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Development and Applications of Transesterification Reactions Catalyzed by N-Heterocyclic Olefins

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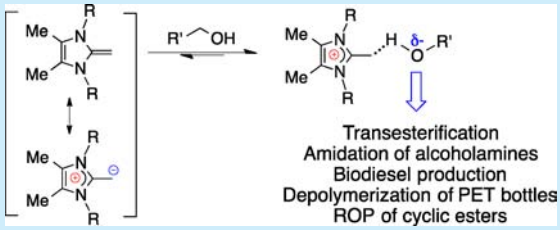
Supporting Information

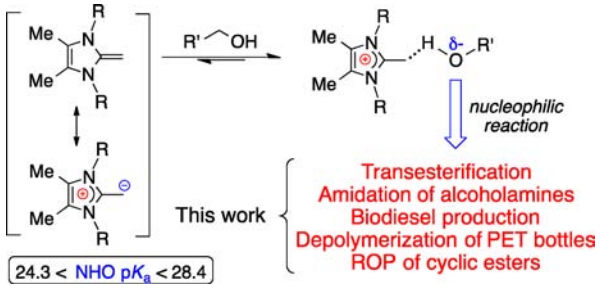
ABSTRACT: A novel method to utilize N-heterocyclic olefins (NHOs), the alkylidene derivatives of N-heterocycic carbenes, as organocatalysts to promote transesterification reactions has been developed. Because of their strong Brønsted/Lewis basicity, NHOs can enhance the nucleophilicity of alcohols for their acylation reactions with carboxylic esters. This transformation can be employed in industrially relevant processes such as the production of biodiesel, the depolymerization of polyethylene terephthalate (PET) from plastic bottles for recycling purposes, and the ring-opening polymerization of cyclic esters to form biodegradable polymers such as polylactide (PLA) and polycaprolactone (PCL).



Organocatalytic chemistry has rapidly risen to prominence over the last 15 years because of its versatility in a broad range of complicated organic transformations.[1] Using specially designed, small, nonmetallic organic compounds to promote chemical reactions, organocatalysis offers selective and efficient alternatives to traditional catalytic chemistry by organometallics or enzymes.[2] Among major organocatalytic systems, N-heterocyclic carbenes (NHCs) have been used extensively as "umpolung" organocatalysts to promote fascinating chemical reactions of carbonyl compounds via the formation of acyl anion intermediates.[3] This very well known role of NHCs overshadows their ability to act as Brønsted/Lewis basic or nucleophilic catalysts.[4] Current NHC-base-catalyzed chemistry has been used only in a few types of transformations such as transesterification, enolate formation, Michael addition, and Morita–Baylis–Hillman reactions.[5]

We have recently highlighted the great potential of N-heterocylic olefins (NHOs), the alkylidene derivatives of NHCs, as a new class of organocatalysts with enhanced Brønsted/Lewis basicity.[6] These compounds have been used by Lu's group for CO_2 sequestration reactions[7] and by Naumann, Thomas, and Dove for ring-opening polymerization (ROP) of propylene oxide.[8] NHOs are highly ylidic olefins with an electron-rich exocyclic carbon center, which can act as a very strong Brønsted/Lewis basic site. Similar to NHCs,[4,5] they are known to coordinate to alcohols to form Brønsted acid–base pairs of NHO–alcohol complexes,[8,9] which are synthetically equivalent to the corresponding alkoxides. On the basis of this intrinsic property of NHOs, we envisioned that NHOs could activate alcohols for nucleophilic transformations such as transesterification reactions. We herein report the development of a new method for NHO-promoted transesterification reactions, which could then be applied to a range of synthetically important chemical transformations such as selective acylation reactions, biodiesel production, depolymerization of polyethylene terephthalate (PET), and ROP of cyclic esters (Scheme 1). This study demonstrates the bright future of NHOs as a new class of versatile *non-covalent* organocatalysts in organic chemistry.

Scheme 1. NHOs Activate Alcohols for Nucleophilic Reactions



The ester functional group is one of the most abundant chemical moieties in organic chemistry.[10] Since the direct condensation reaction between carboxylic acids and alcohols remains a nontrivial task,[11] transesterification reactions from more readily available analogues have become one of the most attractive options to access ester derivatives. Although there have been numerous studies of this type of chemical transformation using organometallic,[12] organocatalytic,[4,5] or bio-organic[13] promoters, a practically efficient method is still in high demand. The highly basic NHOs, which are estimated to have basicities comparable to that of the organic superbase phosphazene *t*Bu-P_1 (Scheme 1),[14] appeared to be ideal catalytic systems for

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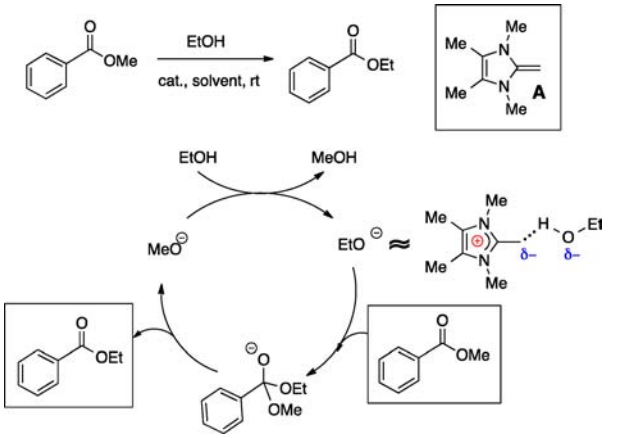
Table 1. Optimization of the NHO-Catalyzed Transesterification Reaction[a]



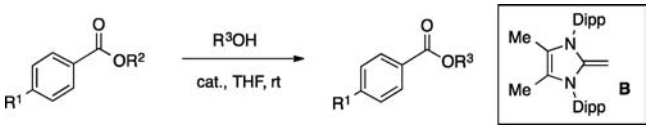
entry	equiv of EtOH	solvent[b]	mol % **A**	additive	yield (%)[c]
1	20	–	5	–	58
2	10	–	5	–	54
3	5	–	5	–	49
4	5	THF	5	–	61
5	5	CH_2Cl_2	5	–	62
6	5	toluene	5	–	41
7	5	THF	5	4 Å MS[d]	80
8	5	CH_2Cl_2	5	4 Å MS[d]	80
9	5	THF	2	4 Å MS[d]	69
10	5	THF	1	4 Å MS[d]	62
11	5	THF	0	4 Å MS[d]	trace
12	5	THF	0[e]	4 Å MS[d]	71

[a]The reactions were carried out with 1.0 mmol of methyl benzoate and ethanol in the presence of a catalytic amount of NHO **A** at rt until the TLC indicated no further change in the reaction. [b]1 mL of solvent was used. [c]Yields of the isolated products. [d]0.5 g of 4 Å MS was used. [e]5 mol % NaOEt was added as the catalyst.

transesterification reactions (Scheme 1). Thus, we started with testing a simple imidazolylidene-derived NHO[6,8] (catalyst **A**, Table 1) for its catalytic activity in the reaction between ethanol and methyl benzoate. To our delight, catalyst **A** smoothly promoted the formation of ethyl benzoate in moderate yield with an excess amount of ethanol (Table 1, entries 1 and 2). When the amount of ethanol was reduced to the standard 5 equiv, a solvent was employed to facilitate the progress of the reaction (Table 1, entries 3−10). THF and CH_2Cl_2 were comparably good media for this reaction. In order to increase the conversion rate, molecular sieves were also added to the reaction mixture to absorb the methanol byproduct, which led to improved yields. We also attempted to optimize the catalyst loading (Table 1, entries 8−10), but 5 mol % seemed to be the optimal amount of catalyst for the reaction. Without the catalyst, we did not observe any noticeable conversion (Table 1, entry 11).

We carried out NMR titration studies of the acid−base exchange between NHO **A** and a range of organic superbases and determined that the pK_a of the conjugate acid of NHO **A** falls between those of DBU (24.3) and ^{t}Bu-P$_1$ phosphazene base (28.4) in acetonitrile-d_3.[14] Studies by Dove's group revealed that NHOs can act as the Brønsted base to complex with the alcohol for activation in a similar fashion to their parent NHCs.[8] We also observed a similar complexation between **A** and ethanol by NMR studies,[14] which led us to propose that the transesterification proceeds through the mechanism illustrated in Table 1. This

Table 2. Effect of the Catalyst and Substrate Structures[a]



entry	R^1, R^2, R^3OH	cat.	time (h)	yield (%)[b]
1[c]	H, Me, EtOH	**A**	2	80
		B[d]	2	83
2	H, vinyl, EtOH	**A**	1.5	90
		B	2	88
3[c]	H, Me, ^{n}BuOH	**A**	3	85
		B	3	84
4	H, vinyl, ^{n}BuOH	**A**	1.5	88
		B	2	85
5[c]	H, Me, BnOH	**A**	1.5	90
		B	4	88
6	H, vinyl, BnOH	**A**	1	91
		B	3	92
7[c]	OMe, Me, ^{n}BuOH	**A**	3	81
8[c]	OMe, Me, ^{i}PrOH	**A**	12	29
9[c]	OMe, Me, ^{t}BuOH	**A**	24	–

[a]The reactions were carried out with 1.0 mmol of ester and 5.0 mmol of alcohol in the presence of 5 mol % catalyst in 1 mL of THF at ambient temperature until the TLC indicated no further change in the reaction mixture. [b]Yields of the isolated products. [c]0.5 g of 4 Å MS was also added. [d]Dipp = 2,6-(^{i}Pr)$_2$C$_6$H$_3$.

mechanism is similar to what has been accepted to most accurately depict NHC-catalyzed transesterification reactions.[4] The use of 5 mol % sodium ethoxide in place of the catalyst (Table 1, entry 12) also led to comparable results, supporting our hypothesis that the NHO−EtOH complex possibly acted as an ethoxide equivalent.

Subsequently, we surveyed the effect of the catalyst and alcohol substrate structures on the reaction outcome. NHO catalyst **B**[15] with bulky aryl substituents on both of the nitrogen centers was used for comparison with the simple tetramethyl-substituted NHO catalyst **A**. Interestingly, the reaction outcomes with a range of primary alcohols were very similar for both catalysts (Table 2, entries 1−6), which was in stark contrast to the NHC-catalyzed reactions.[4,9,10] Presumably, the enhanced Brønsted basicity of NHOs overcomes any structural influence of the cyclic backbone. Furthermore, it cannot be ruled out that the cyclic structure is less influential over the catalytic activity in NHOs than NHCs because the catalyst active site is now one carbon farther from the heterocycle. Vinyl ester (Table 2, entries 2, 4, and 6) can be used to replace the methyl ester substrate to avoid the need to use molecular sieves, as the former substrate led to the formation of acetaldehyde as the byproduct in an irreversible reaction.[10] On the other hand, the structural properties of the alcohols significantly altered the reaction outcome (Table 2, entries 7−9). The reactivity decreased from primary to secondary to tertiary alcohols, with the last one being *totally nonreactive* toward this system. This observation encouraged us to utilize *tert*-butoxide base to generate the NHO catalysts in situ for the transesterification reactions (Scheme 2), since the synthesis and isolation of NHO **A** is complicated because of its air and light sensitivity. KO^{t}Bu has previously been utilized to generate NHO **B** from its corresponding imidazolium precursor.[15] As the *tert*-butanol byproduct of this process did not interfere with the trans-esterification reaction, we postulated that the same results could

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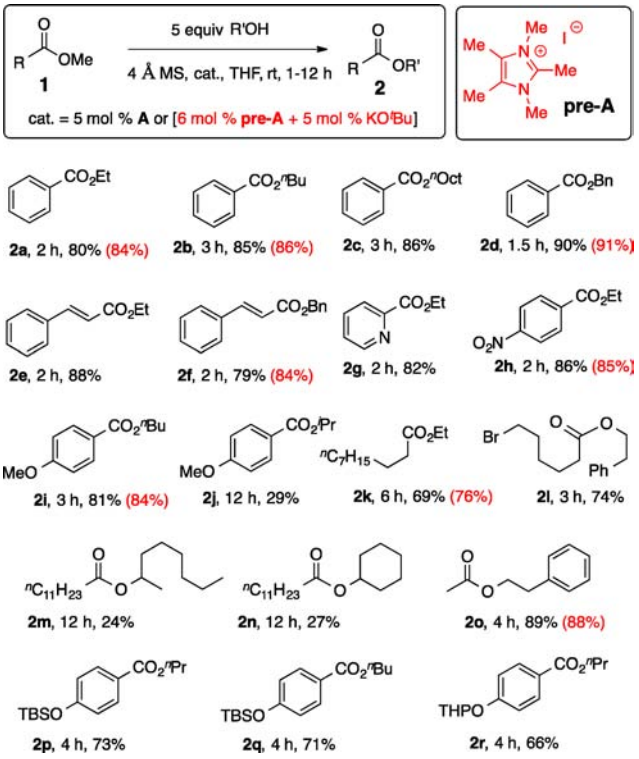
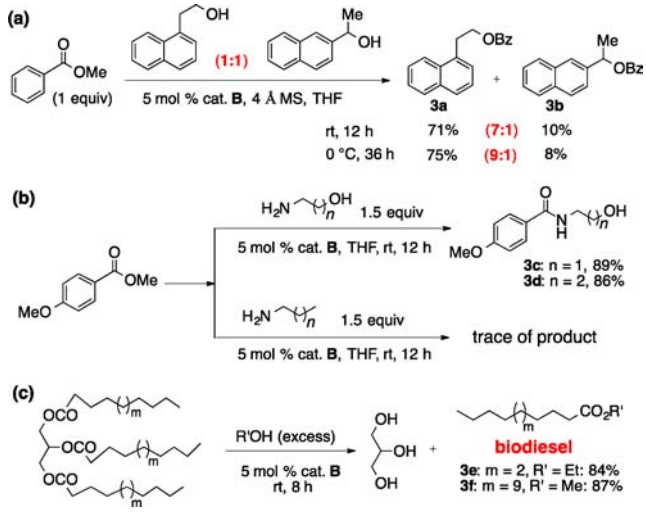
Scheme 2. Substrate Scope of the NHO-Promoted Transesterification Reaction



be achieved with the in situ-generated NHO. Indeed, when we explored the substrate scope of the transesterification reaction (Scheme 2) with a mixture of precatalyst **pre-A** and KO^{t}Bu, NHO **A** was generated in situ. This mixture could conveniently be used to mediate the reaction[14] to afford a range of products in yields (highlighted in red in Scheme 2) that were almost identical to those of the reactions catalyzed by free NHO **A**. Thus, catalyst **A** or the catalytic system **pre-A**/KO^{t}Bu efficiently promoted the transesterification reactions to give numerous aromatic and aliphatic esters (Scheme 2) in good to excellent yields. Many types of functional groups were tolerated in these reactions. Acid-sensitive functionalities such as silyl ether (**2p**, **2q**) and tetrahydropyranyl ether (**2r**) were also retained under these reaction conditions.[16] The limitation of the method was again with bulky secondary alcohols, which afforded low yields of the corresponding ester products (**2m**, **2n**).

We subsequently endeavored to turn this initial limitation into an advantage, as selectivity for primary over secondary alcohols in acylation reactions is very important in organic synthesis.[17] In a reaction catalyzed by catalyst **B**[18] using a 1:1 mixture of 2-(α-naphthyl)ethanol and 1-(β-naphthyl)ethanol with methyl benzoate as the limiting reagent, we obtained a mixture of the corresponding products **3a** and **3b** in a ratio of 7:1 at ambient temperature (Scheme 3a).[14] When the same reaction was carried out at lower temperature, it provided better selectivity for the ester product of the primary alcohol **3a** (9:1).[14] This clearly demonstrated the potential of the NHO-promoted transformation in *selective* acylation reactions. Furthermore, NHO **B** can also be employed to catalyze amidation reactions[9] between a methyl ester and alcoholamines to give hydroxyl-substituted amide products **3c** and **3d** in high yields (Scheme 3b). Since the amidation reaction was nonreversible, no molecular sieve was needed for these reactions. The alcohol functionality is requisite

Scheme 3. Other NHO-Catalyzed Transesterification Reactions



for this type of amidation reaction, as a similar process did not work well on the primary amine analogues (Scheme 3b). This is in good agreement with the corrected Brønsted base mode of action for NHC/NHO alcohol activation.[5a,8] The same catalytic system can be used for the transesterification of stearic and capric triglycerides to produce esters **3e** and **3f** (Scheme 3c), suggesting the potential application of NHOs in biodiesel production.

To further investigate practical applications of this NHO-catalyzed transesterification procedure, we carried out the reaction between dimethyl terephthalate and an excess amount of ethylene glycol (Scheme 4a). The reaction smoothly proceeded to give BHET (**3g**) in excellent yield. BHET is a synthetically valuable compound in plastic chemistry, as it can undergo a direct-melt polycondensation reaction to afford PET. Fascinatingly, the very NHO catalyst **B** could also efficiently break down PET flakes from a recycled plastic bottle into the same BHET monomer in a similar transesterification-type reaction with ethylene glycol (Scheme 4b).[14] This transformation could be carried out under microwave irradiation or conventional heating conditions with similar efficiencies. These NHO-promoted reactions gave results comparable to those for other reported depolymerization reactions using other strong organic bases such as TBD and DBU.[19]

Encouraged by these interesting results and the elegant polymerization of propylene oxide by Naumann, Thomas, and Dove,[8] we decided to further investigate the role of NHOs as organocatalysts for ring-opening polymerization of cyclic esters. After screening a few sets of reaction conditions and monomer:-initiator:NHO-catalyst ratios, we were delighted to observe that catalyst **B**[18] efficiently triggered the ROP reactions of ε-caprolactone and lactide to afford the two biodegradable polyesters PCL and PLA, respectively. These polyesters formed with high molecular weights of 18.21 and 9.56 kg·mol^{-1} and good polydispersities of 1.71 and 1.56, respectively (Scheme 4c,d).[14] The steric bulk of the two *N*-Dipp groups in combination with the decreased steric hindrance at the exocyclic methylene group gave rise to higher molecular weights with similar polydispersities in comparison with the ester ROP with a propylidene imidazole NHO catalyst recently reported by Naumann, Thomas, and Dove.[20] Observation by ^{1}H NMR spectroscopy confirmed that these two polyesters have benzyl head groups and hydroxyl end groups.[14] In addition, the measured molecular weights are in

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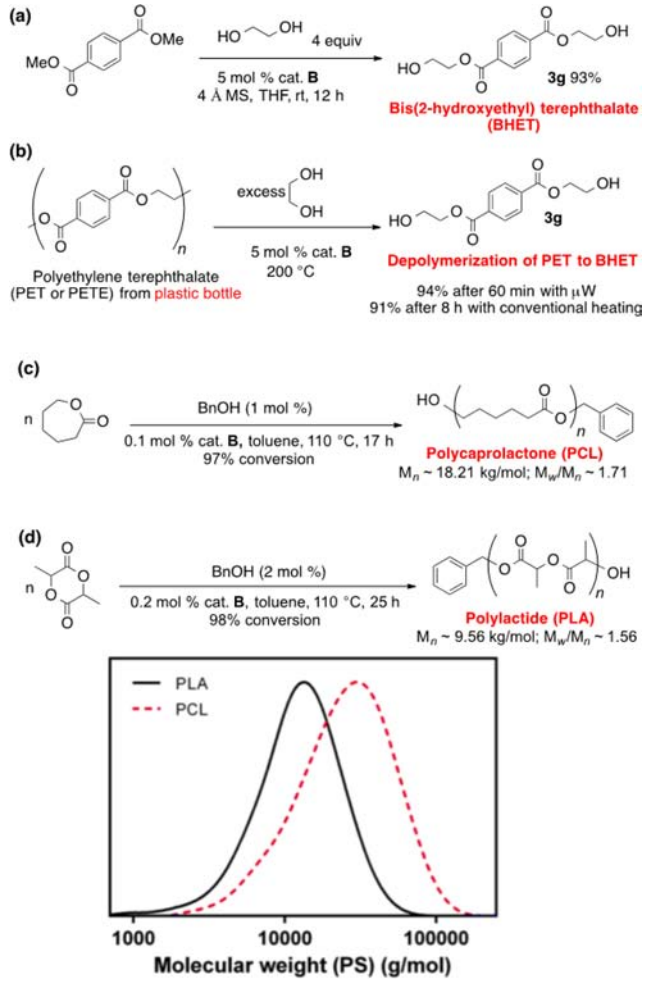
Scheme 4. NHO-Promoted Depolymerization and Polymerization Reactions of Biodegradable Polyesters



close proximity to the expected molecular weights considering the initiator:monomer ratio and a monomer conversion of almost 100%, which is suggestive of a living system. These two polyesters marked the second new type of organopolymerization reaction promoted by NHOs, thus once again emphasizing the great potential of N-heterocyclic olefin organocatalysts in polymer chemistry. Kinetic studies to further understand and optimize these NHO-assisted polymerization transformations are currently underway and will be reported in due course.

In conclusion, we have demonstrated that N-heterocyclic olefins are a novel class of versatile organocatalysts for transesterification reactions. Because of their strong Brønsted basicity, NHOs can enhance the nucleophilicity of alcohols for their reactions with carboxylic esters. This procedure can be employed in various synthetically important applications such as depolymerization of PET, production of biodiesel, and ring-opening polymerization of cyclic esters to give biodegradable polymers. This work once again demonstrates the bright future of NHO organocatalysts in synthetic chemistry. We are currently working on other types of NHO-organocatalyzed chemical transformations and will endeavor to report these studies in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00835.

Experimental details, analytical data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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