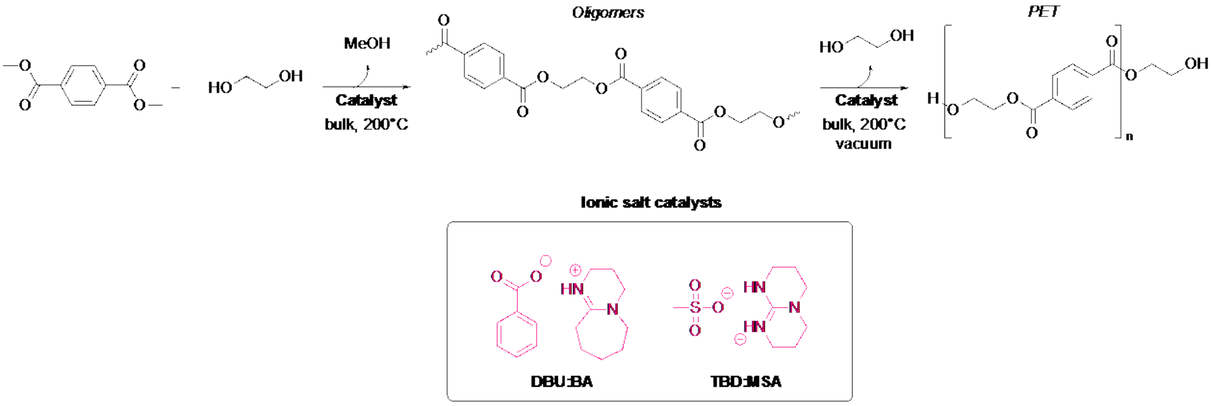
As mentioned earlier, polyesters can be obtained by the self-polyaddition of hydroxy acid. Fradet and colleagues applied this methodology in 2010 to synthesize high molar weight poly(12-hydroxydodecanoic acid)s in BAILs (**Scheme 42**) [164]. Hence, they employed 3-alkyl-1-(butyl-4-sulfony-l)imidazolium hydrogen sulfate as solvent and as catalyst to obtain high molecular weight polyesters (M_n = 40 kg.mol^{-1}, $Đ$ = 2.2) in 2 h at 90 ºC. The found that the optimal conditions to obtain high molecular weights were to use a 1:1 molar ratio between the BAIL and the hydroxy acid. Higher temperature led to an increase in molecular weight (110 °C, M_n = 43.5 kg.mol^{-1}, $Đ$ = 2.11; 130 °C, M_n = 49.9 kg.mol^{-1}, $Đ$ = 2.0). In comparison, following the same procedure at 110 °C, only oligomers were achieved in absence of catalyst or with a catalytic amount of PTSA (M_n < 700 g.mol^{-1}). When the authors intended to reduce the BAIL content, highly viscous reaction mixtures were obtained reducing the final molecular weight. Whereas higher catalyst concentration led to dilute media (as the catalyst also act as solvent) reducing the polymerization rate. Finally, the authors found that only BAILs containing sulfonic acid groups were effective to achieve high molecular weights.



	R1	R2
BAIL1	-Bu	$-(CH_2)_4SO_3H$
BAIL2	-Me	$-(CH_2)_4SO_3H$
BAIL3	-Bu	-Me
BAIL4	-Me	-H

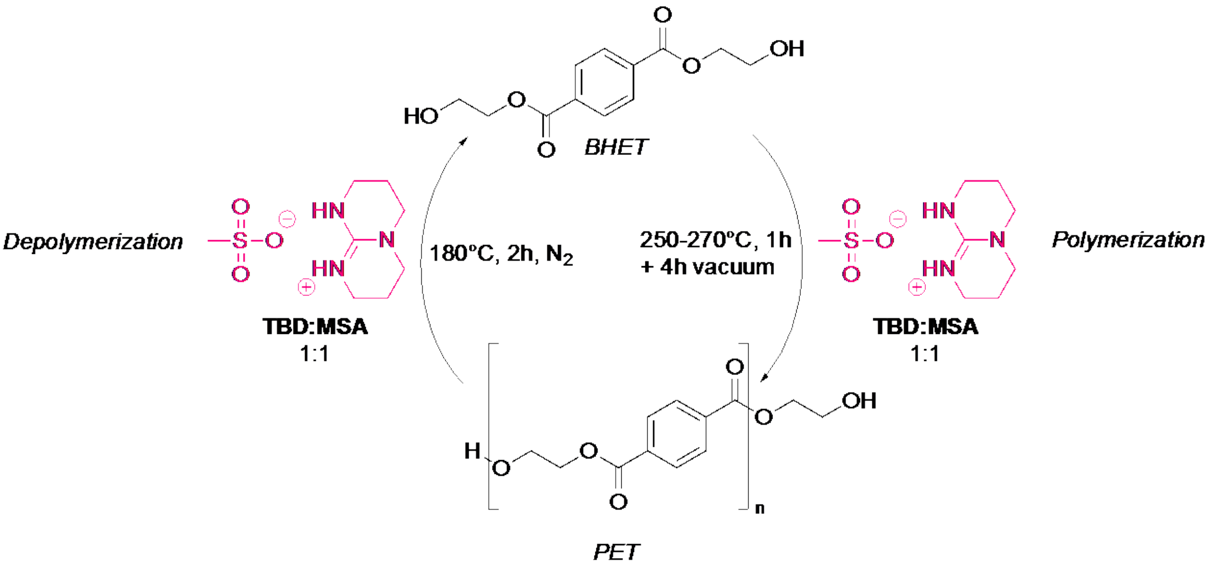
Scheme 42. Self condensation of 12-hydroxydodecanoic acid in the presence of BAIL catalyst. Adapted from ref. [164].

The industrial synthesis of polyesters, such as PET, generally requires high temperatures (270-280 °C), therefore the thermal stability of catalysts employed is a critical parameter that must be taken into account. In this regard, Flores and coworkers investigated differente protic ionic salts for the preparation of PET from dimethyl terephthalate (DMT) and ethylene glycol (EG) in bulk (**Scheme 43**) [139]. The authors prepared two protic ionic salts of 1,5,7-triazabicyclo[4.4.0]dec-5-ene:methane sulfonic acid (TBD:MSA) and 1,8-diazabicyclo[5.4.0]undec-7-ene:benzoic acid (DBU:BA), and they found that the catalytic activity of DBU:BA (1:1) salt was similar to the titanium based catalyst used in industrial PET synthesis. Using 5 mol % of this catalyst the authors reported the ability to obtain PET with molecular weights up to M_n = 10.7 kg.mol^{-1} ($Đ$ = 2.9). The salts resistance to thermal degradation up to > 250 °C indicated that these protic ionic compounds could represent an interesting alternative for the bulk synthesis of PET at high temperatures, in comparison to other organocatalysts that are more susceptible to degradation or sublimation at such high temperatures.



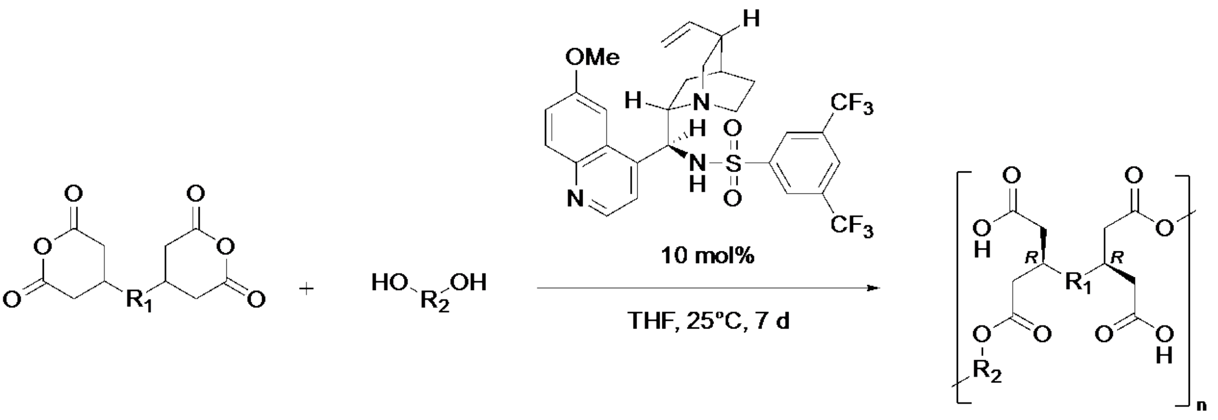
Scheme 43. Bulk polymerization mediated by organic salts for the preparation of PET Adapted from ref. [139].

The same group reported the chemical recycling of PET using TBD:MSA ionic salt as the organocatalyst (**Scheme 44**) [165]. This catalyst was indeed found to completely depolymerise PET in less than 2 h at 180 °C, producing more than 90 % highly pure BHET. The authors demonstrated that the catalyst could be reused at least 5 times. In addition, they showed that using 5 mol % of the same ionic salt catalyst, the BHET obtained from the depolymerization could be re-used as monomer for further the step-growth polymerization forming new PET with similar molecular weights (M_n = 12 kg.mol^{-1}) and thermal properties to those of PET produced from the more conventional polycondensation method.



Scheme 44. Cradle-to-cradle cycle of PET using protic ionic salt as organocatalyst. Adapted from ref. [165].

Semi-crystalline polymers showing high stereoregular microstructure often exhibits an array of mechanical properties superior to those of the corresponding non-stereoregular polymers. Consequently, stereocontrol represents a key factor in these specific polymerization reactions. In this context, Landais and coworkers prepared optically active polyesters in good yields with a high level of stereocontrol, from the specific reaction between prochiral bis-anhydrides and diols (**Scheme 45**) [166]. Asymmetric step-growth desymmetrizing polymerization could thus be implemented in presence of a chiral catalyst transfering its chirality to the growing polymer chains throughout the course of the reaction. Optimized conditions included the use of 10 mol % catalyst in THF (0.1 M) at room temperature, leading to polyesters with M_n up to 5 kg.mol^{-1}. Slightly longer chains were obtained when higher catalyst loading (30 mol %) and pempidine (1 equiv.) as achiral base, were employed (M_n = 9 kg.mol^{-1}, $Đ$ = 2.2).



R_1	R_2
$PhO(CH_2)_5OPh$	$(CH2)_4$
$PhO(CH_2)_2O(CH_2)_2OPh$	CH_2PhCH_2
Ph	$CH_2PhPhCH_2$

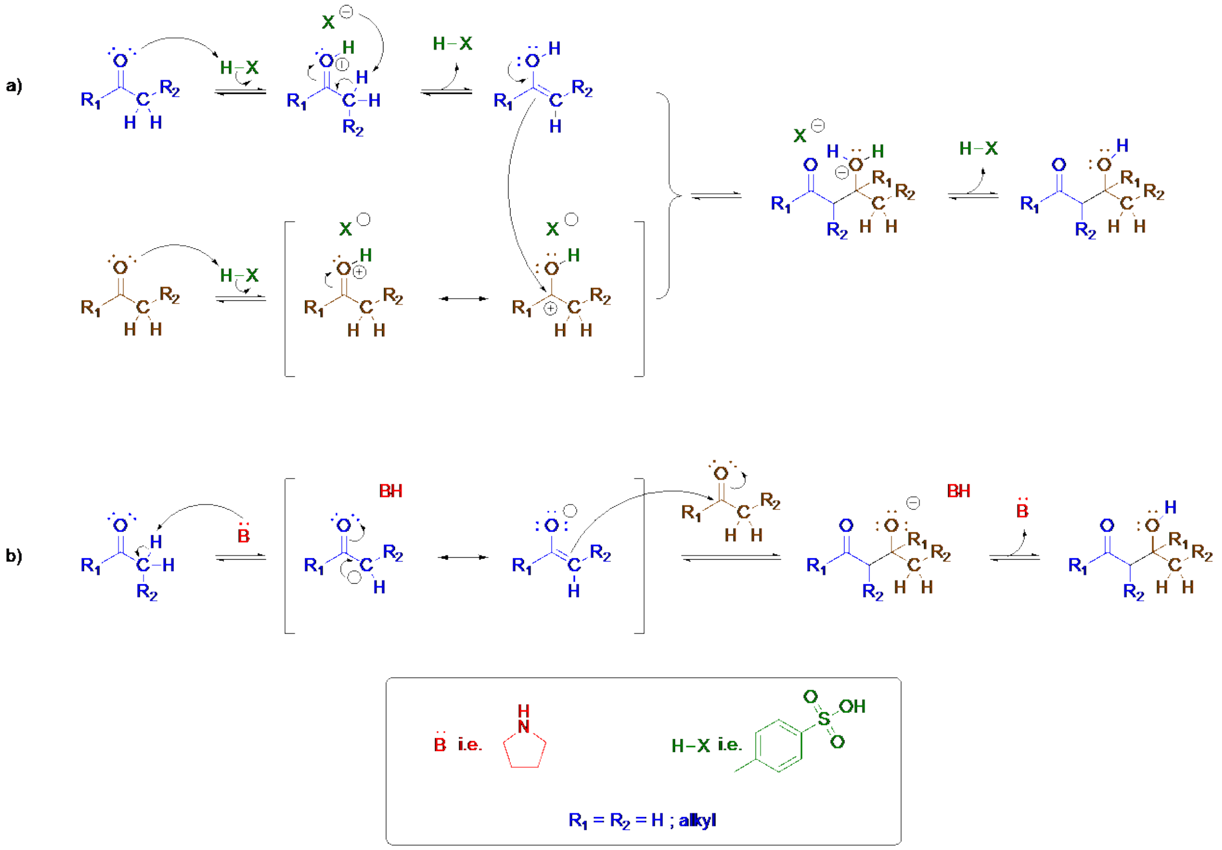
Scheme 45. Synthesis of polyesters by desymmetrizing step-growth polymerization of bis-anhydrides with diols using a chiral catalyst. Adapted from ref. [166].

In summary, the capability of both organic acids and bases to activate either carbonyl substrates or alcohols have enabled the synthesis of polyesters in a competitive fashion to conventional metal-based catalysts. For example, polytransesterification reactions catalyzed with DMAP are approximatively 6 times faster than with titanium(IV) butoxide. However, due to their strong basicity, bases like TBD or DMAP could easily be quenched via deprotonation of the carboxylic acid monomer in polyesterification reaction, inhibiting further molecular weight growth. In order to avoid this shortcoming, sulfonic and sulfonimide-based acids can be employed.

However, lack of thermal stability of organocatalysts prevent them from providing comparable polymerization properties under high temperature conditions. Recent developments have focused on the preparation of novel organocatalysts based on DBU:BA or TBD:MSA mixtures. These protic ionic salts indeed combine the excellent catalytic ability of organocatalysts with the thermal stability of metal catalysts, making them suitable for both synthesis and depolymerization of polyesters in a more sustainable fashion.

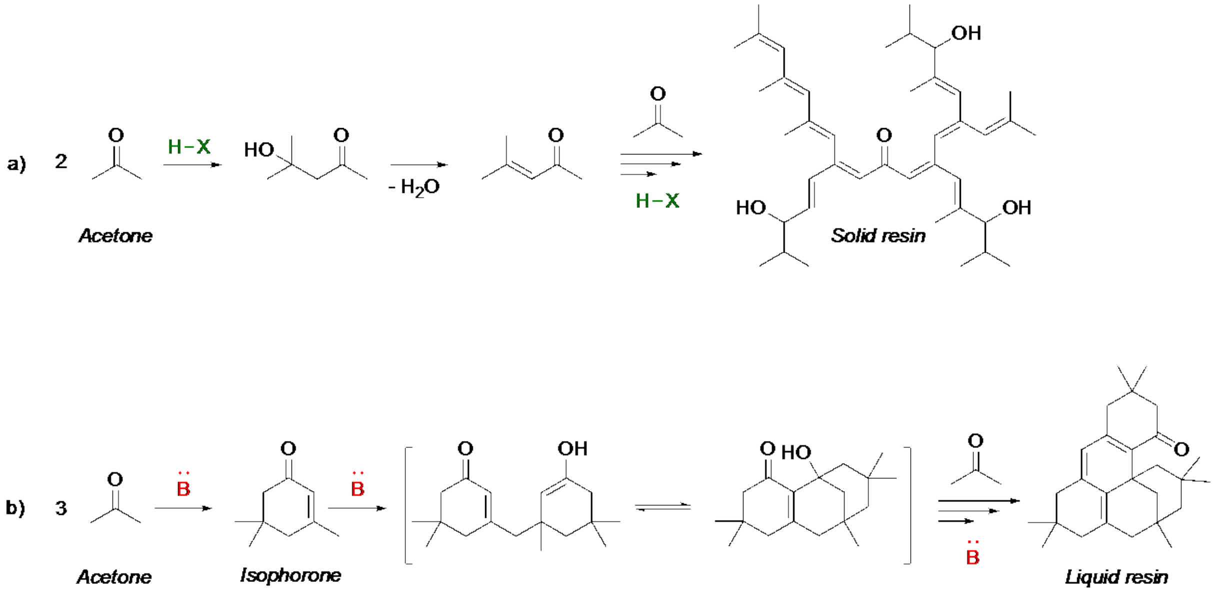
5.4. Polyaldols

An aldol or β-hydroxy aldehyde is an organic compound featuring two chemical functions in its structure, an aldehyde and an alcohol. The aldolisation reaction is a popular atom-economical organic reaction, discovered in 1872. This reaction involves the formation of a C–C bond originally *via* the nucleophilic addition of an enolate with an aldehyde catalyzed by a Brønsted or Lewis acid/base [167–169]. This reaction has been generalized to the addition reaction between any enolizable carbonyl-containing reagents [170]. Concerning the polyaldol synthesis, a few studies have been published about the self-polymerization of aldehydes or ketones using several types of catalysts such as Brønsted or Lewis acids or bases, metal or alkali metal amalgams, or transition metal-based catalysts [171–177]. Depending on the type of catalyst used, different mechanisms can operate in the aldol addition reaction (**Scheme 46**).



Scheme 46. General mechanism of aldol addition reaction in the presence of a) acid or b) base as catalysts.

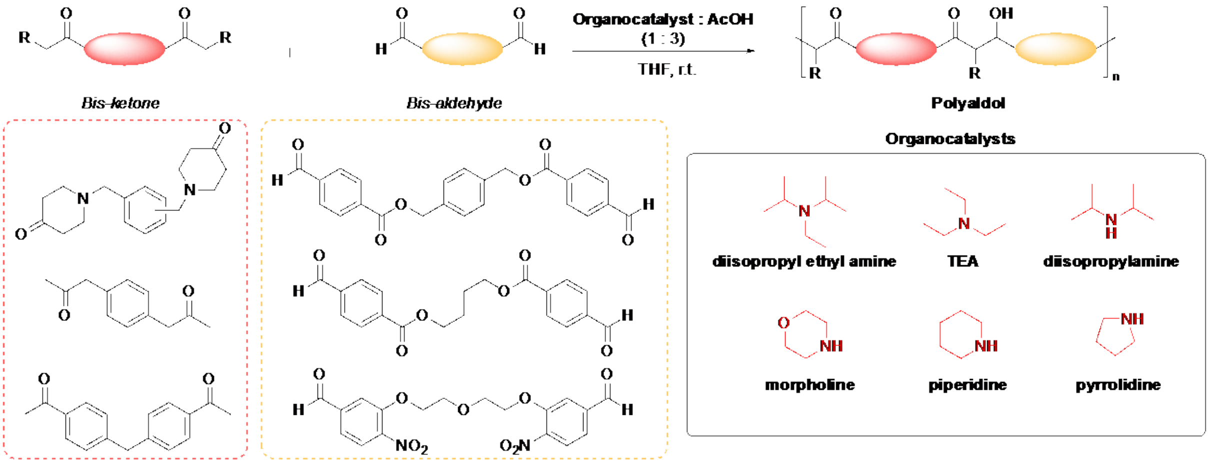
Catalado *et al.* reported the homopolymerization of acetone using protic or Lewis acids/bases [176,177]. Under acidic conditions (H_2SO_4, CF_3SO_3H, or $AlCl_3$), solid resins were obtained in bulk. A molecular weight of 0.8 Kg.mol^{-1}, as determined by osmometry, was reported when 2.5 mol % of H_2SO_4 was incorporated in the reaction mixture (monomer conversion = 54.8 %). The authors hypothesized the formation of a poly(methylacetylene) type polyaldol with carbonyl and hydroxyl groups in the main chain, as confirmed by elemental analysis (**Scheme 47.a**) [176]. In comparison, under basic conditions (NaOH, NaOEt or KOH), liquid resins were achieved [177]. In these cases, the polyaldolic reactions were performed in methanol or ethanol. The liquid resin was obtained with a maximum yield of 60 % (EtOH, 5 mol % NaOEt, reflux). In all cases, the presence of isophorone was reported (up to 15 %), suggesting that the formed resin eventually resulted from both the condensation of acetone with isophorone and the self-condensation of isophorone (**Scheme 47.b**).



Scheme 47. Polyaldolic reaction of acetone under a) acid and b) basic conditions. Adapted from ref. [176,177].

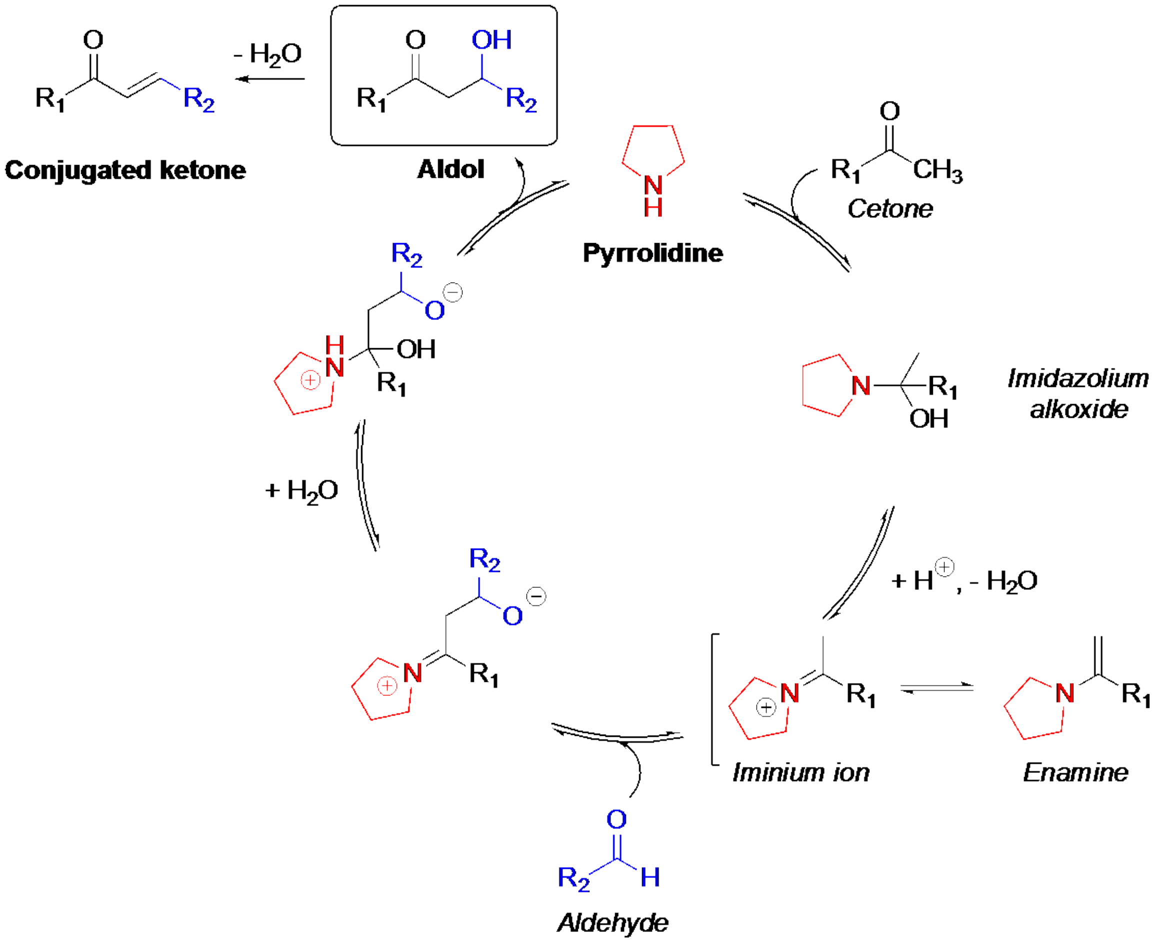
Organic bases

More recently, Taton and coworkers reported a novel synthetic strategy for the synthesis of polyaldols [178]. The reaction took place through repetition of direct intermolecular aldolization reactions between bis(aldehyde)s as electrophilic acceptors and bis(ketone)s as nucleophilic donors. Various cyclic and acyclic secondary and tertiary amine compounds were screened as potential catalysts (**Scheme 48**). Early works in the 1950´s had reported the self-polymerization of acetaldehyde catalyzed by tertiary amines, which proceded by repeated aldol reactions [179].



Scheme 48. Step-growth polymerization between bis(aldehyde)s and bis(ketone)s mediated by amine catalysts. Adapted from ref. [178].

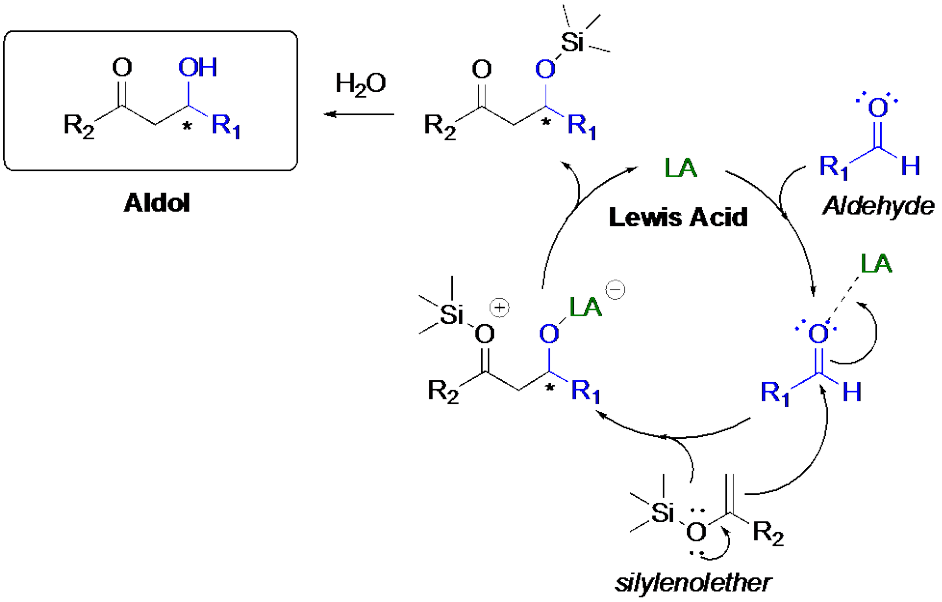
These step-growth polymerizations of bis(aldehyde)s and bis(ketone)s were performed at room temperature in a variety of solvents (THF, DMSO, DMF, DCM or toluene) with a catalyst loading of 30 mol %, and up to 150 mol % of acetic acid as co-catalyst. It was found that the best results were obtained using pyrrolidine catalyst specially when conbining it with acetic acid in a 1 to 3 molar ratio. The authors suggested the nucleophilic substitution of the pyrrolidine and the formation of iminium and enamime intermediates were facilitated by the electrophilic activation mediated by the acetic acid co-catalyst. (**Scheme 49**). NMR spectroscopy analysis evidenced the presence of conjugated ketones that formed from the partial dehydration of the polyaldol (known as the crotonisation reaction).



Scheme 49. Schematic representation of the aldol reaction between aldehyde and ketone in the presence of amine catalyst. Adapted from ref. [178].

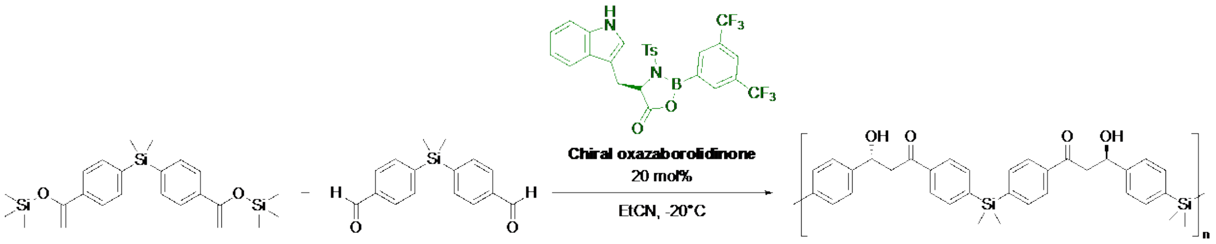
Organic acids

Since its discovery in 1973, the Mukaiyama aldol addition has been used extensively in organic chemistry [180]. The reaction is a Lewis acid-mediated addition of enol silanes on carbonyl compounds (**Scheme 50**). Formation of racemic mixture of isomers has prompted the study of chiral Lewis acid catalysts to favor the formation of a specific enantiomer.



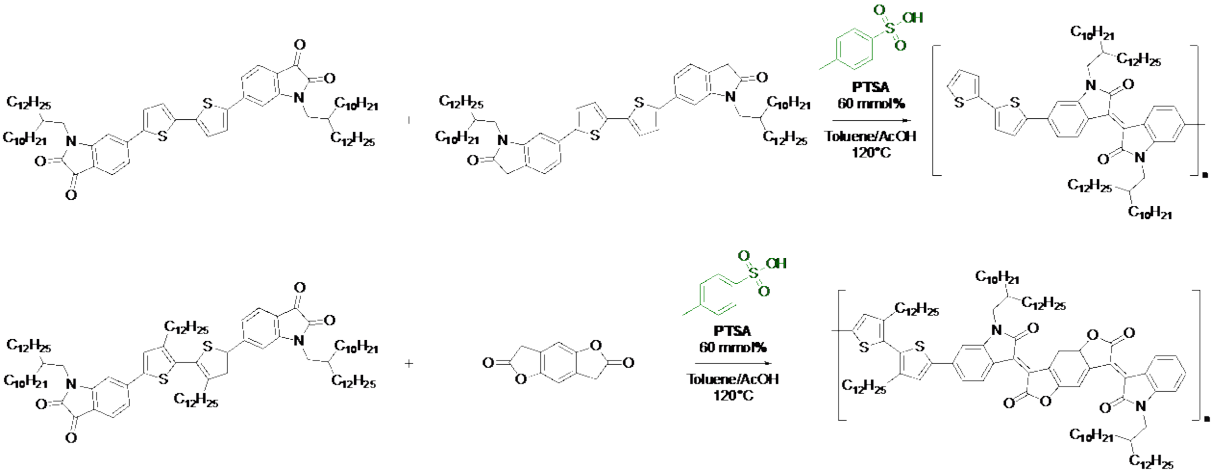
Scheme 50. General mechanism for the repeated asymmetric Mukaiyama aldol addition between silylenolether and aldehyde using Lewis acid as catalyst. Adapted from ref. [181].

For that purpose, Itsuno's group developed optically active aldol polymers using repeated asymmetric Mukaiyama aldol reactions between bis(silylenolether) and bis(aldehyde) monomers [182–184]. For example, step-growth polymerizations were performed in propionitrile at -20 °C using a chiral oxazaborolidinone catalyst. This catalyst is responsible for transferring the chiral information to each monomer unit (**Scheme 51**). A minimum of 20 mol % of catalyst was required to achieve good monomer conversion (> 74 %) and high molecular weights. Overall, the molecular weight of the polymers ranged between 0.9 and 48.2 kg.mol^{-1} and the dispersity between 3.16 and 10.3, depending on the structure of the employed bis(aldehyde)s and bis(silylenolether)s. Incorporation of silyl groups into the monomers improved both yield and molecular weight of the obtained polymers, whereas ether linkages gave poor results due to a lower solubility of ether-containing dialdehydes in propionitrile.



Scheme 51. Step-growth polymerization of bis(silylenolether) and bis(aldehyde) using oxazaborolidinone, a chiral Lewis acid as catalyst. Adapted from ref. [182].

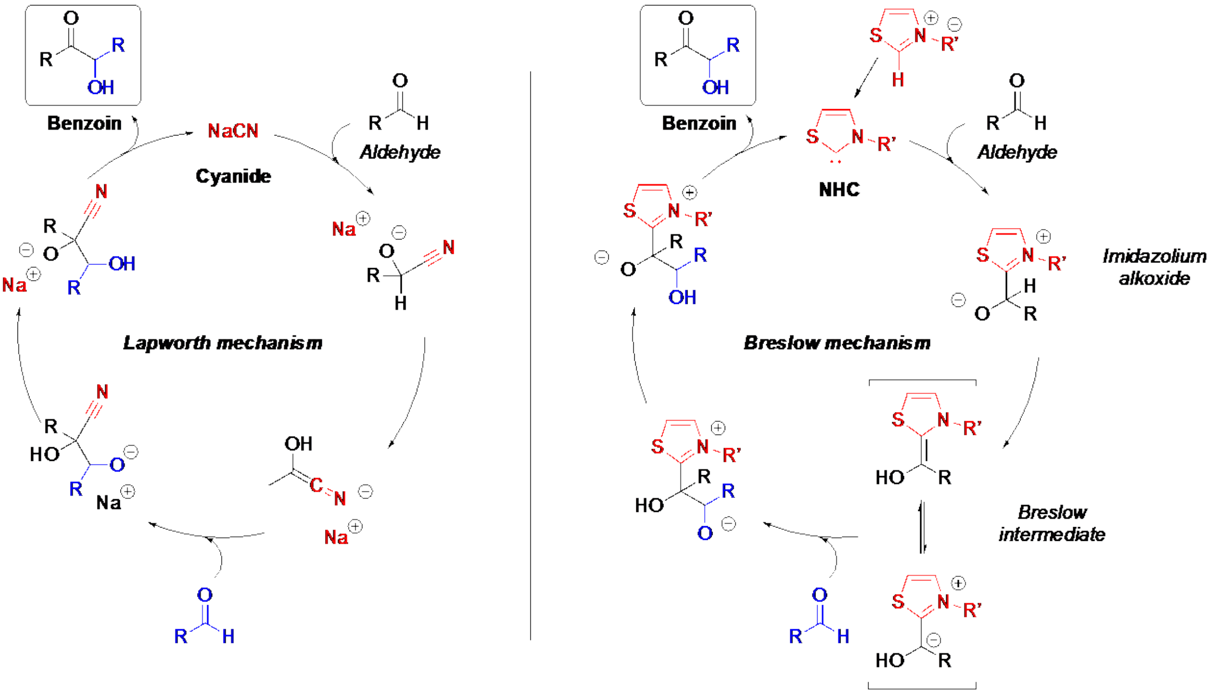
The aforementioned crotonization reaction occurring during aldol synthesis, forming conjugated units, can be exploited to achieve entirely π-conjugated polymers from the complete dehydration of polyaldols [174,175]. For example, Zhang and coworkers synthesized π-conjugated isoindigo-based polymers via aldol polycondensation (**Scheme 52**) [185]. Polymerizations were performed at 120 °C in different acetic acid/toluene mixtures, with 60 mmol % of PTSA or hydrochloric acid (HCl) as catalysts. Although similar conversions and molecular weights could be obtained with both acids, the time required to obtain high molecular weights in the presence of HCl (96 h) was much higher than in the case of PTSA (16 h). With a bulkier monomer, longer reaction time (72 h) were needed to access polymers with M_n values of 31.9 kg.mol^{-1}.



Scheme 52. Organocatalyzed preparation of conjugated polymers via PTSA-catalyzed aldol polycondensation. Adapted from ref. [185].

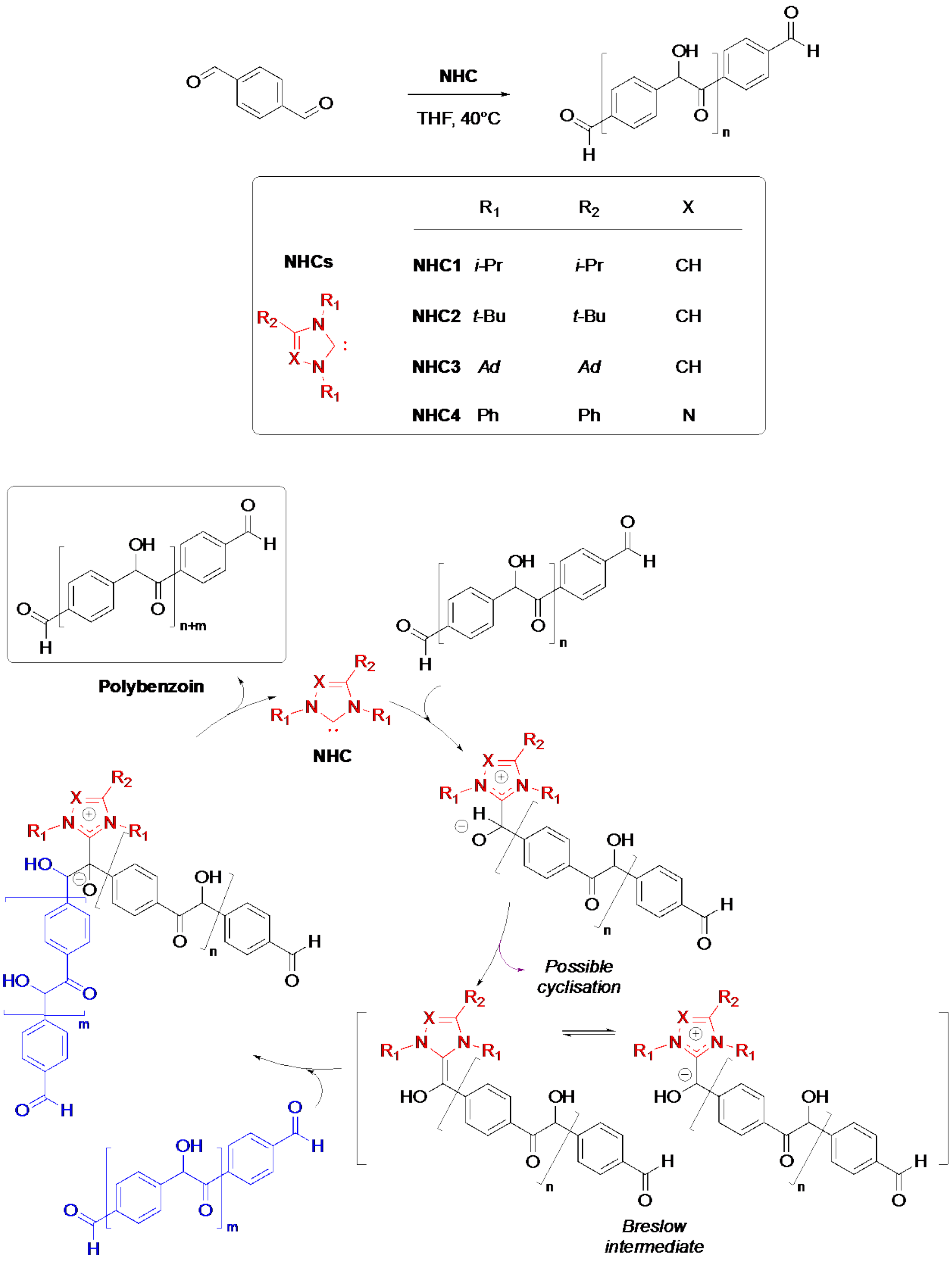
5.5. Polybenzoins

The benzoin condensation is an organic reaction discovered by Wöhler and Liebig in 1832 [186]. It involves the formation of the C-C bond by self-condensation of two benzaldehydes leading to an aromatic β-ketoalcohol labelled a benzoin. Due to the need for a nucleophilic activation, this reaction has been primarily catalyzed using cyanides as catalysts, as described by Lapworth (**Scheme 53.a**) [187]. Comparatively, Ukai *et al.* showed that *N*-ethylbenzimidazolium bromide in the presence of a base can catalyze the benzoin condensation [188]. More recently, Breslow *et al.* disclosed a mechanism in which the active moiety is a carbene formed by deprotonation of the thiazolium salt [189]. The carbonyl of the benzaldehyde can thus be activated by the carbene that acts as a nucleophilic catalyst to form an imidazolium alkoxide that further rearranges to form the "Breslow intermediate". The carbene is subsequently regenerated trough the addition of a second benzaldehyde molecule (**Scheme 53.b**).



Scheme 53. General mechanism for the benzoin condensation using a) cyanide or b) *N*-heterocyclic carbene as catalysts.

The elementary benzoin condensation reaction has been applied in polymer synthesis, to thus achieve polybenzoins by step-growth polymerization of terephthalaldehyde [74]. First attempts employed cyanides as catalysts, forming polybenzoins in fact used as precursors for the synthesis of poly(1,4-phenylenevinylene) (PPV) and high-performance quinoxalines [190,191]. In 2009, Pinaud *et al.* reported the use of various NHCs as alternative catalysts to the toxic cyanide ions to conduct the same step-growth polymerization of terephthalaldehyde (**Scheme 54**) [31]. Four different NHCs were screened, polymerizations being performed at 40 °C in either THF or DMSO. Using THF and 1 mol % 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene (NHC4) as catalyst, high monomer conversion (> 90 %) and moderate molecular weights (M_n = 1-3 kg.mol^{-1}) were obtained. However, under these experimental conditions, the polybenzoin precipitated out of the solution; it was suggested that both linear and cyclic polybenzoins formed during the reaction.



	R1	R2	X
NHC1	*i*-Pr	*i*-Pr	CH
NHC2	*t*-Bu	*t*-Bu	CH
NHC3	*Ad*	*Ad*	CH
NHC4	Ph	Ph	N

Scheme 54. Step-growth polymerization of terephthalaldehyde using *N*-heterocyclic carbenes as catalysts. Adapted from ref. [31].

In summary, NHCs represent safer nucleophilic activators than the cyanide ions used so far, which can release hydrogen cyanide in the presence of water.

5.6. Polyacetals

Polyacetals, also known as polyformaldehydes or polyformals, represent a category of polymers containing acetal linkages [—O—C(R)(R')—O—] where R and R' can be a divalent aliphatic or aromatic sequence. Owing to their degradability under acidic conditions and the generation of relatively benign degradation products, these polymers have gained an increasing interest in the past decade. Similarly to the Brønsted or Lewis acid-catalyzed acetal formation in organic chemistry, different acid-catalyzed routes have been developed to produce polyacetals (**Figure 17**).

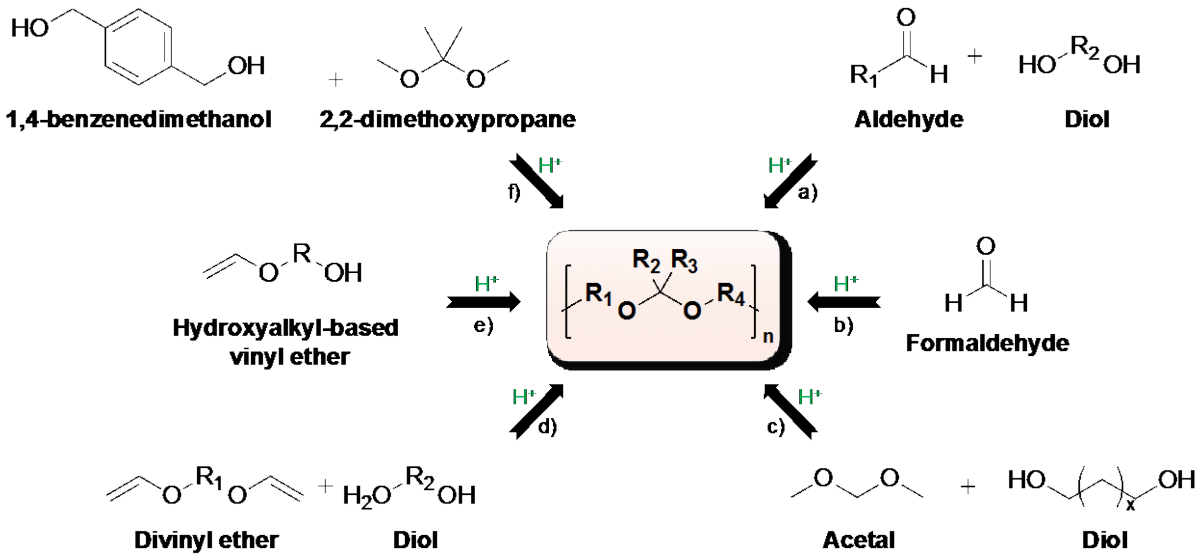
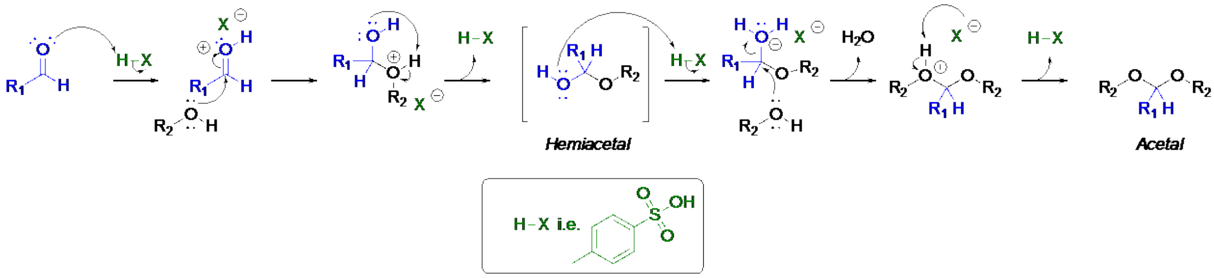


Figure 17. Different routes for the synthesis of polyacetals using acid catalysis.

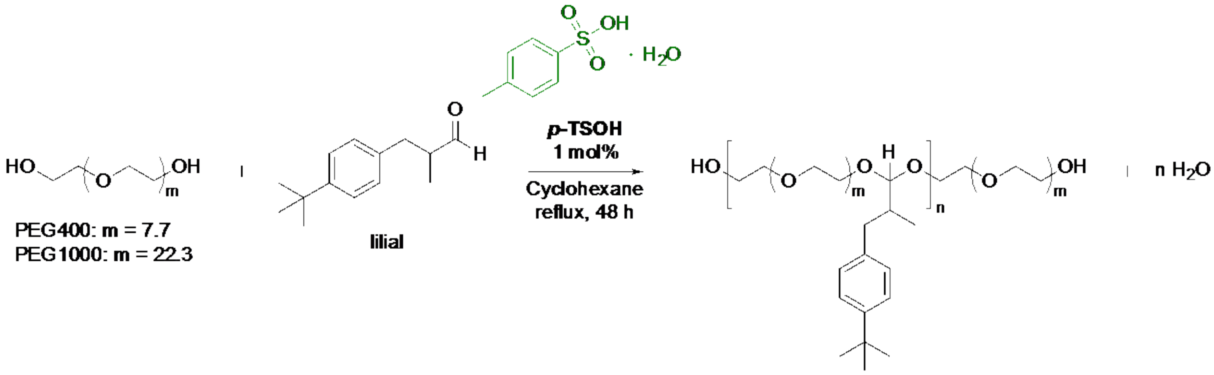
For example, a simple method to achieve polyacetals is through the reaction of a diol with an aldehyde containing molecule in the presence of strong acid catalyst (**Figure 17.a**). The repeated acetalization reaction requires the electrophile activation of the carbonyl by an acid catalyst, followed by the addition of an alcohol to form a hemiacetal. The reaction can be driven to acetal formation, due to the hemiacetal instability under acidic conditions, by addition of a second alcohol if water, as by-product, is removed during the reaction (**Scheme 55**) [192–195].

PTSA is the gold standard to catalyze the polyacetal formation among all Brønsted acids available.



Scheme 55. General mechanism for the acetalization of aldehyde with alcohol using acid as catalyst.

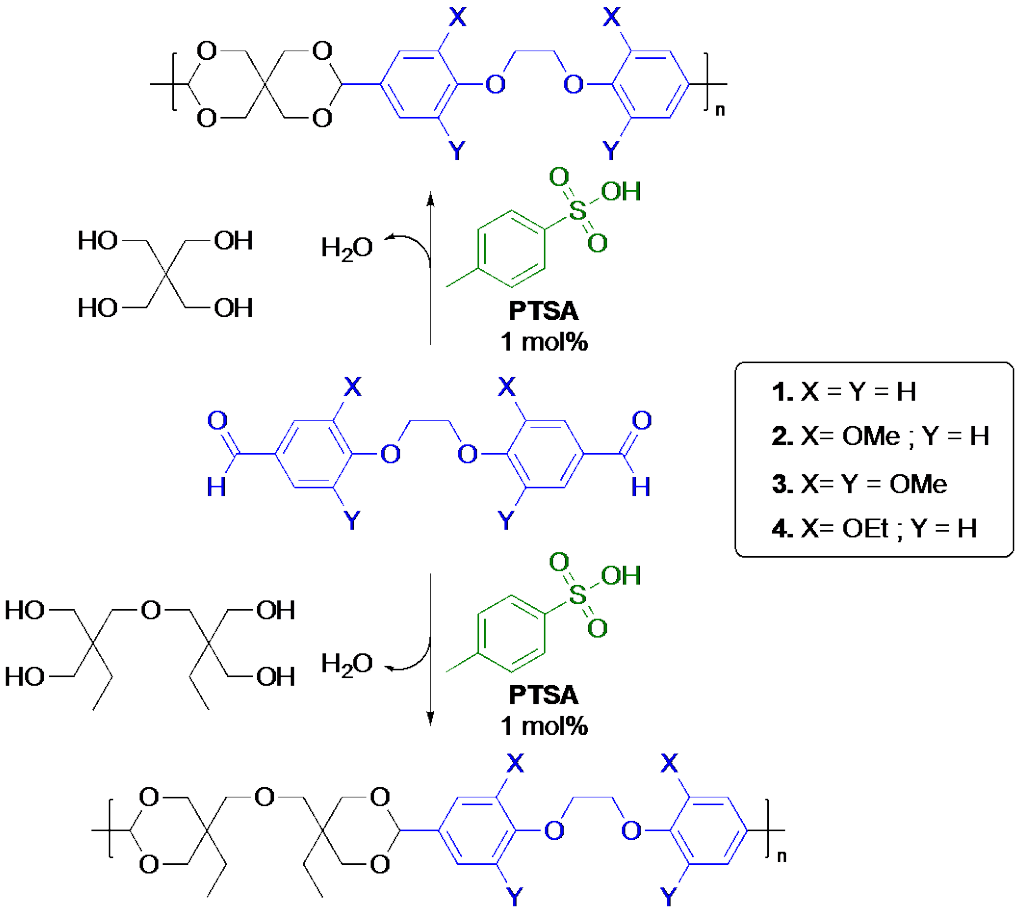
Using this polymerization strategy, Endo and coworkers designed amphiphilic polyacetals containing lilial, a hydrophobic compound used in fragrances. To do so, they copolymerized poly(ethylene glycol) and lilial (which contains aldehyde functionality) in cyclohexene in the presence of 1 mol % of PTSA monohydrate (*p*-TsOH) catalyst (**Scheme 56**) [192]. Using PEG-400, polyacetal having a molecular weight of M_n = 7.6 $kg.mol^{-1}$ (*Đ* = 2.0) were obtained in relative good yields (80 %). In contrast, with PEG-1000, lower conversion and molecular weights were achieved (M_n = 2.5 $kg.mol^{-1}$, Đ = 2.3). Under acidic conditions, polyacetals were in fact hydrolyzed releasing the lilial aldehyde, release rate depending on the PEG chain length.



Scheme 56. Acid-catalyzed polymerization between poly(ethylene glycol) and lilial. Adapted from ref. [192].

Recently, the Miller's group synthesized bioaromatic polyacetals by polymerizing different alcohols and polyols (PVA) with aromatic aldehydes in the presence of PTSA catalyst [193–195]. For example, PVA was reacted with several bioaromatic aldehydes to yield polyvinyl aromatic acetals. The authors first investigated the effect of different acids, such as HCl, AcOH, MSA, H_2SO_4, and PTSA, on the reaction rate as well as the solvation condition of the polyacetalization (DMSO, or N-methyl-2-pyrrolidone (NMP)). Among the tested catalysts, the polymerization occurred only in presence of H_2SO_4 and PTSA. The authors determined experimental molecular weights ranging from 38.2 to 46 kg.mol^{-1} depending on the aldehyde precursor. For example, the acetalization of PVA with vanillin yielded polyvinyl vanillin acetal (M_n = 43.7 kg.mol^{-1}) with 63.3 % of –OH groups converted to acetals.

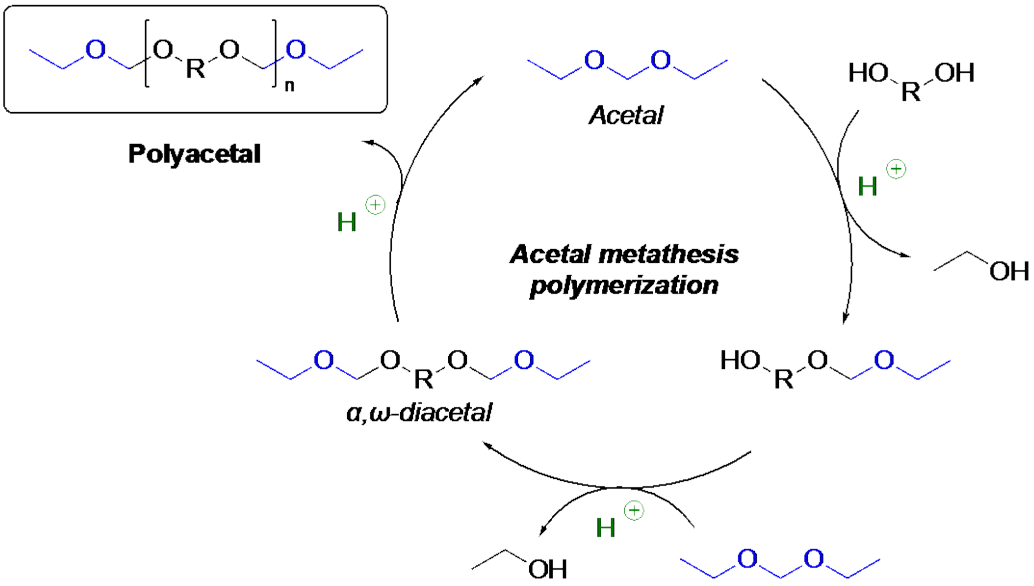
The same authors also reported the preparation of different bioaromatic polyacetal ethers containing cyclic acetals or spirocyclic acetals in their structure, via PTSA-catalyzed acetal formation from dialdehydes and tetraols in DCM (**Scheme 57**) [193,194]. Number average molecular weights, M_n, were in the range of 1.4 to 27.1 kg.mol^{-1}with dispersity, *Đ*, ranging from 1.4 to 2.2.



Scheme 57. Polycondensation of dialdehydes and tetraols using acid as catalyst to obtain bioaromatic polyacetals. Adapted from ref. [193].

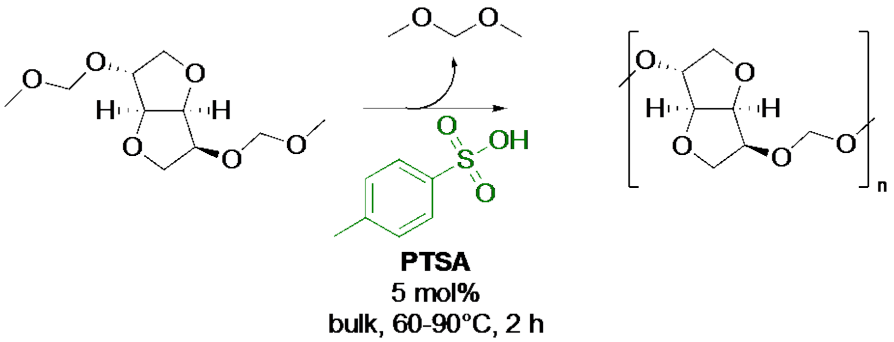
Another route for the preparation of polycatetals is by the self-condensation of α,ω-diacetals (**Figure 17.c**) [196–199]. To do so, he diols are firstly converted into linear α,ω-diacetals, which can polymerize in the presence of acid catalyst. Chikkali *et al.* thus reported the synthesis of novel polyacetals from plant oil-derived α,ω-diacetals [196][195]. Long-chain aliphatic α,ω-diol starting materials were first generated from unsaturated fatty acid esters and reacted with an excess of dimethoxymethane to yield the corresponding α,ω-diacetals. The difunctional acetal monomers were then subjected to self-condensation polymerization at 80-100 °C using 2 to 4 mol % of PTSA catalyst. Reduced pressure was applied here to remove the dimethoxymethane by-product and push the reaction forward. The resulting polyacetals molecular weights ranged from M_n = 1.7 to 3.2 kg.mol^{-1}, as calculated by ^{1}H NMR.

Similarly, Miller's group prepared polyacetals from linear α,ω-diacetals using diethoxy- or dimethoxymethane [197]. Polymerizations were performed by mixing diethoxymethane and diols in a 30:1 ratio using 2 mol% of PTSA as catalyst. Temperatures were increased up to 200 °C over 5 hours, followed by dynamic vacuum for 12 hours. They found that the length of the employed diols was crucial to attain high molecular weights. Short diols (2, 3 and 4 methylene units) led to the formation of cycles via intramolecular acetal formation, reducing substantially the polymer yield. Whereas, using longer diols as the cycle formation is not so favored, the polymerization was successful and high molecular weights could be obtained (M_n = 20.7 to 38.5 kg.mol^{-1}, $Đ$ = 1.8 to 25). Comparing the use of dimethoxymethane and diethoxymethane, the authors found that when using a 30:1 excess of acetal to 1,10-decanediol, the choice of diacetal did not influence molecular weights (M_n > 35 kg.mol^{-1}). However, in a ratio acetal : 1,10-decanediol of 2:1, diethoxymethane (M_n = 32.7 kg.mol^{-1}, $Đ$ = 2.2) far excelled dimethoxymethane (M_n = 17.9 kg.mol^{-1}, $Đ$ = 2.9). The authors described this polymerization as Acetal Metathesis Polymerization (AMP) (**Scheme 58**).



Scheme 58. Step-growth polycondensation of linear α,ω-diacetals derived from α,ω-diols with diethoxy- or dimethoxymethane using acid as catalyst. Adapted from ref. [197].

In other studies, Chikkali and coworkers synthesized polyacetals from the polycondensation of isohexide–diacetals at 60-90 °C, with argon-vacuum purge cycle and catalytic amount of PTSA (2-5 mol %) (**Scheme 59**) [198,199]. The endo-exo structure led to higher molecular weights (M_w = 5.0-8.9 kg.mol^{-1}, Đ = 1.6-2.0) than those obtained with the endo-endo diastereoisomer (M_w = 2.1-3.8 kg.mol^{-1}, Đ = 1.4-1.6) and the exo-exo one (M_w = 2.8-3.7 kg.mol^{-1}, Đ = 1.5-1.7). In some cases, higher temperatures and longer reaction times were required to achieve higher molecular weights. Finally, access to various copolymers was demonstrated [199].

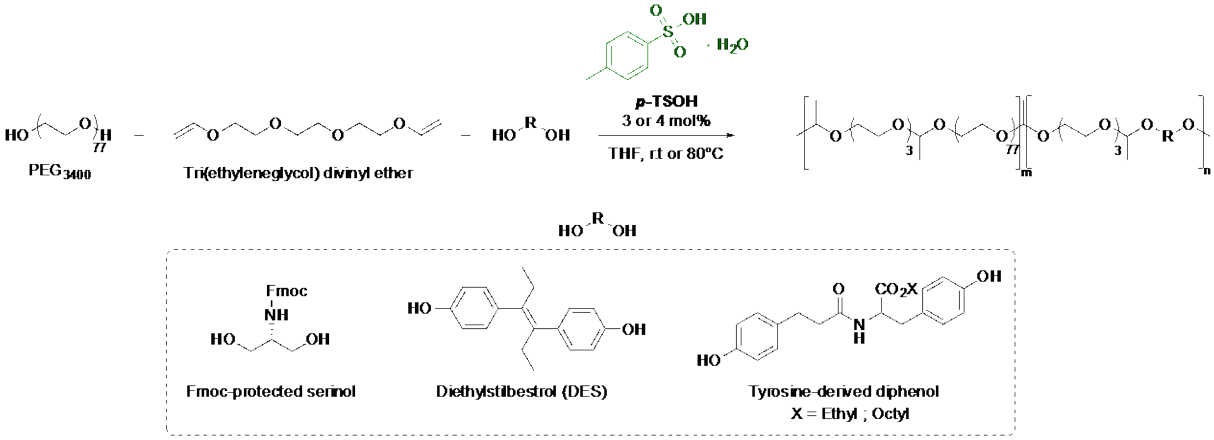


Scheme 59. Step-growth polycondensation of isosorbide diacetal using 5 mol % of PTSA as catalyst. Adapted from ref. [198].

Another route to generate polyacetals, without forming any by-product is by means of the reaction between vinyl ethers and alcohols (**Figure 17.d and 17.e**) [200–210]. This reaction which was developed by Heller *et al.* in 1980 can also be catalyzed by acid compounds, especially PTSA [200]. They found that using different divynil ethers such as 4-divinylbutane or diethyleneglycol divinyl, polyacetals could be obtained straightforward by reacting them with different diols. This strategy was further employed by different groups to incorporate functionalities in polyacetal backbone (**Scheme 60**). For example, pendant chain functionalized polyacetals, which display pH-dependent degradation, were prepared by Brocchini and coworkers [202,204]. First, amino-containing polyacetals were synthesized from the terpolycondensation reaction of tri(ethyleneglycol) divinyl ether, poly(ethylene glycol) (PEG_{3400}, M_n = 3.4 $kg.mol^{-1}$) and Fmoc-protected serinol in THF at 80 °C, using 3 mol % of *p*-TsOH as catalyst. Using different ratio of PEG_{3400}:Fmoc-serinol, an amino-polyacetal with molecular weight of M_w = 19.8-77.5 $kg.mol^{-1}$ ($Đ$ = 1.8 - 2.0) was obtained upon deprotection of the amino group. The resulting polymers were then functionalized with either I-labeled (di-iodo) Bolton-Hunter reagent or Doxorubucin an anticancer drug (DOX). DOX-containing polyacetals were obtained with molecular weights, M_w, ranging from 57 to 99.5 $kg.mol^{-1}$ ($Đ$ = 1.7-2.6) and a maximum DOX content of 8.5 wt %, as determined by HPLC. Biocompatibility studies showed that polymers were non-toxic and degraded under specific pH condition [204].

On this basis, acid-sensitive polymeric anticancer drugs based on polyacetal could be designed through the incorporation into the polymer backbone of diethylstilbestrol (DES), a non-steroidal oestrogen drug having a bishydroxyl functionality [205]. For that purpose, PEG_{3400} was reacted with tri(ethylene glycol) divinyl ether and DES in THF at room temperature with 3 mol % of *p*-TsOH. The DES-polyacetal obtained had a molecular weight of M_w = 43 $kg.mol^{-1}$ ($Đ$ = 1.8).

Similarly, Brocchini and coworkers introduced tyrosine-derived diphenol into polyacetals [207]. A polymerization process at room temperature employing tri(ethylene glycol)divinyl ether, a diphenol, and PEG_{3400} using 4 mol % of *p*-TsOH as catalyst gave the desired water-soluble polyacetals with average molecular weights ranging from 24–71 $kg.mol^{-1}$ ($Đ$ = 1.6–2.9).

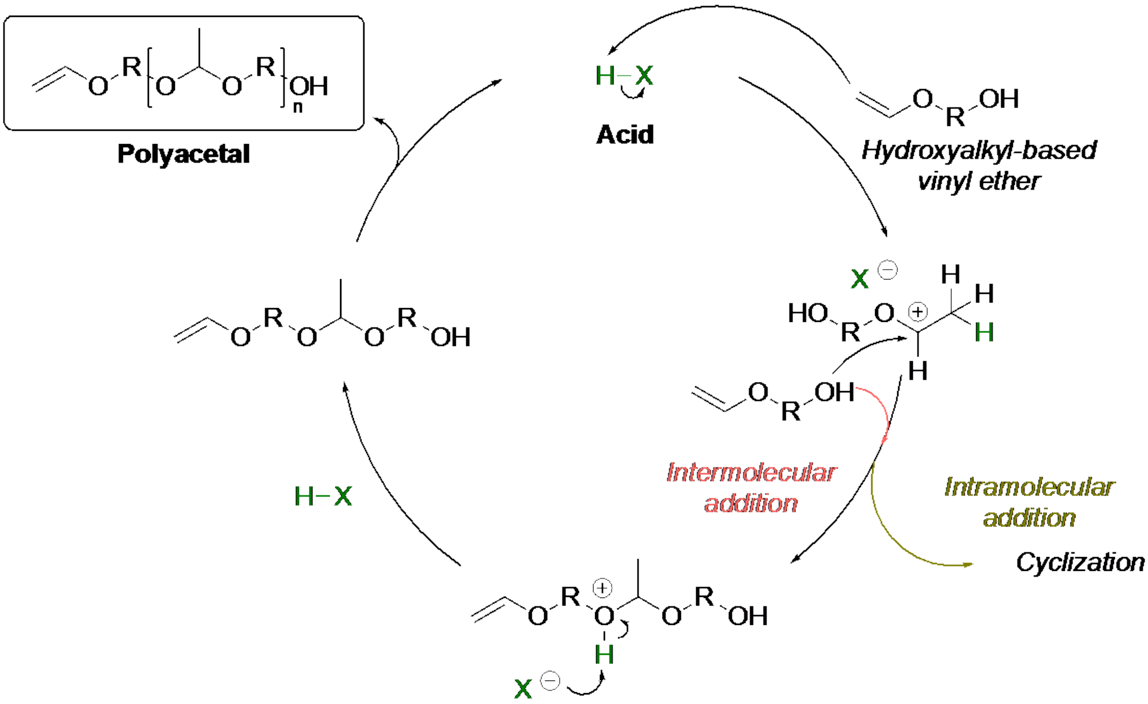


Scheme 60. Synthesis of functional polyacetals from the step-growth polymerization of tri(ethyleneglycol) divinyl ether with poly(ethylene glycol) and functional diols using *p*-TsOH as catalyst. Adapted from ref. [204,205,207].

Based on the same chemistry, Sui *et al.* recently reported acetal-based hydroxyethyl methacrylate-*co*-methyl methacrylate polymer (poly(HEMA-*co*-MMA)) crosslinked networks obtained from the reaction of the hydroxyl pendant groups of HEMA with 1,4-cyclohexanedimethanol divinyl ether, catalyzed by pyridinium *p*-toluenesulfonate (PTS) [208].

In 2000, Zhang and Ruckenstein reported the preparation of polyacetals from the self-polyaddition of hydroxyalkyl based vinyl ethers using pyridinium *p*-toluenesulfonate catalyst [201]. They found that while a small amount of catalyst was needed to activate the reaction ($mol_{monomer}/mol_{PTS}$ = 200–400), while larger amounts ($mol_{monomer}/mol_{PTS}$ = 80) tended to accelerate the polymer decomposition at longer reaction times (M_w = 10.2 kg.mol^{-1}, *Đ* = 2.2 and M_w = 6.6 kg.mol^{-1}, Đ = 2.0, respectively, after 75 hours of reaction).

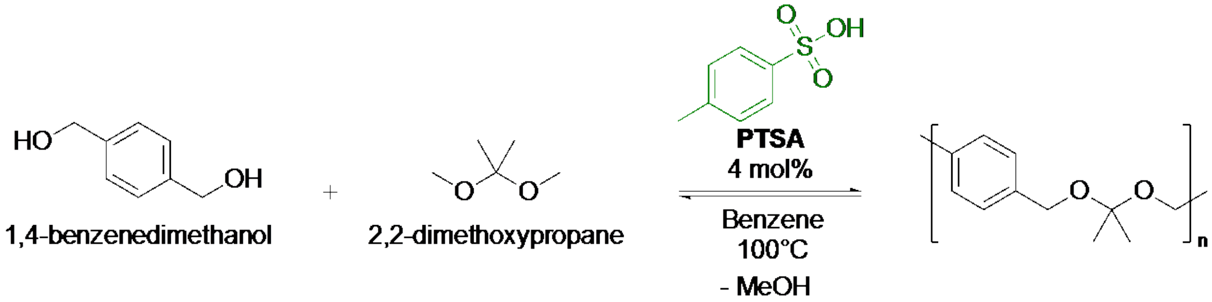
Later, Hashimoto *et al.* investigated the effect of the catalyst nature in the self-condensation of 4-hydroxybutyl vinyl ether. Performing the reaction in THF at 0 °C for 72 h with no catalyst or in the presence of catalytic amount of *p*-toluene sulfonic anhydride (PTSAA), *p*-TsOH, PTS, HCl or BF_3OEt_2, they observed that the polymerization occurred only in the presence of acid catalysts [203]. *p*-TsOH promoted full conversion within 1 h, and polyacetals with a M_n = 66.5 kg.mol^{-1} (*Đ* = 1.6) were thus obtained. However, after 4 h the molecular weight reached a plateau due to possible degradation of the acetal linkages *via* hydrolysis by water derived from the catalyst. In contrast, a higher molecular weight was achieved using PTSAA under the same conditions (M_n = 110 kg.mol^{-1}, *Đ* = 1.6), which was attributed to the ability of the anhydride to react with water forming the corresponding acid. In comparison, PTS led only to low molecular weight polymers (M_n = 3.4 kg.mol^{-1}, $Đ$ = 3.5). This could be explained by the difference in acidity between PTS, PTSAA, and *p*-TsOH. PTS indeed possesses the lowest acidity among the three acids, which results in a slower reaction rate and a lower molecular weight. HCl and BF_3OEt_2 also proved useful to catalyze the polyaddition reaction (M_n = 21.1 kg.mol^{-1}, $Đ$ = 1.9 and M_n = 28.3 kg.mol^{-1}, $Đ$ = 2.9, respectively). The authors proposed a mechanism in which the acid catalyst is able to form a carbocation. This carbocation is subsequently attacked by a hydroxyl group forming an acetal group, releasing a proton and subsequently regenerating the catalyst. The authors also proposed that some cyclic structures could be produced by intramolecular cyclization. (**Scheme 61**).



Scheme 61. Reaction mechanism for the acid-catalyzed self-condensation of hydroxyalkyl vinyl ethers. Adapted from ref. [203].

Similarly, the same authors reported the synthesis of a degradable polyurethane (PU) using polyacetals as soft-segments [206,210]. For example, polyacetal glycol (M_n = 1.6 kg.mol^{-1}, $Đ$ = 2.5) was first synthesized from the reaction between 1,4-butanediol and 4-hydroxybutyl vinyl ether in THF at 0 °C in the presence of *p*-TsOH catalyst. The obtained prepolymer was then reacted with 4,4'-diphenylmethane diisocyanate to afford PU with a molecular weight, M_n, of 49 kg.mol^{-1} and $Đ$ =1.7. For comparison, a conventional PU was prepared using polytetrahydrofuran as soft segment. Overall, the results of molecular weight, mechanical, and thermal properties were comparable to those obtained with a common thermoplastic PU elastomer. However, polyacetal-based PU exhibited superior degradation under acidic conditions [206].

Another strategy for the production of polyacetals which involves a diol and a ketal containing monomers is achieved via the poly(transacetalization) reaction (**Figure 17.f**) [40,211,212]. Linear polyketal could thus be prepared using a diol and 2,2-dimethoxypropane with PTSA catalyst (**Scheme 62**) [211]. Murthy *et al.* prepared poly(1,4-phenyleneacetone dimethyleneketal) using 1,4-benzenedimethanol diol obtaining low molecular weights polyacetals M_w = 4 kg.mol^{-1} ($Đ$ = 1.5). The authors suggested that the polymerization occurred in two steps. In the first step, low molecular weights dimers and trimers are formed, while in the second step, removal of the methanol by-product from the reaction media drives the reaction towards high conversion and high molecular weights. Polyketal nanoparticles that degrade under acidic condition were then formulated from the poly(1,4-phenyleneacetone dimethyleneketal) for drug delivery applications.

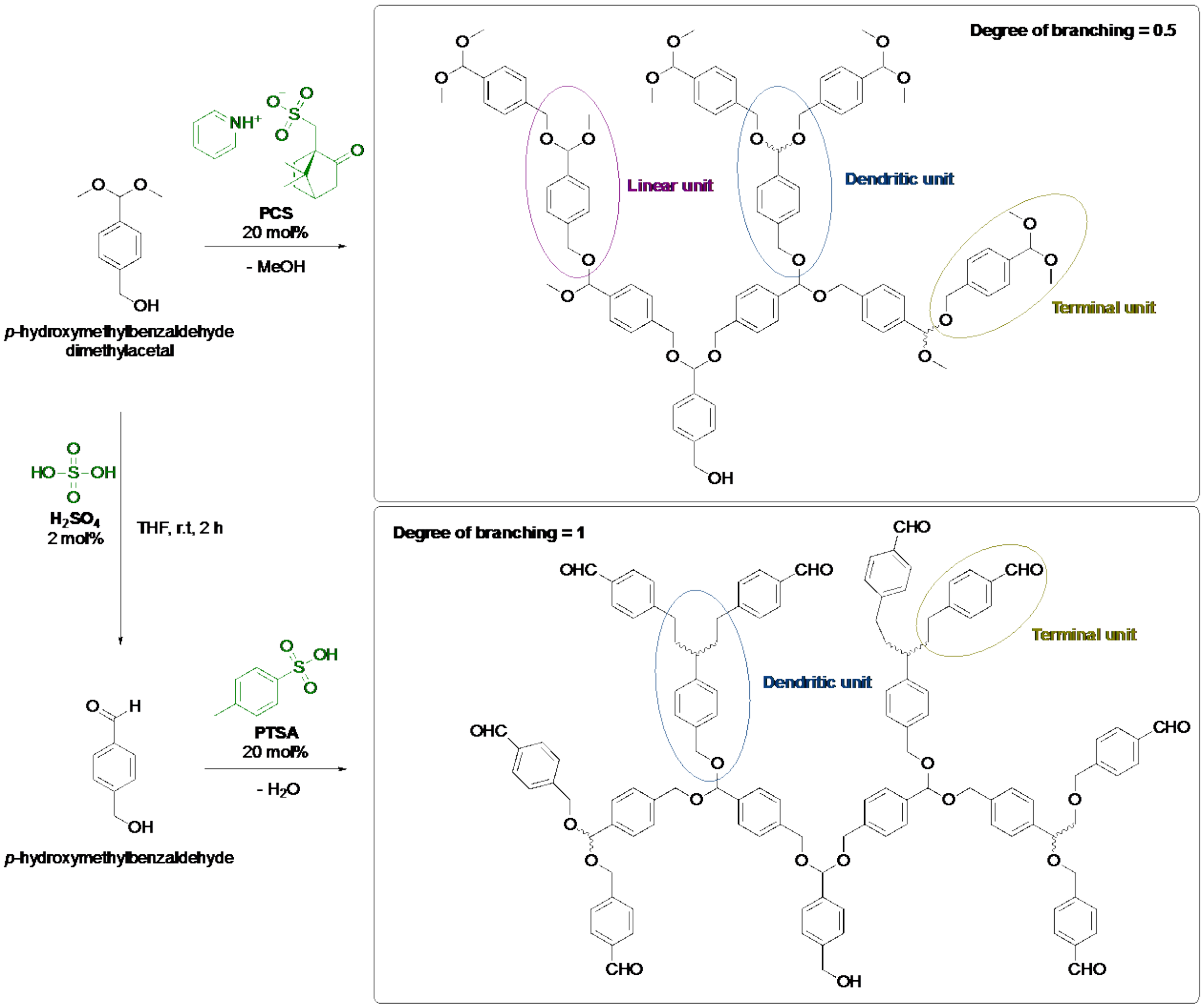


Scheme 62. PTSA-catalyzed polyacetal formation from 1,4-benzenedimethanol and 2,2-dimethoxypropane. Adapted from ref. [211].

The poly(transacetalization) was further exploited by Chatterjee and Ramakrishnan for the preparation of hyperbranched polymers using AB_2-type monomers, A being an alcohol functionality and B an acetal moiety [212]. In this case the authors used pyridinium camphorsulfonate (PCS) as catalyst and reported molecular weights of 21 kg.mol^{-1} and $Đ$ = 3.0 which is in agreement with common values obtained in branched polymerizations.

In a similar fashion, Taton and coworkers investigated different Brønsted acids such as PTSA, camphor-10-sulfonic acid (CSA) or PCS for the poly(transacetalization) and polyacetalization of AB_2-type monomers under inert atmosphere in THF (**Scheme 63**) [40]. The authors found that the presence of molecular sieves as water scavengers could enhance the polymerization. Under these conditions, molecular weights up to M_w = 1.6-3.3 kg.mol^{-1} ($Đ$ = 2-2.3) could be obtained with both PTSA and CSA catalysts at 50°C for the polyacetalization reaction of *p*-hydroxymethylbenzaldehyde. The authors further optimize the reaction by changing the molecular sieves every 2 days, resulting in significant enhancement of both conversion (86 %) and molecular weight (M_w = 19.3 kg.mol^{-1}, $Đ$ = 12.1) using PTSA over 7 days. Overall, PTSA, which possesses a higher acidity than CSA, provided higher conversions and molecular weights in both cases.

In the case of the poly(transacetalization), weak acids such as PCS were found more suitable. In this case the polymerization of *p*-hydroxymethylbenzaldehyde dimethylacetal reached molecular weight of M_w = 20.4 kg.mol^{-1} ($Đ$ = 1.7) in 2 h with a degree of branching near 50 %. The authors found that in this latter case, the degree of branching was lower than in the case of the polyacetalization which was almost quantitative. The authors suggested that this fact could be attributed to the different reactivities of intermediate species formed during the polymerization process.



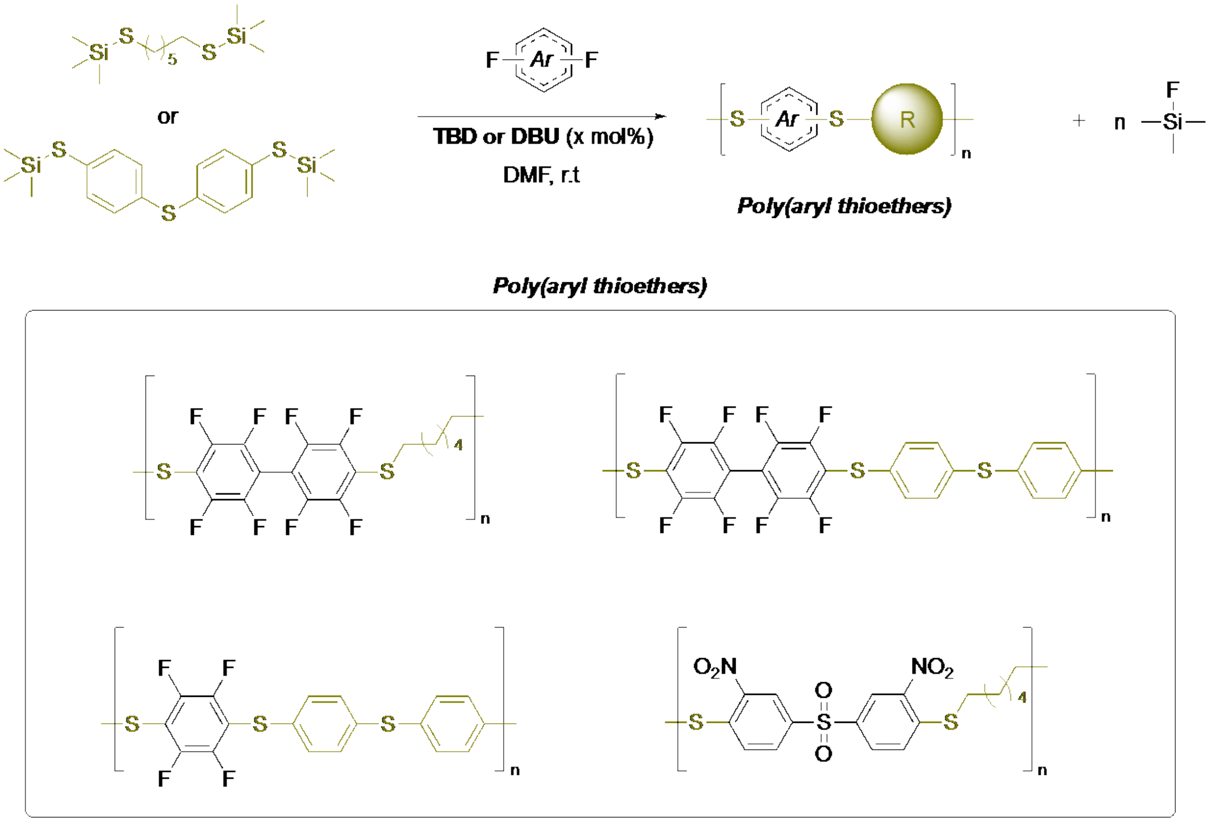
Scheme 63. Preparation of hyperbranched polyacetals from poly(transacetalization) and polyacetalization reactions in the presence of different organic acid catalysts. Adapted from ref. [40].

Another general method to incorporate acetal groups into polymers is by the step-growth or chain growth polymerization of acetal-containing monomers. For example, the Fréchet's group synthesized miscellaneous acid-degradable polyurethanes and polyurea-polyacetals by step-growth polymerization of bis(*p*-nitrophenyl carbamate/carbonate) or diisocyanate monomers possessing a ketal-containing diamine in the presence of triethylamine [213]. Although PTSA represents the most popular catalytic system for the synthesis of polyacetal via step-growth polymerization in all synthetic routes investigated, a complete study of the effect of the acidity strength on the polymerization kinetics, as well as the molecular weight of the polymers is still lacking.

5.7. Other step-growth organocatalyzed polymerizations

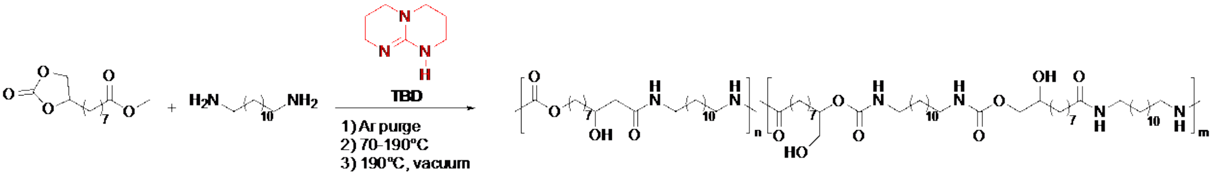
Besides the step-growth polymerization processes reviewed in previous sections, other types of step-growth polymerizations have been reported in the literature, for the preparation of metal-free polyamides, polyimides, and polysulfones. New polymer structures obtained by Ugi or Passerini multicomponent reaction processes, or by transforming the step-growth polymerization into living polymerizations [214,215], have been described. Use of organocatalysis in these polymerization processes remains underexplored, but with the intensive research going in the direction of metal-free polymerization processes, one can expect rapid progress in this area. The following lines discuss recent examples where novel types of organocatalyzed-polymerization processes were implemented.

For instance, Park and coworkers investigated the organocatalyzed polymerization reaction involving fluoroarene electrophiles and silyl thioethers (**Scheme 64**) [216]. Different organic bases such as DBU and TBD were investigated as catalyst to mediate the polymerization. They found that the polymerization occurred at room temperature in DMF with low catalyst loading (0.5 mol %) using TMS-protected 1,6-hexanedithiol and hexafluorobenzene reagents. In only 15 min, the authors reported full conversion and molecular weights of M_n = 6-7 kg.mol^{-1} ($Đ$ = 2.5-4). In the presence of weaker bases, such as TEA, diisopropylethylamine and DABCO, longer reaction times (14 h) were required and the resultant polymers exhibited lower molecular weights and dispersities (M_n = 2.5-3 kg.mol^{-1}, $Đ$ = 1.7-1.9). Under inert atmosphere, a polymer with much higher molecular weights (M_n = 33 kg.mol^{-1}) could be achieved within 15 min using 0.5 mol % of DBU. Computational studies revealed that the organocatalyst has a dual activation role facilitating the nucleophilic aromatic substitution reaction. The authors showed the ability to polymerize other fluoroarene electrophiles and silyl thioethers, and consequently a series of poly(aryl thioether)s were obtained in good yields.



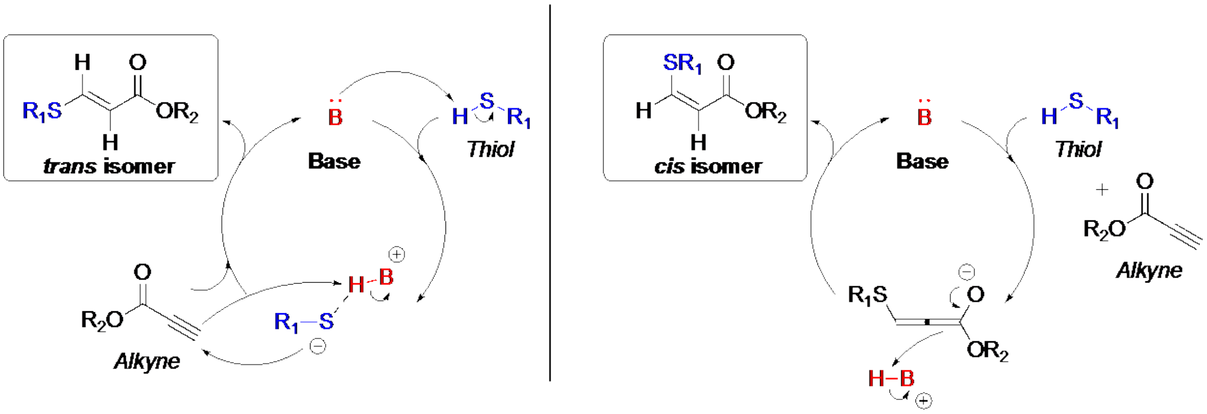
Scheme 64. Organic bases-catalyzed step-growth polymerization between trimethylsilane-protected thioethers with perfluoroarenes. Adapted from ref. [216].

In 2016, Long's group reported the preparation of non-isocyanate poly(amide-hydroxyurethane)s derived from biomass. Utilization of a monomer containing different functionalities, namely, cyclic carbonate and methyl ester, respectively, having the ability to react with primary diamines in the presence of TBD, gave poly(amide-hydroxyurethane)s [217]. The unique feature in this example is that by preparing a monomer with two functionalities, cooperative polymers with different polymer backbones could be synthesized. The polymerization was performed in bulk in a three-step procedure (**Scheme 65**). After being purged with argon, the medium was heating to 70 °C to allow melting of the monomers. The flask was then heated from 70 °C to 190 °C before a final vacuum step which aimed to completely remove the methanol byproduct. The non-segmented copolymer obtained exhibited a semi-crystalline behavior. However, due to solubility issues, no data about the molecular weights was provided. Incorporation into the formulation of varied amounts of poly(tetramethylene oxide) (PTMO)-based polyether diamine (M_n = 1 kg.mol^{-1}) led to copolymer with a segmented morphology, a higher flexibility, and a lower crystallinity compared to the non-segmented copolymer. Overall, the copolymers presented similar thermal properties than conventional polyurethanes, but showed weaker mechanical properties.



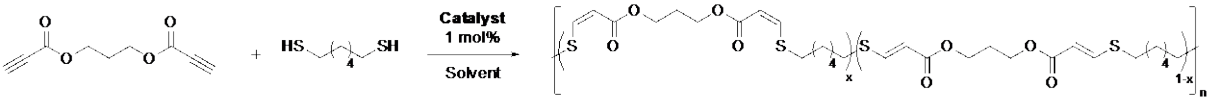
Scheme 65. AB type monomer for the preparation of poly(amide-hydroxyurethane)s in the presence of a diamine catalyzed by TBD organocatalyst. Adapted from ref. [217].

In another example, Truong and Dove demonstrated that properly selecting the organocatalyst for the thiol-yne polyaddition reaction allowed accessing materials with completely different mechanical properties, which was related to the regioselectvity of the polymerization [218]. Various bases, such as primary, secondary and tertiary amines, amidines and guanidines, and phosphine, were tested as potential catalysts for the reaction. Among them, only TEA (10 mol %), DBU (1 mol %), TBD (0.1 mol %) and dimethylphenylphosphine (1 mol %) were effective for the thiol-yne addition, with conversion higher than 85%. The regioselectivity of the reaction could be manipulated by choosing the appropriate catalyst/solvent system. The combination of weak bases, such as TEA, and non-polar solvents such as benzene and chloroform, caused the thiol and the catalyst to behave as hydrogen bonded-pair so that attack and deprotonation took place on the same side (**Scheme 66**) yielding the *trans* isomer. On the other hand, the combination of strong bases, such as DBU and TBD, and polar solvents, such as acetonitrile and DMSO, enabled the *cis* isomer to prevail due to the isolated thiolate anions that obey to the anti-addition rule (**Scheme 66**). Higher catalyst concentrations also increased the reaction rate, but did not affect the regioselectivity of the reaction.



Scheme 66. Proposed mechanism for the regioselective thiol-yne addition using non-polar solvent and/or weak base as catalyst (left) or polar solvent and/or strong base as catalyst (right). Adapted from ref. [218].

Taking advantage of the stereocontrol, using 1,6-hexanedithiol and propane-1,3-diyl dipropiolate difunctional monomers, *cis* and *trans* elastomers could be prepared (**Scheme 67**) [219]. In the presence of 1 mol% of DBU in $CHCl_3$, the *cis* isomer was predominant (M_w = 147.5 kg.mol^{-1}, $Đ$ = 5.6), while in the presence of 1 mol% of TEA in different mixtures of $CHCl_3$/DMF, polymers with different *cis/trans* ratios were obtained (*e.g.* $CHCl_3$/DMF = 3/7, *cis/trans* = 52/48, M_w = 131.1 kg.mol^{-1}, $Đ$ = 4.0).

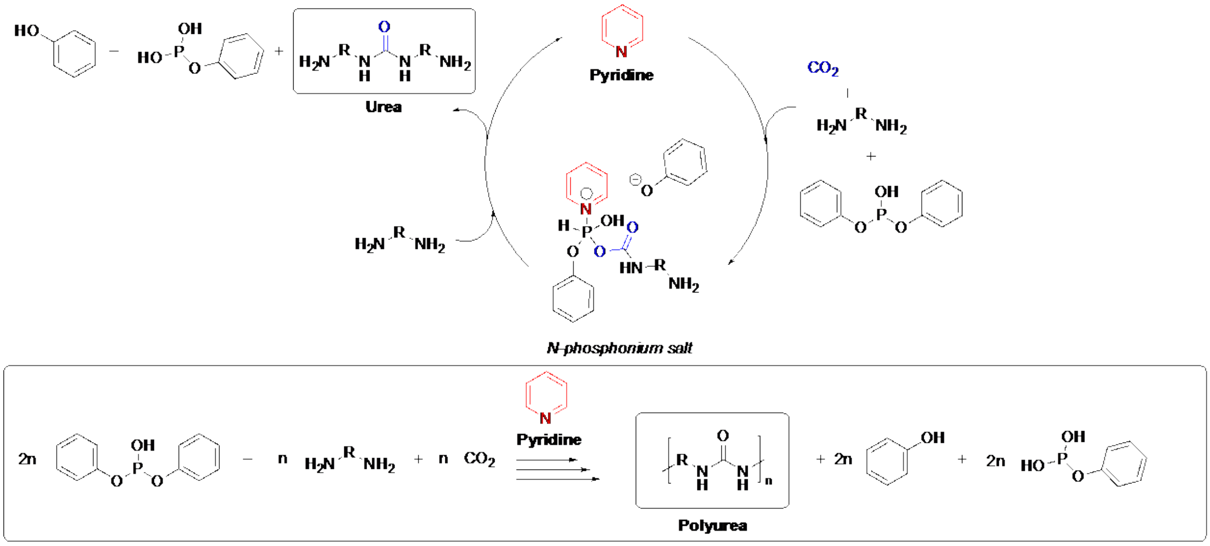


	Catalyst	Solvent	x
1	DBU	$CHCl_3$	0.8
2	TEA	DMF/$CHCl_3$ (1/1)	0.7
3	TEA	DMF/$CHCl_3$ (3/7)	0.52
4	TEA	DMF/$CHCl_3$ (3/17)	0.32

Scheme 67. Stereocontrolled thiol–yne polymerization from dialkyne and dithiol using different base organocatalysts Adapted from ref. [219].

The last examples use of carbon dioxide (CO_2) as a monomer source in polymerization processes. CO_2 is a gas naturally present in the atmosphere that can also be produced as a by-product from fossil fuel combustion, being an abundant, inexpensive, and non-toxic renewable source. For many years, attention paid to global warming have focused on reducing the carbon footprint, as a result lots of consideration has been given to the re-use of CO_2 [220]. While numerous papers can be found about the utilization of CO_2 as monomer for the synthesis of several types of polymers in the presence of metal catalyst, only a few are based on catalyst-free or organocatalyzed step-growth polymerizations.

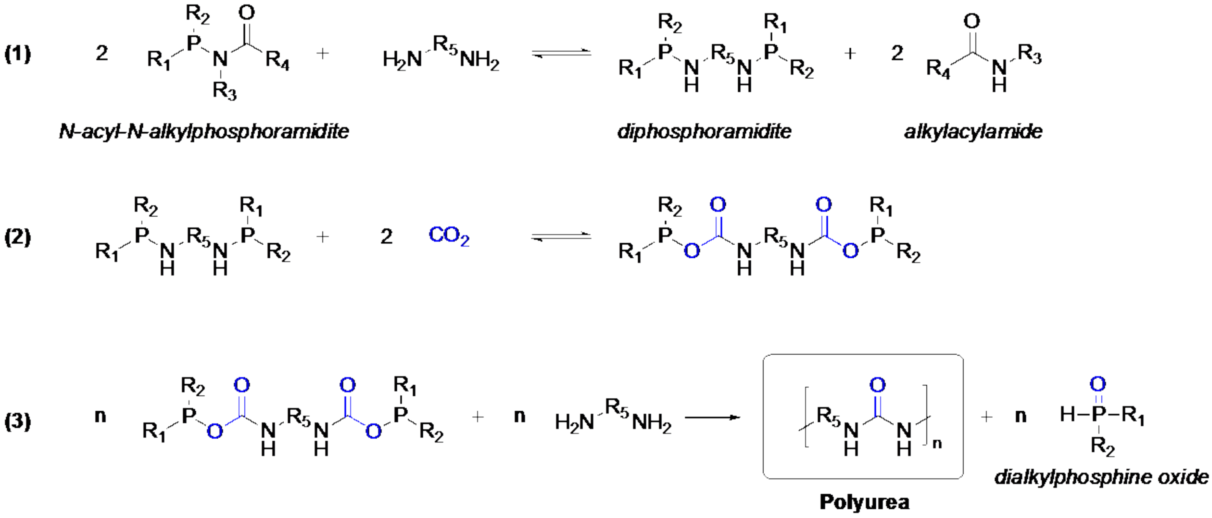
For instance, Yamazaki and coworkers showed that urea and thiourea can be synthesized by the direct reaction of CO_2 or disulfide with amines in the presence of di- or triaryl phosphites in pyridine. Herein, the phosphorous alkyl ester derivative plays the role of the condensing agent. The reaction proceeds via the formation of carbamyl *N*-phosphonium salts of pyridine given by the dephenoxylation of di- or triaryl phosphites with a tertiary amine (**Scheme 68**) [221]. Subsequently, they developed the direct polycondensation of CO_2 with diamines under mild conditions (40°C, 20 atm, 4 hours), in the presence of diphenyl phosphite and pyridine to form polyureas [222–224]. Notably, the reaction of CO_2 with aromatic diamines afforded high conversion under these conditions. Using 4,4'-diaminodiphenylmethane (MDA), molecular weights up to $M_n = 54.1$ kg.mol^{-1} were obtained. The effect of different tertiary amines (TEA, pyridine, 2,6-lutidine, imidazole, picoline isomers) on the formation of the *N*-phosphonium salt during the polycondensation of CO_2 with MDA was studied. Overall, the yield and the polymer viscosity were affected by the basicity of the amine, best results being noted with pyridine or picoline isomers ($5.23 < pKa < 6.02$).



Scheme 68 Synthesis of polyurea from the reaction of CO_2 with diamines in the presence of diphenyl phosphite in pyridine. Adapted from ref. [223].

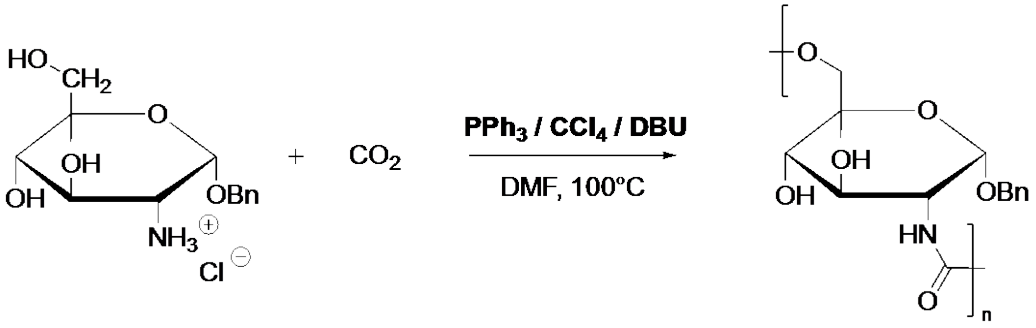
In the presence of other phosphorous catalyst compounds, such as triphenyl phosphite, phosphorous acid, monoethyl and diethyl phosphites, a different behavior was observed. Surprisingly, triphenyl phosphite yielded polymers in the presence of imidazole but not with pyridine. The same authors later found that the addition of pyridine hydrochloride facilitated the cleavage of the P—O—C bond in triphenyl phosphite, thus enhancing the formation of the corresponding phosphonium salt that subsequently reacts with pyridine to form the carbamyl *N*-phosphonium salts of pyridine [225].

Rokicki also performed the polymerization in the presence of *N*-acyl-*N*-alkylphosphoramidite compounds [226]. The reaction mechanism was described as follows: *N*-acyl-*N*-alkylphosphoramidite reacts with diamines leading to a diphosphoramidites and alkylacylamides (1). While subsequent insertion of CO_2 into the P-N bond of the diphosphoramidites yielded a mixture of anhydride of arylcarbamic and dialkylphosphorous acid (2). Polycondensation of the latter with diamines yielded the corresponding polyurea and the simultaneous release of dialkyl phosphine oxide (3) (**Scheme 69**).



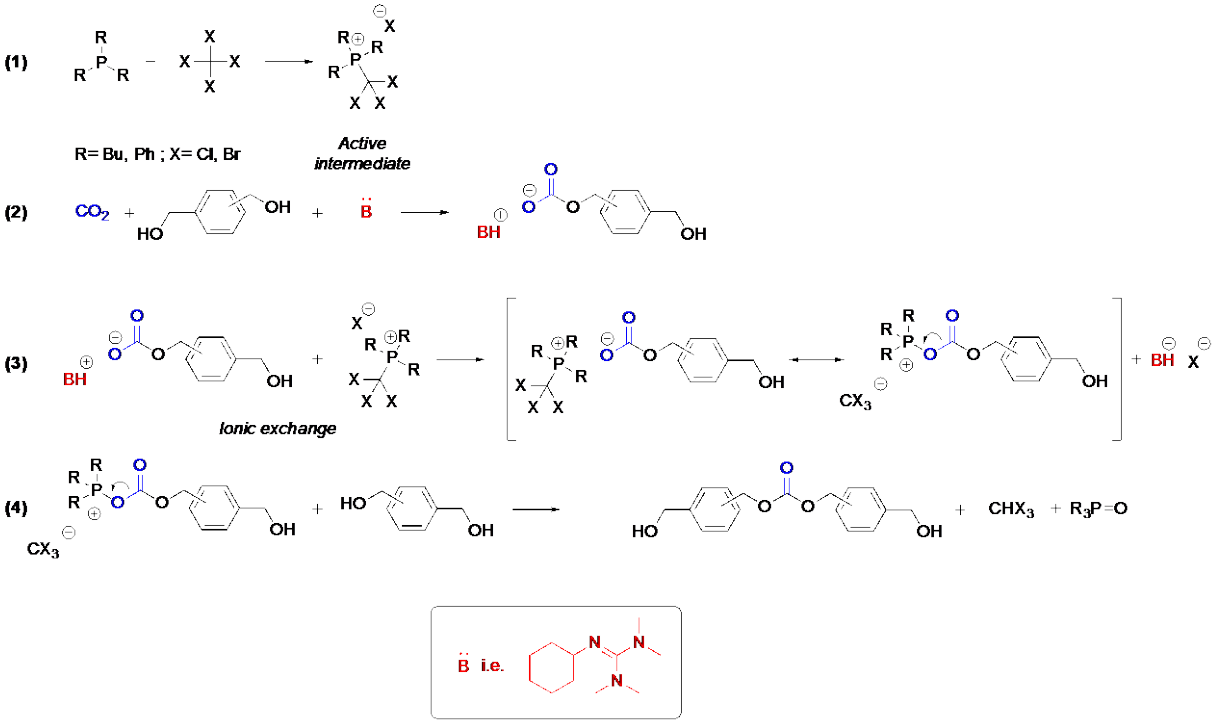
Scheme 69. Proposed mechanism for the synthesis of polyurea from the direct polycondensation of aromatic diamines with CO_2 in the presence of *N*-acyl-*N*-alkylphosphoramidite. Adapted from ref. [226].

Besides the preparation of polyureas, CO_2 was also used as a co-monomer for the preparation of polyurethanes. Chiba *et al.* thus performed the regioselective polycondensation of benzyl 2-amino-2-deoxy-α-D-glucopyranoside hydrochloride with CO_2 employing a triphenylphosphine/carbon tetrachloride/base system as a condensing agent in *N*,*N*-dimethylformamide (DMF) (**Scheme 70**) [227]. While no polymerization occurred with a weak base (TEA), polyurethanes containing glucosamine in their structure were obtained with a strong base (DBU). A temperature of 100 °C and a reaction time of 48 hours gave the best results, in terms of polymer yield and molecular weight. In order to assess the final molecular weights by SEC, the authors performed the acetylation of the polymers using acetic anhydride and reported molecular weight up to 3 $kg.mol^{-1}$ ($Đ$ = 1.7). Under similar conditions, the polymerization of D-glucosamide hydrochloride did not yield any polymer.



Scheme 70. Synthesis of polyurethane from the direct polycondensation of benzyl 2-amino-2-deoxy-α-D-glucopyranoside hydrochloride with CO_2 employing a triphenylphosphine/carbon tetrachloride/base system as a condensing agent. Adapted from ref. [227].

An intensive research related to the use of CO_2 as monomer deals with the preparation of polycarbonates, which represents an attractive alternative to the use of petroleum-based reagents. In 1994, the organocatalyzed direct polycondensation of carbon dioxide with different diols was reported [228]. Polycarbonates were achieved combining CO_2, diols, and dihalides in an aprotic solvent in presence of potassium carbonate. In other studies, polycarbonates were obtained from the reaction between aromatic diols and CO_2 in the presence of condensing agent of trisubstituted phosphine/carbon tetrahalide/base in aprotic solvent [229,230]. Using a [diol]:[Ph_3P]:[$CBrCl_3$]:[*N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine] ratio of 1.0:1.5: 2.0:2.0 in chloroform, a polycarbonate with a molecular weight of 5.8 kg.mol^{-1} was obtained [230]. The related mechanism is similar to that involved in polyurethane synthesis (see section 3.1.). The reaction starts with the formation of an active intermediate from the triarylphosphine and the carbon tetrahalide, which is followed by reaction with CO_2 and the diol in the presence of a base, forming a phosphonium compound. The nucleophilic attack of another alkoxide then produces the corresponding carbonate and phosphine oxide (**Scheme 71**).



Scheme 71. Proposed mechanism for the synthesis of polycarbonate from the direct polycondensation of aromatic diols with CO_2 in the presence of condensing agent of trisubstituted phosphine/carbon tetrahalide/base. Adapted from ref. [230]

Overall, these novel types of organocatalyzed-processes give an idea of the unlimited potential of organocatalysis for step-growth polymerization comparable to metal-based catalysts.

6. Limitations and Opportunities of Organocatalysis in Step-growth polymerizations: Future Outlook

Organocatalysts comprise a large array of compounds that demonstrate significant success in chain growth ROP and, more recently, in step-growth polymerizations. Over the past few years, organocatalysts displayed the ability to achieve high molecular weight polymers at loadings equivalent to traditional metal catalysts (0.1 mol %). This achievement extends a wide range of polymer systems from segmented polyurethanes to high performance polycarbonates and polyesters.

Among the metal based catalysts, metal alkoxides are the gold standards and the most commonly used catalysts in step-growth polymerizations. These compounds, such as titanium isopropoxide, antimony trioxide, and tin derivatives (i.e. DBTDL), undergo a complexation with carbonyls inducing a positive charge on the carbonyl carbon favoring nucleophilic attack. While there is no doubt that these catalysts produce high molecular weight polyurethanes, polycarbonate, polyesters and others at low catalyst loading, many detrimental issues arise in their use that lead researchers to investigate alternatives, such as organocatalysis.

Removal of catalysts from the final polymer still plagues materials using metal catalysts. Due to the extremely oxophilic nature of transition metal catalysts, removal after polymerization becomes incredibly difficult and costly. Residual metal catalysts have been linked to a range of unwanted properties including undesired aging, toxicity, and effects on dielectric constants [50]. In the case of dielectric materials in the microelectronics industry, the presence of residual metals impacts the insulating properties of these materials detrimentally [37,231,232]. Even in general use situations, if catalysts remain active, their continued reactions with the polymer often result in degradation pathways during processing or the increased rate of weathering [55,64,233]. The continued presence of metal catalysts in polyesters was previously linked to depolymerization under air at high temperatures and the overall decrease in thermal degradation temperatures [54,234]. Catalysts further accelerate the degradation reactions present in natural environments, such as hydrolytic cleavage and oxidation [37,231]. In the case of polyurethanes, organic acid catalysts exhibited none of the degradation products that were normally observed for DBTDL [38]. While not the focus of most current studies, it is understood that organocatalysts not covalently bonded to the polymer can be removed through common purification techniques. This fact has been emphasized in many research articles when synthesizing polymers for biomedical applications.

The toxicity of DBTDL, a commonly used catalyst in polyurethanes, provoked the implementation of regulations by the European Union to restricted its use [50,55]. Other studies of organo tin and aluminum catalysts demonstrated the possibility for endangering the functions of tissues through slow penetration into the blood circulation system [52–54]. Although less toxic alternatives, such as titanium based catalysts, have been implemented to fight against these regulations, these catalysts still do not overcome the detrimental effects from degradation. In contrast to these issues, organocatalysts currently used in step-growth polymerization (DMAP, TBD and *m*-trimethylammoniumphenolate betaine) only demonstrate toxicity when studied at concentrations much higher than the residual levels that would remain in polymers

[50]. A study of aliphatic polyurethanes demonstrated excellent biocompatibility when utilizing 5 mol % DBU catalyst [64]. This poses many unique opportunities for synthesis of materials in the biomedical industry that include stringent toxicity requirements.

Color formation during polymerization often arises through the use of metal catalysts. Titanium tetraisopropoxide was linked to the formation of color during polymerization of poly(ethylene terephthalate). This yellow discoloration resulted from a complexation occurring with the ethylene glycol monomer [149]. While this does not pose a huge threat to polymer use on the small scale, this represents an important consideration for many commercial polymers. This represents one of the main limitations organocatalysis will have to overcome to be industrially implemented. Nevertheless, Flores *et al*. and Jehanno *et al*. have demonstrated that using protic ionic compounds there is not any discoloration in the resulting polymer which could facilitate the implementation in industrial processes [139,165].

Organocatalysis in polymerization processes will continue to revolutionize the field, ranging from more thermally stable polymers that are more amenable to recycling to novel sequences where regioselectivity will enable novel thermomechanical performance. Organocatalysis will also expand the current scope of reactions that are amenable to the formation of high molecular weight, ensuring high degrees of conversions at reaction conditions that were previously unattainable. Although step-growth polymerization has been present in the literature since the early 1900s, the potential synthetic methods to achieve high molecular weight polymers remains relatively small, thus there is a need to expand the toolbox of reactions to prepare high performance engineering polymers. In addition to enabling new compositions, organocatalytic mechanisms will fundamentally point to new reactions, tailoring of sequence control, and the introduction of functional group at modest temperatures. These new reaction conditions that were previously not attainable are expected to expand the range of processing techniques, including recent advances in additive manufacturing, particularly for rapid reactions and photo-allowed reactions for extrusion and lithography, respectively. It is important to note that many of the catalysts used in commodity polymers were discovered many decades ago, yet a fundamental understanding of the catalytic mechanism for many traditional catalysts is lacking. Key questions including the mechanism of the catalysts at exceptionally high temperatures and low pressures complicates an interpretation of catalytic mechanisms, thus rationale design of organic catalysts will allow for the first time fundamental advances in catalytic mechanism relative to their inorganic counterparts. The use of more sustainable approaches for polymer production such as organocatalysis or biobased compounds is gaining a lot of attention specially in step-growth polymers to modify the currently unsustainable polymerization processes. From a green and sustainable chemistry standpoint, the current challenge in the industry is to switch from petrobased to biobased polymers in certain applications where we believe that the choose of the appropriate organocatalysis will be the key.

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