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Expanding the Catalytic Activity of Nucleophilic N-Heterocyclic Carbenes for Transesterification Reactions

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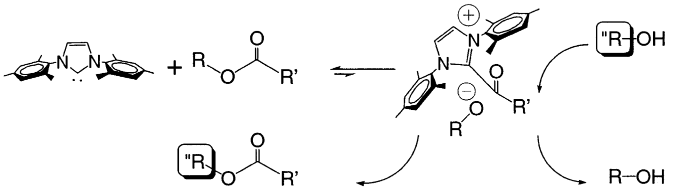
ABSTRACT



Currently, there is a renewed interest in reactions that are catalyzed by organic compounds. Typical organic catalysts for acylation or transesterification reactions are based on either nucleophilic tertiary amines or phosphines. This communication discusses the use of nucleophilic N-heterocyclic carbenes as efficient transesterification catalysts. These relatively unexplored and highly versatile organic catalysts were found to be mild, selective, and more active than traditional organic nucleophiles.

Growing trends in asymmetric synthesis for classic reactions that use organic molecules as promoters have provided an alternative to traditional organometallic reagents. Simple organic molecules in enantiomerically pure form have demonstrated high reactivity and stereospecificity for a number of useful organic transformations.[1−5] MacMillan has reported the first highly enantioselective organocatalytic inter- and intramolecular Diels−Alder 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.[1] Several groups have reported effective nonenzymatic catalysts for the kinetic resolution of secondary alcohols using chiral phosphines[2] or amine catalysts.[3] These nucleophilic catalysts, particularly the "planar-chiral" heterocycles based on the tertiary phosphine and amine frameworks, provide good levels of enantiomeric excess. To some degree this strategy mimics that carried out by enzymes.[4] These trends toward environmentally sound catalysts have been reviewed in a recent issue of *Chemical and Engineering News*: "Improving classics: organocatalysts inspire "greener" asymmetric versions of classic synthetic reactions".[5]

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[1] For example: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243−4244. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 9874−9875. (c) Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2001**, *123*, 2448−2449. (d) Fu, G. C. *Acc. Chem. Res*. **2000**, *33*, 412−420. (e) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed*. **2001**, *40*, 234. (f) Tao, B.; Lo, M. C.; Fu, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 353−354. (g) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc***.** **2002**, *124*, 1842. (h) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc*. **2002**, *124*, 1866.

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[3] For example: (a) Fu, G. C. *Acc. Chem. Res*. **2000**, *33*, 412−420. (b) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed*. **2001**, *40*, 234. (c) Tao, B.; Lo, M. C.; Fu, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 353−354. (d) Fu, G. C. *Adv. Organomet. Chem*. **2001**, *47*, 101. (e) Fu, G. C. *Pure Appl. Chem*. **2001**, *73*, 347. (f) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 1578−1579.

[4] Liu, L.; Breslow, R. *J. Am. Chem. Soc*. **2002**, *124*, 4978−4979.

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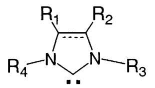
Recently, we reported the first example of N-heterocyclic carbenes (NHC) as catalysts for the living ring-opening polymerization (ROP) of cyclic esters. We believed that the extension of organic catalysis to controlled polymerization procedures would be a highly desirable alternative to traditional organometallic approaches, and ongoing work in this area shows promise. During our initial survey of a variety of potential nucleophilic catalysts including tertiary amines and phosphines for ROP, it was discovered that the N-heterocyclic carbenes were by far the most active. It was postulated that the NHC activates the substrate toward attack from the initiating/propagating alcohol.[6] Breslow, Setter, and others demonstrated that thiazolium-based carbenes promoted organic transformations such as the benzoin condensation reaction, where Breslow proposed acyl activation by a carbene intermediate.[7]

One can regard the conversion of a cyclic ester to a polymer as successive transesterification reactions that selectively give a ring-opened product where the length of polymer chains is controlled by the amount of initiator added. With this in mind, we decided to extend this general transesterification principle to the synthesis of organic molecules. Moreover, as a general transesterification catalyst, we wish to extend the NHC catalysts platform to effect polycondensation polymerization reactions as a practical route to engineering polyesters.

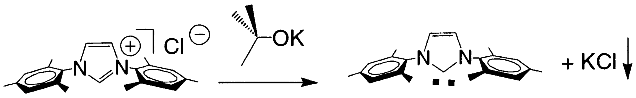
Since the initial description of the synthesis, isolation and characterization of stable carbenes by Arduengo,[8] the exploration of their versatility and chemical reactivity has become a major area of research.[9] Carbenes can be synthesized with considerable diversity by the sterics and electronics of the groups attached to the imidazole ring (R_{1-2}) and the nitrogen(s) (R_{3-4}) and the ethylene backbone (e.g., saturated vs unsaturated), (Scheme 1). The high reactivity of the 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, **1**, for the ring-opening polymerization of lactide inspired us to investigate **1** as a general transesterification catalyst together with 1,3-bis(2,6-diisopropyl)imidazol-2-ylidene, **2**. We were also interested in exploring the effect of replacing bulky mesityl and 2,6-diisopropylphenyl groups with smaller substituents at the 1,3-positions. Alkylation of 1-methyl imidazole with methyl iodide provides a convenient synthesis of 1,3-dimethylimidazolium iodide salt precursor that can subsequently be deprotonated to yield 1,3-dimethylimidazol-2-ylidene, **3**. In addition, 1-ethyl-3-methylimidazol-2-ylidene, **4**, can be synthesized from commercially available 1-ethyl-3-methyl imidazolium chloride. To demonstrate the feasibility of imidazolin-2-ylidene nucleophilic catalysts, we were prompted to explore the utility of “Wanzlick” carbenes as potential polymerization catalysts (**5**).[10] 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.

Scheme 1. Electronic and Steric Versatility of Nucleophilic N-Heterocyclic Carbenes



The isolation of NHC is complicated by their extreme air and moisture sensitivity and, in some cases, their tendency to dimerize. Recent investigations by Nolan and Grubbs demonstrated that free carbenes can be generated in situ and directly used to form N-heterocyclic carbene-coordinated catalysts in a greatly simplified process.[11] The in situ generation of the N-heterocyclic carbene catalysts directly from their respective salts allowed the rapid screening of these catalyst libraries and reaction conditions for both the organic transformations and polycondensation reactions (Scheme 2).[12] Importantly, isolated carbene **1** and in situ generated carbene **1** gave nearly identical results.

Scheme 2. Procedure for in Situ Generation of **1**



To demonstrate the feasibility of NHC-catalyzed transesterification, methyl benzoate was chosen because it mimics the central building block for important polyesters. Methyl benzoate reacted with a 20-fold excess of either ethanol, 2-propanol, or *tert*-butyl alcohol (Table 1) to drive the

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(6) Olmstead W. N.; Margolin Z.; Bordwell F. G. *J. Org. Chem.* **1980**, *45*, 3295.

(7) Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719. (b) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. (c) Enders, D.; Breuer, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217. (d) Teles, J.; Melder, J.; Ebel, K.; Enders, D.; Breuer, J. H. *Helv. Chim. Acta* **1996**, *79*, 61. (e) Kerr, M. S.; De Alaniz, J. R.; Roves, T. *J. Am. Chem. Soc.* **2002**, ASAP. (f) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743.

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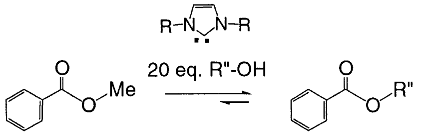
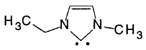
(10) Wanzlick, H. W.; Kleiner, H. J. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75.

(11) For example: (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (b) Morgan, J. P.; Grubbs, R. H. *Org. Lett*. **2000**, *2*, 3153. (c) Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67−70. (d) Jafarpour, L.; Nolan, S. P. *Organometallics* **2000**, *19*, 2055. (e) Grasa, G. A.; Nolan, S. P. *Organometallics* **2001**, *20*, 3607.

(12) To ensure complete consumption of *tert*-butoxide in the in situ formation of carbenes **1**−**5**, a 20% excess of imidazolium salt precursor was used. See Supporting Information for details.

Table 1. Model Transesterification Reactions with Subsitituted Alcohols[a]

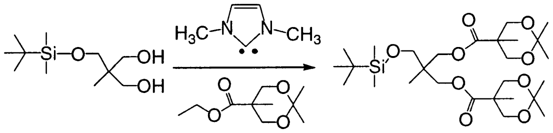


Catalyst	Alcohol	Cat./methyl Benzoate (mol%)	Conv. %
 1	EtOH	4.4	85
	i-PrOH	3.7	11
	t-BuOH	3.8	<1
 3	EtOH	4.6	79
	i-PrOH	3.7	72
	t-BuOH	3.7	<1
 4	EtOH	4.7	81
	i-PrOH	3.9	61
	t-BuOH	3.8	<1

[a] Typical procedure: inert atmosphere, 6.6×10^{-5} mol of N-heterocyclic carbene in 2 mL of THF (generated in situ; 0.8 equiv of KO-*t*Bu/1 equiv of carbene salt, 25 °C, 1 h and then filtered) was added to 20 mol of EtOH and 0.0015 mol of methylbenzoate, 20 h, 25 °C. Yield from GC/MS.

reaction to completion. For **1**, transesterification with primary alcohols was extremely effective and considerably better than secondary or tertiary alcohols, consistent with the nucleophilic character of the alcohol and perhaps the sterics. However, transesterifications in the presence of 2-propanol with smaller catalysts **3** and **4** were much more efficient. Transesterification reactions with tertiary alcohols, such as tert-butyl alcohol, were ineffective irrespective of the catalyst used.

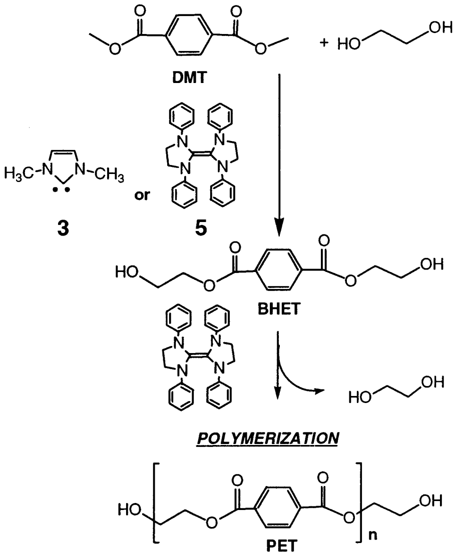
Scheme 3. Acylation of Disubstituted Alcohol through N-heterocyclic Carbene Catalysis



6 7 8

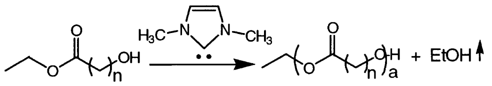
In addition, we examined the transesterification of **6** with **7** in the presence of either **2** or **3** carbene catalysts (Scheme 4). In this case, **7** was used in 20% excess and the reaction was accomplished in bulk under vacuum to remove the condensation byproduct. Only a 60% yield of **8** was obtained with catalyst **2**, whereas quantitative conversion to **8** was achieved for the less sterically hindered catalyst, **3**. In this example, catalyst structure clearly plays an important role. Removal of excess **7** was accomplished by distillation at 75 °C. This general procedure may provide an extremely simple and accelerated route to dendrons, dendrimers, etc.,[13] somewhat analogous to the procedure by Frechet using DMAP, and will be elaborated in a subsequent publication.

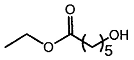
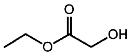
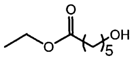
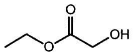
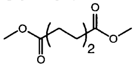
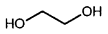
Scheme 4. Polymerization via Transesterificaton Reactions with N-Heterocyclic Carbenes



It is of great interest to extend this catalyst's platform to show polymerizations via typical transesterification/polycondensation reactions (Table 2). Examples of polyesters were directed toward those traditionally obtained by classical

Table 2. Transesterification Reactions That Generate Biodegradable Polyseters[a]



Substrate	Substrate	Mn	PDI	Conv. %[c]
100 mol% 		21,000	1.57	95
50 mol% 	50 mol% 	8,000	1.85	90
100 mol% 		(b)	(b)	80
50 mol% 	50 mol% 	9800	1.60	95

[a] Typical procedure: reduced pressure (0.1 mm/Hg), 6.6×10^{-5} mol of N-heterocyclic carbene (generated in situ; 0.8 equiv of KO-*t*Bu/1 equiv of carbene salt, 2 mL of THF, 25 °C, 1 h and then filtered) added to 20 mol of AB monomer, 20 h, 25 °C. M_n, molecular weight; PDI, (M_n/M_w) polydispersity index, measured by gel permeation chromatography (THF). [b] Insoluble in THF. [c] Isolated yield.

ring-opening methods including poly(ϵ-caprolactone), poly(glycolide), etc. Toward this goal, ethyl 6-hydroxyhexanoate and ethyl glycolate were self-condensed in bulk at 60 °C under vacuum for 24 h (Table 2). High molecular weight poly(ϵ-caprolactone) was obtained and characterized, but the poly(glycolide) formed was highly crystalline and insoluble in our GPC solvents. Thermal analysis of the poly(glycolide) was comparable to that reported for high molecular weight poly(glycolide). To facilitate solubility, a copolymer was obtained simply by the condensation of the two monomer types (Table 2). In addition, dimethyl adipate and ethylene glycol were condensed in bulk at 65 °C under vacuum (24 h). This AA/BB monomer system also produced high molecular weight polymer.

Another 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. Catalysts **3** and **5** were investigated to condense DMT with excess ethylene glycol (EG) in THF at room temperature. Quantitative conversion of DMT to BHET was realized in 1 h, irrespective of the catalysts employed (Scheme 4). The success of this strategy prompted us to investigate the use of the corresponding ionic liquid directly as a reactive media for the condensation of DMT and EG. The room-temperature ionic liquid 1-pentyl-3-methylimidazolium iodo salt proved an outstanding medium for the formation of BHET.[14] The ionic liquid was activated with potassium *tert*-butoxide, dissolved in a drop of THF, and the BHET could be retrieved by extraction using THF or precipitation. In each case the ^{1}H NMR spectra was identical to that of the commercial BHET. The melt condensation of BHET was performed in the presence of catalyst **5** using a slow heating ramp to 280 °C under vacuum, generating PET polymer. Importantly, the spectral and thermal (mp of 280 °C) characteristics of the polymer made from **5** are identical to commercial PET polymer (see Supporting Information).

In conclusion, NHCs are efficient transesterification catalysts. Transesterification reactions with primary alcohols were the most successful, and little to no reaction was observed in the presence of tertiary alcohols. Transesterification reactions with secondary alcohols were difficult with the sterically demanding catalyst **1** but more facile when smaller NHC catalysts (**3** and **4**) were used. We have also demonstrated the utility of NHC catalysts for polymer-forming reactions. NHC-mediated poly-condensation polymerization reactions provide a convenient route to biodegradable and commodity polymers as well as rapid entry into dendrimer precursors. Applications of NHC catalysts as a general platform for synthesis are ongoing.

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Supporting Information Available: References to syntheses of known compounds and experimental procedures are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Ihre, H.; Padilla, O. L.; De Jesus, P.; M. J.; Frechet, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5908−5917.

[14] 1-Pentyl-3-methylimidazolium iodide was synthesized by heating 1-methy imidazole and 1-iodopentane in isopropyl alcohol at 60 °C for 6 h. For a recent review on ionic liquids, see: Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083 and references therein.