

## Author Manuscript

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

**Authors:** Reece Douglas Crocker; Thanh Vinh Nguyen, Ph.D

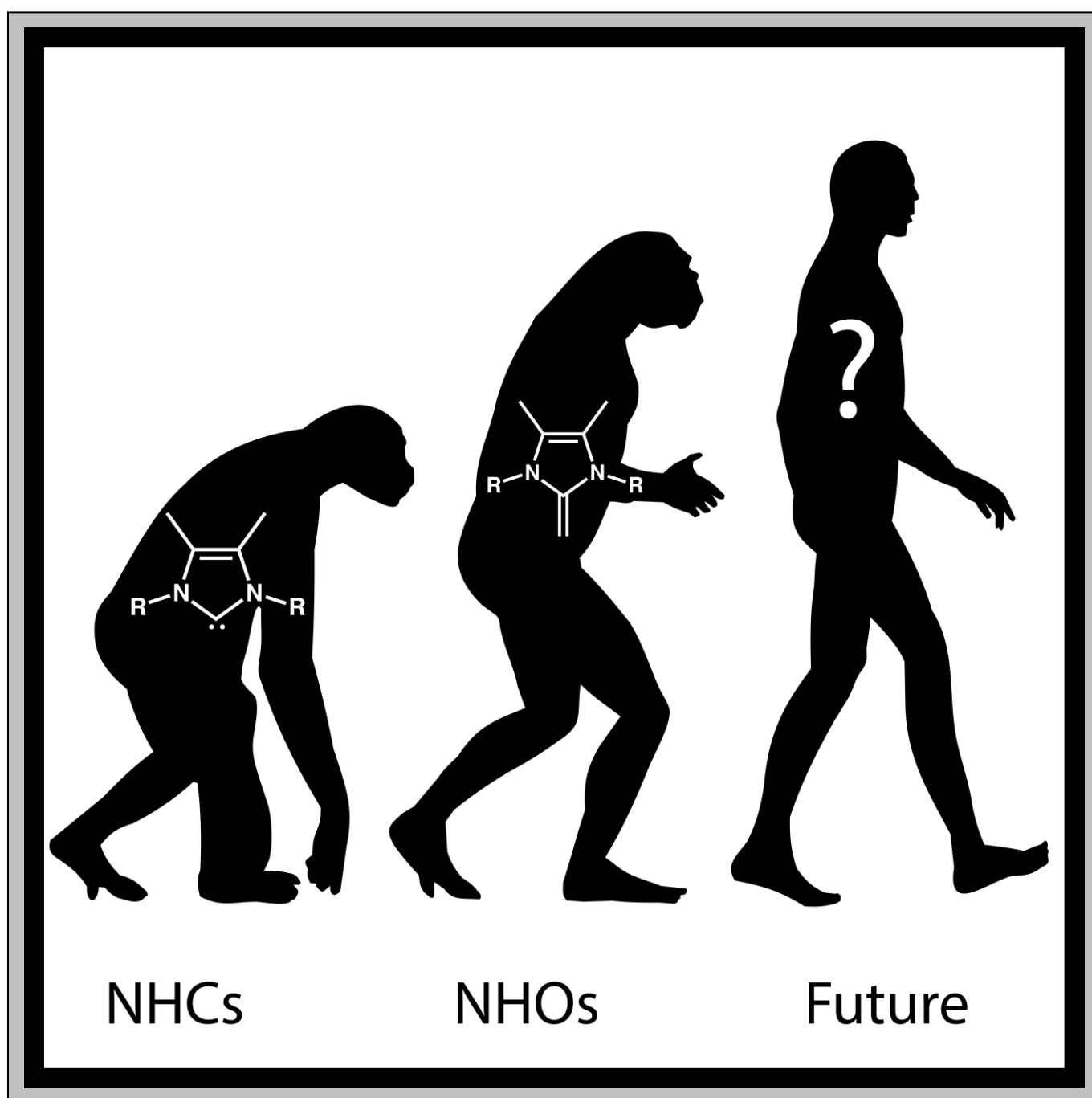
This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record.

**To be cited as:** 10.1002/chem.201503575

**Link to VoR:** <https://doi.org/10.1002/chem.201503575>

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

Reece D. Crocker and Thanh V. Nguyen\*



Author Manuscript

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

Reece D. Crocker and Thanh V. Nguyen\*

**Abstract:** N-Heterocyclic Olefins, the alkylidene derivatives of the prevalent N-heterocyclic carbenes, have recently emerged as efficient promoters for CO<sub>2</sub> 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)<sup>[1]</sup> and carbon (0) carbodicarbenes.<sup>[2]</sup> The existence of these compounds has helped to significantly expand the chemical space known to chemists in several dimensions.<sup>[3]</sup> The computational and experimental studies of these species have also enriched the knowledge about chemical bonds, molecular orbitals and reactivity of fundamental organic compounds.<sup>[3]</sup> These particular chemical species have also played critical roles in the development of captivating organocatalytic methods as well as novel transition metal complexes and catalysts.<sup>[1,3]</sup>

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.<sup>[4]</sup> These NHOs are structurally analogous to the deoxy-Breslow intermediates in NHC-catalytic chemistry of Michael acceptors.<sup>[5]</sup> NHOs can also be conveniently produced in free form from 2-alkylated NHC precursors in one step (Scheme 1a).<sup>[5]</sup> 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,<sup>[6]</sup> 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  $\alpha$ -carbon ( $C_{\alpha}$ ) up to  $-0.44$ ,<sup>[7]</sup> making it even *more nucleophilic than the nitrogen centers* on the same molecule.<sup>[7]</sup> This interesting feature of NHOs offers multinucleophilic reactivity over the ketene aminal frameworks.<sup>[8]</sup> Over the last three decades, there have been numerous investigations on synthetic utilities of NHOs as enaminic substrates in nucleophilic addition and substitution reactions.<sup>[8]</sup> NHOs typically react with azides, nitrile oxides and nitrile imines to give access to the

corresponding triazoles, isoxazoles and pyrazoles.<sup>[8]</sup> They can also be used as dienophiles in inverse electron demand Diels-Alder and other cycloaddition reactions.<sup>[8]</sup> Due to the strong nucleophilicity of the  $\alpha$ -carbon, NHOs are often stronger Lewis bases than their parent NHCs,<sup>[9]</sup> leading to several applications of NHOs as end-on ligands<sup>[10]</sup> in transition metal coordination and catalysis,<sup>[7,9,10a-10g]</sup> as well as stabilization of the metalloids boron and silicon in borenium ions<sup>[10h,10i]</sup> and silylenes.<sup>[10j]</sup> 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 CO<sub>2</sub> sequestration,<sup>[11,12]</sup> and polymerization reactions (Figure 1).<sup>[4,13,14]</sup> 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.

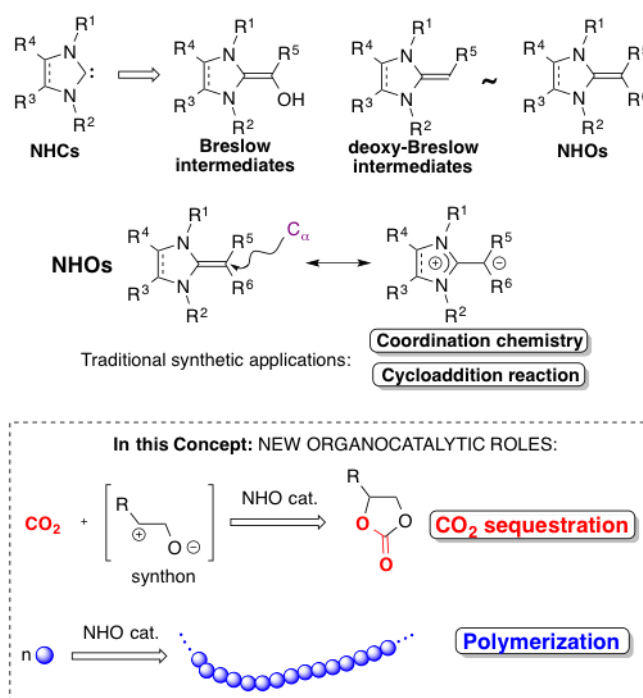


Figure 1. New important synthetic roles of N-Heterocyclic Olefins (NHOs).

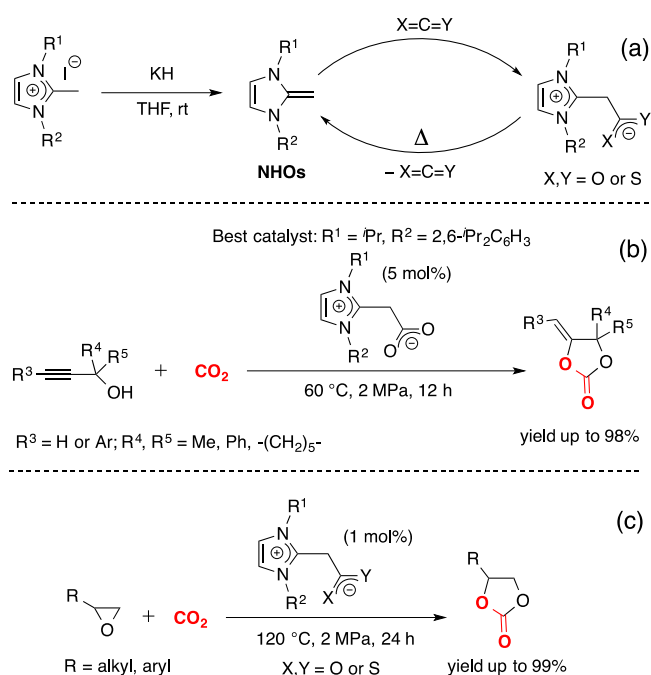
## CO<sub>2</sub> Sequestration Reactions

The sequestration of CO<sub>2</sub>, 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.<sup>[11]</sup> To date, most of the

[\*] R. D. Crocker, Dr. T. V. Nguyen  
School of Chemistry, University of New South Wales  
Sydney, NSW 2052, Australia  
E-mail: [t.v.nguyen@unsw.edu.au](mailto:t.v.nguyen@unsw.edu.au)

[\*\*] Support from the Australian Research Council (grant DE150100517) is gratefully acknowledged.

efficient CO<sub>2</sub>-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 CO<sub>2</sub> sequestration.<sup>[15]</sup> In 2013, Lu and co-workers published an elegant breakthrough in which they used the strongly nucleophilic N-heterocyclic olefins to capture CO<sub>2</sub> and activate it for further transformations (Scheme 1a).<sup>[11]</sup> This work involves a simple procedure to produce NHO-CO<sub>2</sub> adducts and the utilization of these adducts as organocatalysts for the carboxylative cyclization of propargylic alcohols. The zwitterionic NHO-CO<sub>2</sub> adducts were presumably formed via nucleophilic addition of the electron-rich  $\alpha$ -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 C <sub>$\alpha$</sub> -C<sub>CO<sub>2</sub></sub> bonds were lengthier than their analogous bonds in the known NHC-CO<sub>2</sub> adducts,<sup>[11]</sup> hinting that NHOs might actually be better than NHCs in capturing/releasing CO<sub>2</sub>. Indeed, Lu and co-workers found out that the thermolytic decarboxylation of NHO-CO<sub>2</sub> adducts could be carried out significantly easier than that of NHC-CO<sub>2</sub> or other organocatalyst-CO<sub>2</sub> adducts.<sup>[16]</sup> This encouraged the authors to utilize NHO-CO<sub>2</sub> adducts as organocatalysts for CO<sub>2</sub> sequestration. Gratifyingly, their preliminary results showed that these systems were very efficient in catalyzing the carboxylative cyclization of propargylic alcohols to give  $\alpha$ -alkylidene cyclic carbonate ester products (Scheme 1b) in excellent yields under mild reaction conditions. In contrast, the analogous NHC-CO<sub>2</sub> 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.



**Scheme 1.** NHO-CXY adducts as organocatalysts for CO<sub>2</sub> sequestration.

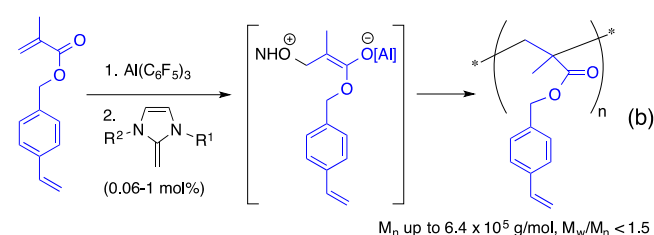
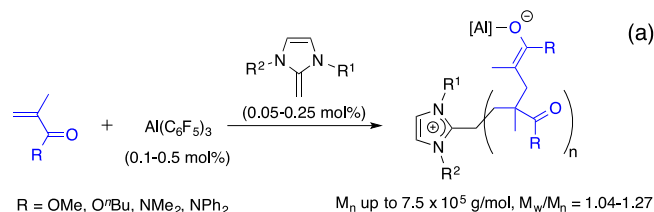
Furthermore, Lu and co-workers have recently reported the synthesis of a series of NHO-COS and NHO-CS<sub>2</sub> adducts<sup>[12]</sup> for comparison to their previously synthesized NHO-CO<sub>2</sub> catalysts. These new catalytic systems were used to promote coupling reactions of CO<sub>2</sub> with epoxides (Scheme 1c). The catalytic efficiency appeared to increase in order of NHO-CS<sub>2</sub> < NHO-COS < NHO-CO<sub>2</sub> adducts, with the latter two being able to smoothly promote the fixation of CO<sub>2</sub> 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 C <sub>$\alpha$</sub> -C<sub>CO<sub>2</sub></sub> 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 CS<sub>2</sub> 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-CO<sub>2</sub> adduct as organocatalyst in the same reaction afforded comparable product yield.<sup>[12]</sup>

## 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).<sup>[13]</sup> In a study reported in 2014, Lu and co-workers used NHOs, in combination with Al(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, to initiate the polymerization of several acrylate ester monomers (Scheme 2a).<sup>[13]</sup> The approach was based on the prior concept of the closely related NHC/Al Lewis pairs.<sup>[17]</sup> Thus, the monomers were pre-activated by mixing with Al(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (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(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> Lewis pairs were ineffective for this transformation, which can be attributed to their high stability. Replacement of Al(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> with aluminium halides or B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> also led to unsatisfactory results. The polymers from NHO-Al(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> 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 co-polymerization, 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 disfavoring the sequential block co-polymerization.<sup>[18]</sup>

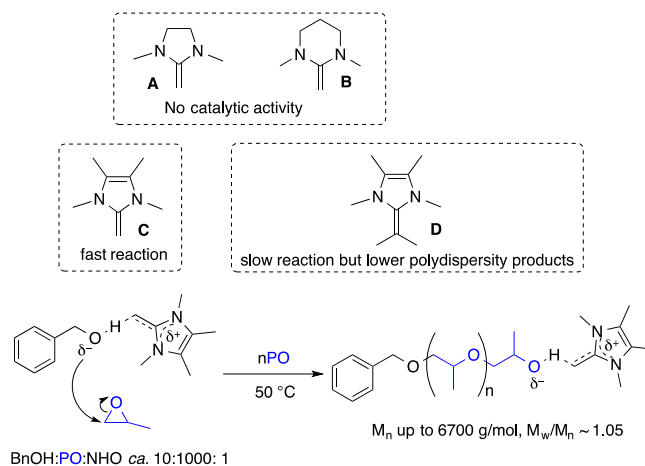
Immediately following that first application of NHOs in polymer chemistry, Lu and co-workers reported another interesting approach for polymerization of dissymmetric divinyl polar monomers using NHO-Al(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> pairs (Scheme 2b).<sup>[14]</sup> The divinyl monomers are 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

chemistry.<sup>[14]</sup> Using similar procedures to their previous work,<sup>[13]</sup> Lu's group were able to convert the dissymmetric divinyl monomers to linear polymers with high molecular weight and narrow polydispersity. This NHO-Alane catalyzed polymerization was completely chemoselective at the more polar methacrylic double bonds.



**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.<sup>[4]</sup> 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,<sup>[4]</sup> affording well-defined polypropylene oxide with low dispersity and monomodal molecular weight distribution. The addition of benzylic 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),<sup>[13,14]</sup> which is in stark contrast to the 'anionic' transformations examined by Naumann and Dove.<sup>[4]</sup> 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).

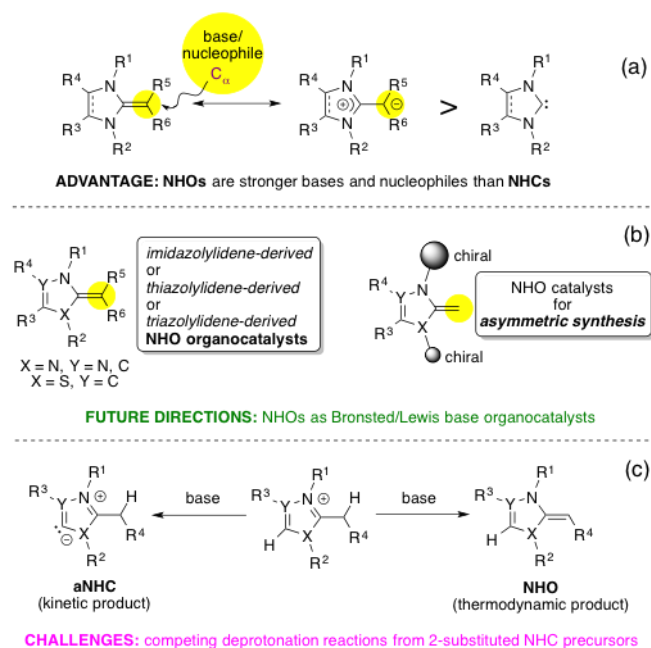


**Scheme 3.** NHOs as 'anionic' organocatalysts for polymerization of PO.

## 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).<sup>[5a,7]</sup> NHOs are also confirmed to be better nucleophiles than NHCs.<sup>[11]</sup> 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<sup>[19]</sup> or Lewis<sup>[20]</sup> 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  $\alpha$ -carbon or the steric 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)<sup>[21]</sup> 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  $\alpha$ -carbon, aNHCs can be the kinetic side-products with NHOs being the thermodynamic ones.<sup>[22]</sup> Therefore, it should always be confirmed that NHOs are being formed exclusively in any *in situ* catalyst generation for NHO-mediated 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.



**Scheme 4.** Future directions and challenges for NHOs in organocatalysis.

## Summary and Outlook

In summary, the elegant studies from Lu,<sup>[11-14]</sup> Naumann and Dove<sup>[4]</sup> have demonstrated the great synthetic potential of N-Heterocyclic Olefins in promoting CO<sub>2</sub> 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

- [1] For recent reviews on NHCs, see: a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485-496; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9037-9387.
- [2] S. Klein, R. Tonner, G. Frenking, *Chem. Eur. J.* **2010**, *16*, 10160-10170.
- [3] a) J. L. Moore, T. Rovis in *Topics in Current Chemistry*, Vol. 291 (Eds.: B. List), Springer, Berlin, **2009**, pp. 77-144; b) G. Frenking, R. Tonner, *WIREs Comput. Mol. Sci.* **2011**, *1*, 869-878.
- [4] S. Naumann, A. W. Thomas, A. P. Dove, *Angew. Chem. Int. Ed.* **2015**, *54*, 9550-9554.
- [5] a) B. Maji, M. Horn, H. Mayr, *Angew. Chem. Int. Ed.* **2012**, *51*, 6231-6235; b) for a recent report on the improved synthesis of NHOs, see: K. Powers, C. Hering-Junghans, R. McDonald, M. J. Ferguson, E. Rivard, *Polyhedron* **2015** (in press, DOI = 10.1016/j.poly.2015.07.070).
- [6] a) C. H. Tieman, W. D. Kollmeyer, S. A. Roman, *Ger. Offen.* **2445421**, **1976**; b) C. H. Tieman, W. D. Kollmeyer, *US Patent* **3948934**, **1976**.

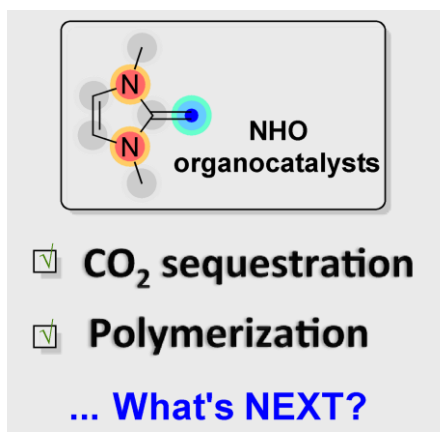
- [7] N. Kuhn, H. Bohnen, J. Kreutzberg, D. Blaeser, R. Boese, *J. Chem. Soc. Chem. Commun.* **1993**, 1136-1137.
- [8] K-M. Wang, S-J. Yan, J. Lin, *Eur. J. Org. Chem.* **2014**, 1129-1145.
- [9] A. Fuerstner, M. Alcarazo, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 3210-3214.
- [10] a) N. Kuhn, H. Bohnen, D. Blaeser, R. Boese, *Chem. Ber.* **1994**, *127*, 1405-1407; b) H. Schumann, M. Glanz, J. Winterfeld, H. Hemling, N. Kuhn, H. Bohnen, D. Blaeser, R. Boese, *J. Organomet. Chem.* **1995**, *493*, C14-C18; c) D. Kunz, E. O. Johnsen, B. Monsler, F. Rominger, *Chem. Eur. J.* **2008**, *14*, 10909-10914; d) S. M. Ibrahim Al-Rafia, A. C. Malcolm, S. K. Liew, M. J. Ferguson, R. McDonald, E. Rivard, *Chem. Commun.* **2011**, *47*, 6987-6989; e) A. Gloeckner, S. Kronig, T. Bannenberg, C. G. Daniliuc, P. G. Jones, M. Tamm, *J. Organomet. Chem.* **2013**, *723*, 181-187; f) S. Kronig, P. G. Jones, M. Tamm, *Eur. J. Inorg. Chem.* **2013**, 2301-2314; g) M. Iglesias, A. Iturmendi, P. S. Sanz Miguel, V. Polo, J. J. Perez-Torrente, L. A. Oro, *Chem. Commun.* **2015**, *51*, 12431-12434; h) Y. Wang, M. Y. Abraham, R. J. Gilliard Jr., D. R. Sexton, P. Wie, G. H. Robinson, *Organometallics* **2013**, *32*, 6639-6642; i) R. S. Ghadwal, C. J. Schürmann, F. Engelhardt, C. Steinmetzger, *Eur. J. Inorg. Chem.* **2014**, 4921-4926; j) R. S. Ghadwal, S. O. Reichmann, F. Engelhardt, D. M. Andradab, G. Frenking, *Chem. Commun.* **2013**, *49*, 9440-9442.
- [11] Y-B. Wang, Y-M. Wang, W-Z. Zhang, X-B. Lu, *J. Am. Chem. Soc.* **2013**, *135*, 11996-12003.
- [12] Y-B. Wang, D-S. Sun, H. Zhou, W-Z. Zhang, X-B. Lu, *Green Chem.* **2015**, *17*, 4009-4015.
- [13] Y-B. Jia, Y-B. Wang, W-M. Ren, T. Xu, J. Wang, X-B. Lu, *Macromolecules* **2014**, *47*, 1966-1972.
- [14] Y-B. Jia, W-M. Ren, S-J. Liu, T. Xu, Y-B. Wang, X-B. Lu, *ACS Macro Lett.* **2014**, *3*, 896-899.
- [15] For examples, see: (a) J. D. Holbrey, W. M. Reichert, I. Tkatchenko, E. Bouajila, O. Walter, I. Tommasi, R. D. Rogers, *Chem. Commun.* **2003**, 28-29; (b) H. A. Duong, T. N. Tekavec, A. M. Arif, J. Louie, *J. Chem. Commun.* **2004**, 112-113; (c) A. Tudose, A. Demonceau, L. Delaude, *J. Organomet. Chem.* **2006**, *691*, 5356-5365; (d) A. M. Voutchkova, M. Feliz, E. Clot, O. Eisenstein, R. H. Crabtree, *J. Am. Chem. Soc.* **2007**, *129*, 12834-12846; e) H. Zhou, W-Z. Zhang, C-H. Liu, J-P. Qu, X-B. Lu, *J. Org. Chem.* **2008**, *73*, 8039-8044;
- [16] For a recent review, see: G. Fiorani, W. Guo, A. W. Kleij, *Green Chem.* **2015**, *17*, 1535-1389.
- [17] For examples, see: Y. Zhang, G. M. Miyake, E. Y-X. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 10158-10162; Y. Zhang, G. M. Miyake, M. G. John, L. Falivene, L. Caporaso, L. Cavallo, E. Y-X. Chen, *Dalton Trans.* **2012**, *41*, 9119-9134; J. He, Y. Zhang, L. Falivene, L. Caporaso, L. Cavallo, E. Y-X. Chen, *Macromolecules* **2014**, *47*, 7765-7774; J. He, Y. Zhang, E. Y-X. Chen, *Synlett* **2014**, *25*, 1534-1538.
- [18] We thank one of the reviewers for suggesting this. For possible side reactions and chain terminations, see: A. H. E. Müller, K. Matyjaszewski (eds.), *Controlled and Living Polymerizations*, Wiley-VCH, Weinheim, **2009**.
- [19] For a recent review of Bronsted base catalysis, see: A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145-200.
- [20] For a recent review of Lewis base catalysis, see: S. E. Denmark, G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560-1638.
- [21] For a recent review on aNHCs, see: M. Melaimi, M. Soleihavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 8810-8849.
- [22] O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.* **2009**, *109*, 3445-3478.

**Entry for the Table of Contents**

Layout 1:

**CONCEPT**

**One carbon better:** N-Heterocyclic Olefins, the alkylidene derivatives of the prevalent N-heterocyclic carbenes, have recently emerged as efficient promoters for CO<sub>2</sub> fixation and polymerization reactions. Their extraordinarily strong Lewis/Bronsted basicity suggests great potential as a new class of organocatalysts for a broad range of reactions in synthetic chemistry.

*Reece D. Crocker, Thanh V. Nguyen\****Page No. – Page No.****The Resurgence of the Highly Ylidic N-Heterocyclic Olefins as a New Class of Organocatalysts**

Author Manuscript