Title: The Resurgence of the Highly Ylidic N-Heterocyclic Olefins as a New Class of Organocatalysts

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The Resurgence of the Highly Ylidic N-Heterocyclic Olefins as a New Class of Organocatalysts

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Abstract: N-Heterocyclic Olefins, the alkylidene derivatives of the prevalent N-heterocyclic carbene, have recently emerged as efficient promoters for CO₂ fixation and polymerization reactions. Their extraordinarily strong Lewis/Bronsted basicity suggests their great potential as a new class of organocatalysts for a broad range of reactions in synthetic chemistry.

Introduction

Over the last two decades, organic chemistry has been engulfed with the prominence of several classes of active neutral carbon species such as N-heterocyclic carbenes (NHCs) and carbon (0) carbodi-carbenes. The existence of these compounds has helped to significantly expand the chemical space known to chemists in several dimensions. The computational and experimental studies of these species have also enriched the knowledge about chemical bonds, molecular orbitals and reactivity of fundamental organic compounds. These particular chemical species have also played critical roles in the development of catalytic organocatalytic methods as well as novel transition metal complexes and catalysts.

Recently, the alkylidene derivatives of NHCs, termed N-Heterocyclic Olefins (NHOs, Figure 1), have emerged as a new class of valuable reaction promoters with interesting activation mechanisms. These NHOs are structurally analogous to the deoxy-Breslow intermediates in NHC-catalytic chemistry of Michael acceptors. NHOs can also be conveniently produced in free form from 2-alkylated NHC precursors in one step (Scheme 1a). NHOs, also known as heterocyclic ketene aminals (HKAs), belong to a unique family of ene-1,1-diamines. Originally being targeted as a series of active agrochemicals in the 1970s, NHOs slowly revealed to be a far more interesting family of compounds. Due to the donating ability of the two nitrogen atoms, the exocyclic C-C double bond is very electron-rich and highly polarized. NHOs have been regarded amongst the most ylidic alkenes with localized electron density on the exocyclic α-carbon (Cα) up to -0.44, making it even more nucleophilic than the nitrogen centers on the same molecule. This interesting feature of NHOs offers multinucleophilic reactivity over the ketene aminal frameworks. Over the last three decades, there have been numerous investigations on synthetic utilities of NHOs as enimic substrates in nucleophilic addition and substitution reactions. NHOs typically react with azides, nitrile oxides and nitrile imines to give access to the corresponding triazoles, isoxazoles and pyrazoles. They can also be used as dienophiles in inverse electron demand Diels-Alder and other cycloaddition reactions. Due to the strong nucleophilicity of the α-carbon, NHOs are often stronger Lewis bases than their parent NHCs, leading to several applications of NHOs as end-on ligands in transition metal coordination and catalysis as well as stabilization of the metalloid boron and silicon in borenium ions and silylenes. Very recently, NHOs have stirred up great interest among synthetic chemists for their new intriguing roles as organocatalysts in very important chemical transformation such as CO₂ sequestration and polymerization reactions (Figure 1). With suitable structural design, NHOs can serve as a new class of Bronsted/Lewis base organocatalysts for a wide range of chemical reactions. This ‘concept’ article will give a general overview on the aforementioned recent synthetic applications of NHOs (Figure 1) and provide an outlook for the future of N-heterocyclic olefins in organic chemistry.

CO₂ Sequestration Reactions

The sequestration of CO₂, an abundant natural C1 source, has always been an attractive and thought-provoking major topic in sustainable chemistry, although the molecule is thermodynamically and kinetically stable. To date, most of the
efficient CO₂-organic product transformations involve complicated coordination chemistry on transition metal catalysts. There have also been a number of studies reporting the application of NHC in CO₂ sequestration. In 2013, Lu and co-workers published an elegant breakthrough in which they used the strongly nucleophilic N-heterocyclic olefins to capture CO₂ and activate it for further transformations (Scheme 1a). This work involves a simple procedure to produce NHO-CO₂ adducts and the utilization of these adducts as organocatalysts for the carboxylative cyclization of propargylic alcohols. The zwiterionic NHO-CO₂ adducts were presumably formed via nucleophilic addition of the electron-rich α-carbon to the center of carbon dioxide in an end-on fashion (Scheme 1a). Such adducts were stable at ambient temperature in solution and solid-state that the authors could obtain X-ray crystallographic data of these compounds. The newly formed C₂-CO₂ bonds were lengthier than their analogous bonds in the known NHC-CO₂ adducts, hinting that NHOs might actually be better than NHCs in capturing/releasing CO₂. Indeed, Lu and co-workers found out that the thermolytic decarboxylation of NHO-CO₂ adducts could be carried out significantly easier than that of NHC-CO₂ or other organocatalyst-CO₂ adducts. This encouraged the authors to utilize NHO-CO₂ adducts as organocatalysts for CO₂ sequestration. Gratifyingly, their preliminary results showed that these systems were very efficient in catalyzing the carboxylative cyclization of propargylic alcohols to give α-alkylidene cyclic carbonate ester products (Scheme 1b) in excellent yields under mild reaction conditions. In contrast, the analogous NHC-CO₂ adducts, studied in parallel for comparative purposes, proved to be about 10-200 times less effective for the same reaction. Such a minor alteration in the catalyst structure from NHC to NHO has led to a huge improvement in catalytic activity for the studied transformation, signifying the potential values of N-heterocyclic olefins in organocatalysis for the first time.

Furthermore, Lu and co-workers have recently reported the synthesis of a series of NHO-COS and NHO-CS₂ adducts for comparison to their previously synthesized NHO-CO₂ catalysts. These new catalytic systems were used to promote coupling reactions of CO₂ with epoxides (Scheme 1c). The catalytic efficiency appeared to increase in order of NHO-COS < NHO-CO₂ < NHO-CS₂ adducts, with the latter two being able to smoothly promote the fixation of CO₂ onto epoxides to produce cyclic carbonate esters in high to excellent yields. The determining factor for catalytic activity was again the thermal stability of the Cₓₐ-Cₓₒ bond in the NHO-CXY (X, Y = O or S) organocatalysts. Although thiocarbonate esters are also compounds of various synthetic interests, Lu and co-workers did not report the similar catalyzed addition of COS or CS₂ themselves to propargylic alcohol or epoxide substrates. Most inspiringly, the authors have proved that the free NHOs are probably the actual active species in the catalytic cycle, as the use of a NHO instead of NHO-CO₂ adduct as organocatalyst in the same reaction afforded comparable product yield.

### Polymerization Reactions

At the same time, Lu’s group also investigated another important synthetic utility of NHOs. They envisioned that the highly polarized N-heterocyclic olefins can be used as nucleophilic Lewis bases in conjunction with strong Lewis acids for similar applications to frustrated Lewis pairs (FLPs). In a study reported in 2014, Lu and co-workers used NHOs, in combination with Al(C₅F₅)₃, to initiate the polymerization of several acrylate ester monomers (Scheme 2a). The approach was based on the prior concept of the closely related NHC/Al Lewis pairs. Thus, the monomers were pre-activated by mixing with Al(C₅F₅)₃ (0.13-0.50 mol%); and the polymerization reactions generally proceeded to completion within minutes after the addition of the NHO Lewis base catalysts (0.05-0.25 mol%). Interestingly, the pre-formed NHO-Al(C₅F₅)₃ Lewis pairs were ineffective for this transformation, which can be attributed to their high stability. Replacement of Al(C₅F₅)₃ with aluminium halides or B(C₅F₅)₃ also led to unsatisfactory results. The polymers from NHO-Al(C₅F₅)₃ catalyzed reactions were generally high in molecular weight with relatively narrow molar mass distributions. The statistical co-polymerization of two different acrylate ester monomers also worked well but sequential block copolymerization, however, cannot be obtained using these Lewis pairs. This is probably due to side reactions occurring with the aluminium-enolate growing species (Scheme 2a), which can undergo different termination reactions, hence disfavouring the sequential block co-polymerization.

Immediately following that first application of NHOs in polymer chemistry, Lu and co-workers reported another interesting approach for polymerization of dissymmetric divinyl polar monomers using NHO-Al(C₅F₅)₃ pairs (Scheme 2b). The divinyl monomers are generally challenging substrates for radical or anionic polymerization as the reaction normally occurs concurrently on both types of vinyl groups, leading to insoluble cross-linked gel. However, if chemoselective polymerization of these monomers occurs, it gives access to polymers bearing pendant vinyl groups for many important applications in material science.

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*Scheme 1. NHO-CXY adducts as organocatalysts for CO₂ sequestration.*
chemistry. Using similar procedures to their previous work, Lu’s group were able to convert the disymmetric divinyl monomers to linear polymers with high molecular weight and narrow polydispersity. This NHO-alkane catalyzed polymerization was completely chemoselective at the more polar methacrylic double bonds.

\[
\begin{align*}
R &= \text{OMe, OPh, NMMe, NPh}_2 \\
M_n &= \text{up to 7.5 x } 10^5 \text{ g/mol, } M_w/M_n = 1.04-1.27
\end{align*}
\]

\[
\begin{align*}
R &= \text{OMe, OPh, NMMe, NPh}_2 \\
M_n &= \text{up to 6.4 x } 10^5 \text{ g/mol, } M_w/M_n < 1.5
\end{align*}
\]

Scheme 2. NHOs as Lewis base organocatalysts for Lewis-pair mediated polymerization reactions.

In a very recent study, Naumann and Dove have further extended the synthetic potential of NHO organocatalysts in polymerization chemistry. They initially used a series of simple NHOs (A-C, Scheme 3) to promote ring-opening polymerization reaction of propylene oxide (PO) with very promising outcomes. After fine-tuning the NHO structure to impose steric hindrance at the terminal alkene (D, Scheme 3), the authors were able to suppress the side zwitterionic initiation, affording well-defined polypropylene oxide with low dispersity and monomodal molecular weight distribution. The addition of benzyl alcohol was crucial for these polymerization reactions. The authors carried out a series of NMR experiments on BnOH-NHO mixtures and concluded that the NHO, presumably behaving as a Bronsted base, coordinated to the alcohol to form the alkoxide-like complex. This added to propylene oxide to initiate the polymerization process (Scheme 3). As Lu and co-workers have to use aluminium Lewis acids as co-catalysts in their reactions, Naumann and Dove’s study marked the first example of direct NHO-catalyzed organo-polymerization. It should also be emphasized that Lu’s polymerization reactions likely involved the zwitterionic intermediates during chain initiation and propagation steps (Scheme 2), which is in stark contrast to the ‘anionic’ transformations examined by Naumann and Dove. Nonetheless, in all these works, conjugation on the unsaturated heterocyclic moiety seemed to be crucial for catalytic activity, which can be attributed to better stabilization of the active charge-separated resonance structures (Figure 1).

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\text{Scheme 3, NHOs as ‘anionic’ organocatalysts for polymerization of PO.}
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Future Directions and Challenges of N-Heterocyclic Olefins in Organocatalysis

Although lacking the ‘carbene’ valent availability of NHCs, NHOs are considered better Bronsted/Lewis bases than their parent NHC compounds (Scheme 4a). NHOs are also confirmed to be better nucleophiles than NHCs. Hence, NHOs are likely to have a very bright future in organocatalytic chemistry where they can be used to promote a very wide range of Bronsted or Lewis base-mediated chemical reactions. These include several atom-economic and frequently used reactions such as the Morita-Baylis-Hillman, Michael addition and aldol reactions. Since NHOs inherit the heterocyclic moiety from their NHC precursors, it is obvious that NHOs’ structures can also be tuned to optimize the reaction outcomes with respect to yield and stereoselectivity. For example, various substituents can be installed on the nitrogen atoms to control the electronic properties of the α-carbon or the sterical hindrance around that active center. Chiral NHOs may also be used to promote asymmetric chemical reactions. All of the NHOs explored to date were derived from imidazolium salts, inviting further investigations on NHO derivatives of other heterocyclic frameworks (Scheme 4b).

Predictable challenges of this field include the co-existence of abnormal NHCs (aNHCs) if the NHOs are to be produced from the deprotonation reaction of 4(5)-H N-heterocyclic systems (see an example in Scheme 4c). With the hydrogen atom at C4 or C5 being less sterically hindered, although also being less acidic, than the hydrogen atoms on the exocyclic α-carbon, aNHCs can be the kinetic side-products with NHOs being the thermodynamic ones. Therefore, it should always be confirmed whether the aNHCs are being formed exclusively in any in situ catalyst generation for NHO-mediated reactions. Reactions 4,5-substituted N-heterocyclic precursors are ideal substrates, as there is no competing side-reaction associated with the deprotonation of these compounds. Furthermore, the NHO catalysts with extremely high Bronsted/Lewis basicity should be avoided, otherwise the acid-base exchange process between the reaction intermediates and the conjugate acids of NHOs cannot occur to regenerate NHOs back for another catalytic cycle.
Summary and Outlook

In summary, the elegant studies from Lu,[11–14] Naumann and Dove[5,6] have demonstrated the great synthetic potential of N-Heterocyclic Olefins in promoting CO$_2$ fixation and polymerization processes. With their highly ylidic characteristic and inherently tunable structures as observed with the parent NHC species, it is expected that NHOs will soon triumph as vital organocatalysts for a much broader range of important Lewis/Bronsted base catalyzed reactions.

Keywords: N-Heterocyclic Olefins • organocatalysis • ylidic alkenes • ene-1,1-diamines • Bronsted/Lewis bases

CONCEPT

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