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# *N*-Heterocyclic carbenes: Effective organic catalysts for living polymerization

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**Abstract**

An organocatalytic approach to living and condensation polymerization using *N*-heterocyclic carbenes as nucleophilic catalysts is detailed. The *N*-heterocyclic carbene catalyst platform is extremely versatile with the nature of the substituents having a pronounced effect upon catalyst stability and activity towards different substrates. Rapid screening of libraries of catalysts provided a basic understanding of catalyst structure (sterics, electronics, etc.) as it influences the polymerization rate, control, substrate and range of molecular weights. ROP from an immiscible ionic liquid (precatalyst reservoir) and a THF solution of monomer and initiator is presented as a simplified method of carbene formation. In situ activation of the ionic liquid generated a nucleophilic *N*-heterocyclic carbene, which migrates to the organic phase effecting ROP. Other simplified methods of generating carbene thermally from carbene adducts are also presented as polymerization catalysts.
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*Keywords:* Carbene; Ring-opening polymerization; Lactide

## 1. Introduction

The last few years have witnessed significant advancement in the use of simple organic compounds to improve or facilitate classic organic synthesis, owing, in part, to the ready availability of enantiopure molecules [1]. These catalysts are generally inexpensive, easily tethered to solid supports, readily reused and, unlike biocatalyst and bioinorganic catalysts, can be used without stringent purification of solvents and reagents. For example, proline has been used as a benign organocatalyst for the Mannich reaction (precursor to β-lactam), as well as a number of other transformations in place of the traditional organometallic catalysts [2]. The organocatalytic asymmetric hetero-Diels–Alder reaction of aldehydes with enones as well as the asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds and α,β-unsaturated ketones were demonstrated by Jorgensen [3]. Along similar lines, MacMillan has reported the first highly enantioselective organocatalytic inter- and intramolecular Diels–Alders reactions, 1,3-dipolar cycloadditions, and 1,4-conjugate Friedel–Crafts additions involving pyrroles as well as the first enantioselective organocatalytic alkylation of indoles catalyzed by imidazolidinone [4]. Miller has devised several new functional peptides that catalyze the kinetic resolution of selected secondary alcohols [5] as well as a variety of other transformations [6]. Several groups have reported effective non-enzymatic catalysts for the kinetic resolution of secondary alcohols using 'planar–chiral' heterocycles, these catalysts, based on tertiary phosphine and amine frameworks, provide good levels of enantiomeric excess [7]. Other noteworthy examples of organic catalysts for similar reactions include those of Fuji [8], Spivey [9], Oriyama [10] and Vedejs [11]. To some degree this strategy mimics that carried out by enzymes. Alternatively, Lewis bases including tertiary amines and phosphines, pyridines and imidazoles have been shown to be effective nucleophilic catalysts that accelerate a wide variety of processes. For example, 4-(dimethylamino)pyridine (DMAP) and related Lewis bases such as tertiary phosphines are widely used and extremely efficient reagents for acylation, alkylation, silylation, phosphorylation, condensation and trans-esterification reactions [12]. These trends towards environmentally sound organocatalysts have stimulated 'greener' versions of classic synthetic asymmetric reactions [13]. The extension of organic catalysis to controlled polymerization procedures is a highly desirable alternative to traditional organometallic approaches.

Our interest is in the ring-opening polymerization (ROP) of cyclic esters, particularly lactide and ε-caprolactone. To date,

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there are only a few reports on the ROP of cyclic ester monomers that do not employ organometallic promoters. The synthesis of biomacromolecules generally involves in vivo enzyme-catalyzed chain growth polymerization reactions within cells. Enzymes exhibit high stereo-, reaction- and substrate specificity, and come from renewable resources that can be easily recycled. Recent advances in non-aqueous enzymology have permitted alternative reaction environments including organic solvents, resulting in new biocatalytic methodologies for the controlled ROP of a wide variety of monomers [14]. In the search for organic catalysts for the ROP of cyclic esters, we considered biocatalysts, many of which employ nucleophiles in the active site or as cofactors. Abiological strategies employing nucleophilic tertiary amines [15] and phosphines [16] as catalysts for the ROP of lactide yield modest molecular weights, but are not general for other strained cyclic esters. *N*-Heterocyclic carbenes are another class of potent nucleophilic compounds that can be exploited as catalysts to effect polymerizations.

Wanzlick's [17] pioneering studies of the chemistry of bis-1,3-diphenyl imidazolin-2-ylidene carbenes [18] laid the groundwork for Arduengo's [19] and Bertand's [20] elegant studies on the synthesis, isolation, and characterization of the first stable imidazolin-2-ylidene and imidazol-2-ylidene carbenes [21]. Enders described a carbene based on the triazole heterocycle that was stable to high temperatures in the absence of air and water, and became the first commercial carbene available in gram quantities [22]. The chemistry of *N*-heterocyclic carbenes (NHC) has since become a major area of research [23] as these stable carbenes have proven to be outstanding ligands for transition metals [24] as well as potent nucleophilic organic catalysts [25]. It is well established that thiazole carbenes are catalysts for many relevant biological transformations. Early work by Breslow, Stetter and others illuminated the role of thiamine cofactors in nucleophilic catalysis, and postulated the general concept that a carbene can participate in an organic transformation of an aldehyde as a reactive intermediate [26]. For example, in the benzoin condensation reaction, Breslow proposed acyl activation by a carbene intermediate [25a]. Recently, Murry et al. suggested a similar mechanism in the thiazolium-catalyzed cross-coupling of aldehydes with acylimines [27]. In several related thiazolium-catalyzed transformations, the mechanism was postulated to proceed through the bis(thiazolin-2-ylidene) reactive intermediate; generated in situ from the thiazolium salt. Both Enders and Rovis [26a,b] have reported that the triazole carbenes are effective catalysts for the intermolecular Stetter reaction and Benzoin condensation with high enantioselectivities. In addition, the triazole-based carbene catalyst proved to be very powerful for the formoin condensation converting formaldehyde to glycolaldehyde. Recently, we and Nolan [28] have demonstrated that NHCs are also potent trans-esterification catalysts for a variety of esters and alcohols. Moreover, as a general trans-esterification catalyst, we extended the NHC catalysts platform to effect polycondensation polymerization reactions as a practical route to engineering polyesters [28t]. Along similar lines, Bode has demonstrated carboxylates from epoxyaldehydes using NHC catalysis [29].

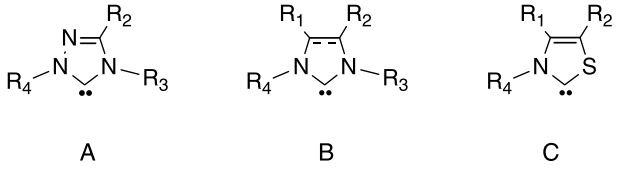



Fig. 1. Structural diversity of *N*-heterocyclic carbenes.

We envision that the carbene catalyst platform has the potential to become a general methodology for the ROP of a variety of cyclic esters in much the same way that controlled radical polymerization procedures are to vinyl monomers [30]. Herein, we describe our recent efforts toward the ring-opening polymerization (ROP) of strained cyclic esters using a variety of NHCs as organic catalysts with the objective of controlling molecular weight, polydispersity, end-group fidelity as well as the synthesis of block copolymers and complex macromolecular architectures [25]. Carbenes can be synthesized with considerable diversity by varying the heteroatom in the ring (X = N or S), the steric and electronics of the groups attached to the imidazole ring ($R_{1-2}$) and the nitrogen(s) ($R_{3-4}$), and the ethylene backbone (i.e. saturated versus unsaturated) (Fig. 1(a)–(c)). These structural and electronic variations were used to tailor the activity towards different strained esters. In addition, we were prompted to examine in situ methods for generating carbene catalysts as well as protected NHCs to avoid the difficulty of isolating sensitive carbene complexes and to facilitate polymerization studies.

## 2. Experimental

### 2.1. Characterization

$^1$H NMR spectra were recorded in either $CDCl_3$ or acetone-$d_6$ with a Bruker Avance 2000 (400 MHz) spectrometer with the solvent proton signal as an internal standard. $^{13}$C NMR spectra were recorded at 100 MHz on a Bruker Avance 2000 spectrometer with the solvent carbon signal as internal standard. Gel permeation chromatography (GPC) or size exclusion chromatography (SEC) were carried out on a Waters chromatograph connected to a Waters 410 differential refractometer. Polystyrene samples of known molecular weight were used as calibration standards. Four 5 μm Waters columns ($300 \times 7.7$ mm$^2$) connected in series in order of increasing pore size (100, 1000, $10^5$, $10^6$) were used with THF as a solvent.

### 2.2. General procedure for in situ imidazolium and imidazolinium based catalyst formation and solution polymerization of L-lactide

In the glovebox, a vial equipped with a stirbar was charged with 1,3-bis-(2,4,6-timethylphenyl)imidazolium chloride salt

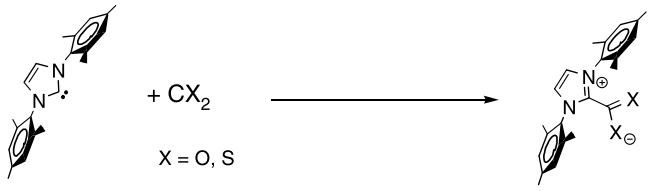
(8.2 mg, 24 μmol) and potassium *tert*-butoxide (2.4 mg, 21 μmol). 2 mL of THF was added and the reaction was stirred for 10 min. After 10 min a light yellow solution was observed. The reaction mixture was filtered through a 10 μm filter. Benzyl alcohol (1.5 mg, 14.4 μmol) was added by microsyringe. To the stirring reaction mixture a solution of L-lactide, (120 mg, 8.3 mmol) dissolved in 3 mL of THF, was added. After completion, the reaction was quenched with $CS_2$. The polymer was precipitated from methanol and dried to a constant weight.

### 2.3. Typical polymerization from adduct

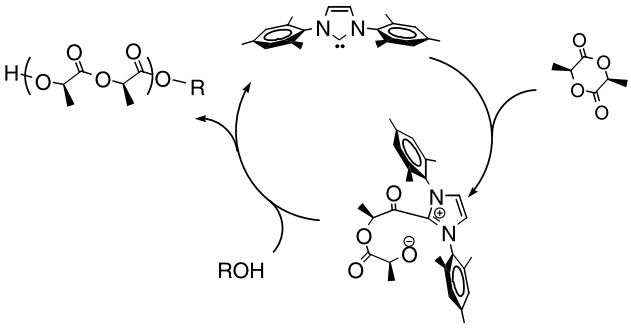
In the glove box, **8** (8.1 mg, 17.1 μmol), benzyl alcohol (1.8 mg, 17.1 μmol), and L-lactide (240 mg, 1.7 mmol) were combined in a 20 mL vial equipped with a stir bar. 10 mL of THF was then added to the reaction mixture. The vial was then capped and sealed with electrical tape. The vial was taken out of the glovebox and place in a 65 °C oil bath. After 10 min the solution color changed from colorless to light yellow. After 3 h of stirring, the reaction was removed from the oil bath and quenched with $CS_2$. The polymer was precipitated from cold methanol and isolated by filtration. The polymer was dried under reduced pressure to yield poly(L-lactide) as a white powder (192 mg, 80%).

## 3. Results and discussion

Living polymerization strategies provide a powerful means of generating well-defined polymers of predictable molecular weights, narrow molecular weight distributions and controlled chain-end functionality as well as the means to tailor the physical and solution properties through novel chain topologies and block copolymers. We have demonstrated that NHCs are extraordinarily active ring-opening polymerization (ROP) catalysts for cyclic esters including lactones and lactides [25g,h]. The living character (i.e. no termination side reactions) of the polymerization was demonstrated by the linear correlation of molecular weight versus monomer conversion, narrow dispersities and predictable molecular weights. Catalytic activity showed little solvent dependence; rates of lactide polymerization were indistinguishable in THF, dichloromethane or toluene. High molecular weight polylactides ($M_n > 25{,}000$ g/mol) were readily synthesized within 10 min at room temperature. Catalyst ratios of 0.25–1.5 equiv. relative to initiating alcohol for targeted DP's of >100 produced narrowly dispersed polylactides in 1–2 M THF lactide solutions. Higher monomer concentrations or catalyst/initiator ratios resulted in polydispersities greater than 1.2. Significant reduction of the catalyst/initiator/monomer ratio was necessary to achieve narrowly dispersed oligomers. Importantly, the controlled polymerization of lactide at a catalyst/initiator/monomer ratio of 1:80:1200, demonstrates the astonishing efficiency of this catalytic process. Termination of the polymerization and deactivation of the catalyst was accomplished by the addition of acetic acid, $CO_2$ or $CS_2$, the latter of which form a zwitterionic species that are easily removed upon precipitation, precluding exhaustive extractions (Scheme 1).




Scheme 1. Carbene trapping reaction.




Scheme 2. Polymerization of lactide by NHCs.

We propose a mechanism in which the monomer is activated by the carbene, with propagation occurring by acyl-oxygen cleavage and esterification with alcohol present in solution. Propagation through chain extension of the alcohol species affords high molecular weight polymers (Scheme 2). Whilst the polymerizations demonstrate remarkable controll, with the final polymers displaying narrow polydispersities, the ability of these catalysts to perform trans-esterification reactions leads to broadening of the polymer polydispersities at very high monomer conversions (>95%).

We were interested in exploring the influence of NHC structure on catalytic activity for lactide polymerization. Arduengo has reported that replacing bulky mesityl or 2,6 diisopropylphenyl groups with smaller substituents at the 1,3 positions results in less sterically demanding carbenes however, **2** and **3** are only modestly stable oils when isolated but are significantly more stable in solution [31]. Carbenes **2** and **3** (Fig. 2) were extremely active toward lactide polymerization generating narrowly dispersed

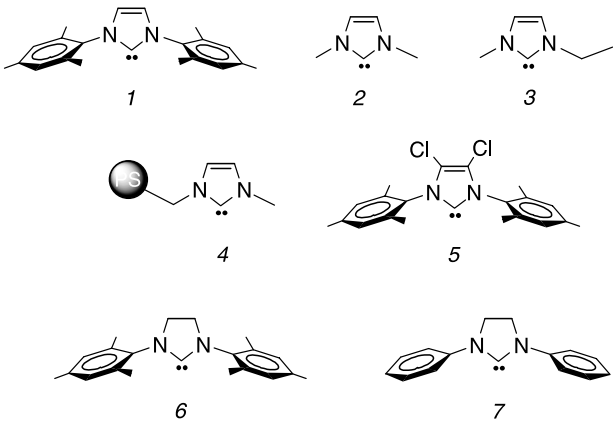



Fig. 2. NHCs **1**–**7**.

Table 1
Variation of carbene for polymerization of lactide

| Entry | Precatalyst | Time (h) | Conv. (%)[a] | DP[a] | PDI[b] |
|---|---|---|---|---|---|
| 1 | **1**-$H^+Cl^-$ | 0.25 | 85 | 173 | 1.18 |
| 2 | **2**-$H^+Cl^-$[c] | 1 | 60 | 123 | 1.16 |
| 3 | **3**-$H^+Cl^-$ | 0.25 | 97 | 194 | 1.31 |
| 4 | **4**-$H^+Cl^-$ | 1 | 95 | 190 | 1.52 |
| 5 | **6**-$H^+Cl^-$ | 0.25 | 99 | 190 | 1.23 |
| 6 | **7**-$H^+Cl^-$ | 0.25 | 99 | 197 | 1.46 |

*Conditions*. All experiments were performed in THF at 20 °C, initiated using benzyl alcohol, catalysts were generated in situ with 1 equiv. potassium *tert*-butoxide, [M]/[I]/[C] = 200:1:1.5, $[LA]_0 = 0.16$ M.
[a] Determined by $^1H$ NMR.
[b] Determined by gel-permeation chromatography.
[c] [M]/[I]/[C] = 200:1:0.25.

products of predictable molecular weight, but polymerizations were less controlled than those utilizing **1** (Table 1, entries 1–3). Catalyst:initiator ratios of less than 0.5:1 were required to obtain controlled lactide polymerization reactions while monomer concentrations of $\leq 1$ M were necessary to obtain narrowly dispersed polymers. Methyl imidazole reacts with Merrifield resin to afford a solid supported precatalyst, **4**. This catalyst is active for polymerization although the polymers produced are typically less well-controlled in comparison to **3**.

The effect of introducing electron withdrawing subtituents at the 4,5 positions of the imidazole ring was examined. Arduengo and coworkers have demonstrated that the stability of **1** was significantly enhanced upon chlorination of the olefin backbone, suggesting that *N*-heterocyclic carbene reactivity may be 'electronically' tunable. For example, 97% conversion was achieved within 10 s with catalyst **2**, while only 15% conversion is observed with catalyst **5** under identical conditions, clearly showing that the chloride substituents have a pronounced effect on reducing the carbene reactivity. Saturation of the *N*-heterocyclic carbene backbone (imidazolin-2-ylidene carbenes) also gives rise to distinct differences in stability relative to unsaturated imidazol-2-ylidene carbenes. For example, unlike imidazol-2-ylidenes, imidazolin-2-ylidene carbenes readily dimerize if bulky substituents are not introduced at the 1,3 positions to provide kinetic stability [32]. We were interested in determining how these differences effect lactide polymerization. Carbene **1** and 1,3-bis-(2,4,6-trimethylphenyl)imidazolin-2-ylidene, **6**, provide a direct comparison. The carbene **6**, synthesized in situ from the appropriate salt precursor, was an extremely active lactide polymerization catalyst and produced high molecular weight polylactides at room temperature in $<10$ min (Table 1, entry 5). However, no significant differences in ROP reactivity between **1** and **6** were observed. Like **1**, polymerization reactions with **6** require attention to catalyst and monomer concentrations to obtain narrowly dispersed polymers. Catalyst:initiator ratios of 0.5–1:1 in $\leq 1$ M solutions of lactide monomer routinely resulted in controlled polymerization reactions.

Although the imidazolin-2-ylidene carbenes are prone to dimerize in the absence of bulky groups at the 1,3 positions, Wanzlick's original work demonstrated that tetraaminoethylene complexes have reactivity characteristic of nucleophilic carbenes [33]. To further investigate the scope of imidazolin-2-ylidene nucleophilic catalysts, we were prompted to explore the utility of 'Wanzlick' carbenes as potential polymerization catalysts. Bis-1,3-diphenyl-imidazolin-2-ylidene, **7**, prepared in situ from its salt precursor was indeed a potent lactide polymerization catalyst (Table 1, entry 6). Controlled polymerizations were difficult to achieve with these catalysts; the resulting polymers had broad polydispersities (PDI = 1.5–1.6).

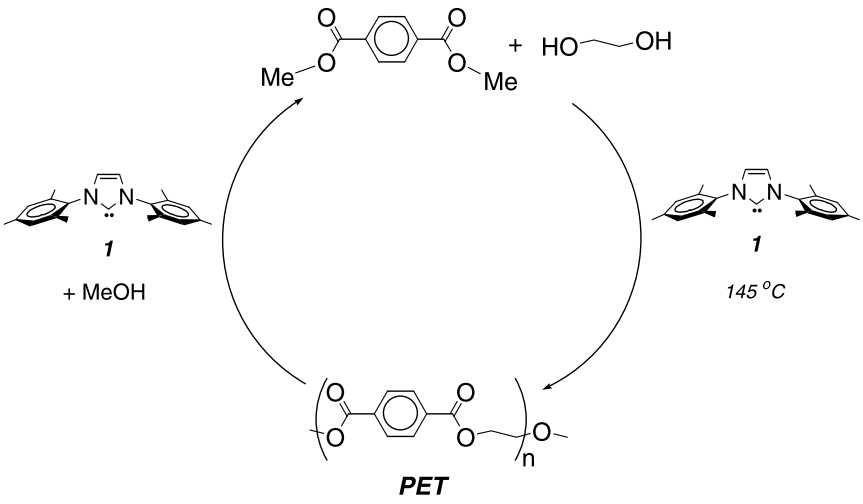
### 3.1. Condensation polymerization/trans-esterification reactions

The ester moiety is perhaps the most ubiquitous functional group in chemistry and biology, and serves as a key intermediate in organic transformations. Consequently, an efficient and selective method for the generation of ester groups is very useful. We and Nolan have demonstrated one of the first organocatalytic methods to prepare ester linkages using NHCs as nucleophilic trans-esterification catalysts [28].

An important commercial polyester, poly(ethylene terephthalate) (PET), is generally prepared by a two step process: condensation of dimethyl terephthalate (DMT) with excess ethylene glycol (EG) to generate bis(2-hydroxyethyl) terephthalate (BHET) followed by the self- condensation of BHET at high temperatures (270–290 °C) using mixed organometallic catalysts optimized for their reactivity and selectivity for each process. It is of great interest to extend this catalyst platform to show polymerizations via typical trans-esterification/polycondensation reactions. Catalytic amounts of NHC were found to effect each reaction of this vital commercial material using mild polymerization conditions in near quantitative yields (Scheme 3).

### 3.2. Living polymerization in ionic liquids (solvent/precatalyst reservoir)

We have been interested in developing facile methods for the delivery of NHCs to efficiently effect the polymerization of lactide and lactones. One such possibility is the application of ionic liquids as catalyst reservoirs. Ionic liquids (IL) have recently received significant attention as an environmentally preferred solvent alternative [34]. Owing to their low vapor pressures they may be used to replace particularly volatile solvents and they are readily recycled. Interestingly, we realized that ionic liquids can be readily activated to generate the desired NHC in situ and in this way, the IL can serve a dual function as both a solvent and catalyst [25j]. Two strategies were demonstrated: (1) neat IL and (2) biphasic polymerization comprised of IL as a precatalyst reservoir and an immiscible THF solution of monomer and initiator. Polymerization in neat IL proceeded to ca. 50% conversion before polymer precipitation in the IL occurred, however, the biphasic system led to a well controlled, novel phase transfer organocatalytic ring-opening

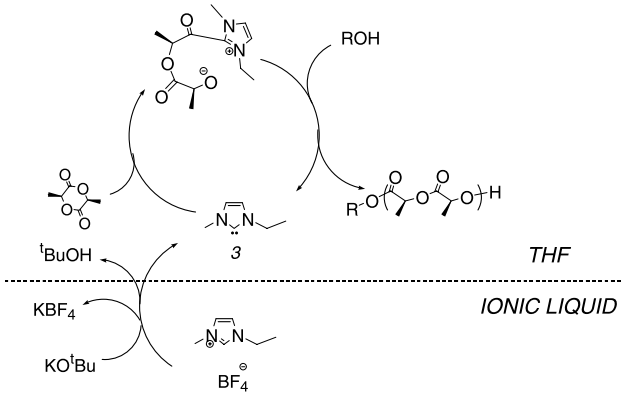



Scheme 3. Polymerization and depolymerization of poly(ethylene terephalate) by NHCs.

polymerization. In situ activation of the ionic liquid generated a nucleophilic NHC, which migrates to the organic phase effecting ROP leading to high molecular weight PLAs ($M_n > 24{,}000$ g/mol) with relatively narrow polydispersities (PDI = 1.4) (Scheme 4). Pre-catalyst (ionic liquid) regeneration terminates polymerization in a fully recyclable system. This reaction/recycle protocol allows repetitive ROP from the ionic liquid.

### 3.3. Thermally generated N-heterocyclic carbenes

Arduengo and others observed that the saturated (1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) *N*-heterocyclic carbene, **6**, cleanly undergoes a C–H insertion reaction with compounds containing acidic C–H bonds to form stable NHC adducts, whereas the corresponding unsaturated carbenes lead to more complicated mixtures of products [35]. Arduengo implicated that this adduct yielded the free carbene upon melting. Lappert [36] and Grubbs [37] have utilized the chloroform adducts to generate transition metal carbenes and implicated that free carbenes were generated in these reactions.



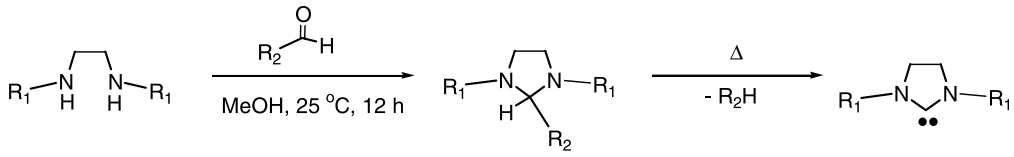

Scheme 4. Polymerization of lactide using an ionic liquid reservoir to generate NHC catalyst.

Enders carried out analogous investigations on the methanol adduct of the 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4,-triazol-5-ylidene: thermolysis of this methanol adduct cleanly liberated the free carbene and methanol [38]. The elimination of alcohols from methanol or *tert*-butanol adducts of carbenes has proven a useful strategy for generating transition metal carbene complexes [37–39], but the role of free carbenes in these processes has never been clearly demonstrated.

We described a general strategy for generating a variety of carbene adducts from the corresponding diamines and aldehydes (Scheme 5), and showed that thermolysis of these adducts provides a convenient source of carbenes in a tunable manner depending on the nature of the adduct [40]. NHC adducts were prepared by acid-catalyzed diamine/aldehyde condensation from readily available starting materials. Unlike adducts derived from chloroform, the pentafluorobenzene-based adducts are stable at room temperature. Thermolysis of these adducts generates the carbenes in solution, which we have shown are effective organic catalysts for trans-esterification reactions and ring-opening polymerization reactions. These adducts also provide convenient synthons for the generation of transition metal complexes. The thermal elimination of the arenes from the carbene adducts depends on the substituents on the carbene and the adduct, providing a convenient method for tuning the rate of carbene generation in situ (Fig. 3).

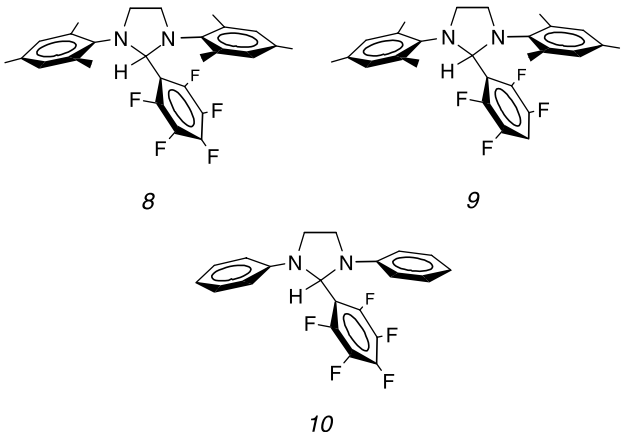
The in situ thermal generation of NHCs from these adducts and polymerization of lactide generally resulted in well-controlled polymerization. However, it is noticeable from Table 2 that not all NHC adducts are efficient pre-catalysts for ROP. Both the reduction in fluoro substitution and steric bulk of the carbene-aryl substituents lead to a less well-controlled polymerization, with **9** and **10** requiring significantly higher temperatures than **8** to reach comparable conversions. It is believed that this is a result of the enhanced thermal stability, in **9** being afforded by lower fluorine substitution.

The use of alcohol adducts of carbenes has also been investigated and as previously demonstrated by Grubbs et al.




$R_1$ = 2,4,6-$Me_3C_6H_2$, 2,6-$^iPr_2C_6H_3$, Ph
$R_2$ = $C_6F_5$, $C_6F_4H$, $C_6F_3H_2$, 4-$NO_2C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, Ph

Scheme 5. Generation of free carbene from thermally cleavable adducts.



*8* *9* *10*

Fig. 3. Fluorobenzene NHC adducts **8**–**10**.

[37a] provides an excellent method of generating carbenes in situ at ambient temperature. Initial experiments using bis(2,4,6-trimethylphenyl)-2-ethoxy-imidazolidine, **11**, (the ethanol adduct of **6**) show that this precatalyst provides a unimolecular catalyst/initiator that is able to rapidly polymerize lactide at room temperature to produce polymer of controlled molecular weight and narrow polydispersity (Table 2, entry 5) [41].

## 4. Summary

An organocatalytic approach to living and condensation polymerization using *N*-heterocyclic carbenes as nucleophilic catalysts was detailed. This catalyst platform is extremely versatile with the nature of the substituents having a pronounced effect upon catalyst stability and activity towards different substrates. The in situ generation of the *N*-heterocyclic carbene catalysts directly from their respective salts allowed the rapid screening of libraries of catalysts for the ROP for lactide. No appreciable differences between imidazol-2-ylidene and imidazolin-2-ylidene catalysts were observed with lactide. However, less sterically demanding carbenes were found to be more active towards ROP than their sterically encumbered anologs. Extension to commercially available materials and solid supported catalysts were demonstrated as the ultimate goals in providing a universal catalysts platform. In most cases, narrowly dispersed products can be obtained with predictable molecular weights from the monomer to initiator ratio. Moreover, the condensation of diamines with aldehydes provided a convenient and general source of alkane adducts of saturated *N*-heterocyclic carbenes. Thermolysis of these adducts generates the carbenes in solution, which we have shown are effective organic catalysts for trans-esterification reactions and ring-opening polymerization reactions.

Table 2
Application of thermally cleavable carbene adducts for the polymerization of lactide

| Entry | NHC adduct | Temperature (°C) | Time (h) | Conv. (%)[a] | $M_n$[b] (kg/mol) | PDI[b] |
|---|---|---|---|---|---|---|
| 1 | **8** | 65 | 3 | 80 | 9890 | 1.13 |
| 2 | **9** | 65 | 24 | 30 | 4030 | 1.10 |
| 3 | **9**[c] | 110 | 24 | 66 | 4700 | 1.11 |
| 4 | **10**[d] | 144 | 12 | 68 | 3200 | 1.52 |
| 5 | **11**[e] | 25 | 0.17 | 94 | 12,500 | 1.28 |

*Conditions*. All experiments initiated using benzyl alcohol in THF, [M]/[I] = 100, $[LA]_0$ = 0.16 M.
[a] Determined by $^1H$ NMR.
[b] Determined by gel-permeation chromatography.
[c] Experiment performed in toluene.
[d] Experiment performed in *o*-xylene.
[e] Polymerization performed in absence of added benzyl alcohol.

## Acknowledgements

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