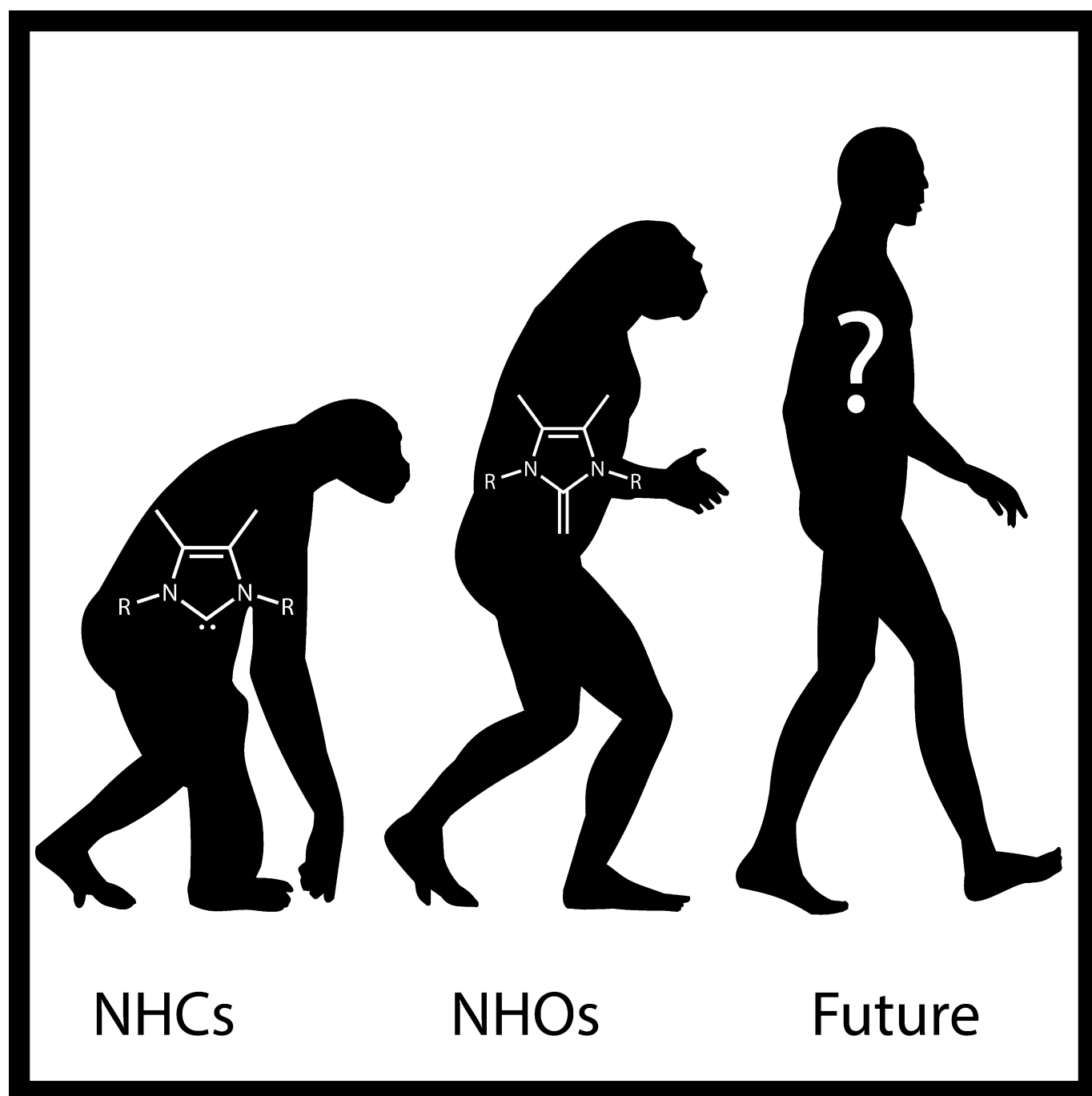▌ Organocatalysis

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

Reece D. Crocker and Thanh V. Nguyen*[a]

NHCs   NHOs   Future

Abstract: In recent decades, N-heterocyclic carbenes have become established as a prevalent family of organocatalysts. N-Heterocyclic olefins, the alkylidene derivatives of N-heterocyclic carbenes, have recently also emerged as efficient promoters for CO_2 fixation and polymerization reactions. Their extraordinarily strong Lewis/Brønsted basicity suggests great potential as a new class of organocatalysts for a broad range of reactions in synthetic chemistry.

Figure 1. Structure and synthetic roles of N-heterocyclic olefins (NHOs).

Introduction

During the last two decades, several classes of active neutral carbon species, such as N-heterocyclic carbenes (NHCs)[1] and carbon(0) carbodicarbenes,[2] have ascended to prominence within the field of organic chemistry. The development of these compounds has helped to significantly expand the chemical space known to chemists in several dimensions.[3] Computational and experimental studies of these species have also led to enriched knowledge about chemical bonds, molecular orbitals, and reactivity of fundamental organic compounds.[3] 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.[1,3]

Recently, the alkylidene derivatives of NHCs, termed N-heterocylic olefins (NHOs, Figure 1), have emerged as a new class of valuable reaction promoters with interesting activation mechanisms.[4] These NHOs are structurally analogous to the deoxy-Breslow intermediates in NHC catalytic chemistry of Michael acceptors.[5] NHOs can also be conveniently produced in their free form from 2-alkylated NHC precursors in one step (Scheme 1a).[5] 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,[6] NHOs slowly emerged 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 (C_α) up to −0.44, making it even more nucleophilic than the nitrogen centers on the same molecule.[7] This interesting feature of NHOs offers multinucleophilic reactivity over the ketene aminal framework.[8]

During the last three decades, there have been numerous investigations on the synthetic utilities of NHOs as enaminic substrates in nucleophilic addition and substitution reactions.[8] NHOs typically react with azides, nitrile oxides, and nitrile imines to give access to the corresponding triazoles, isoxa-
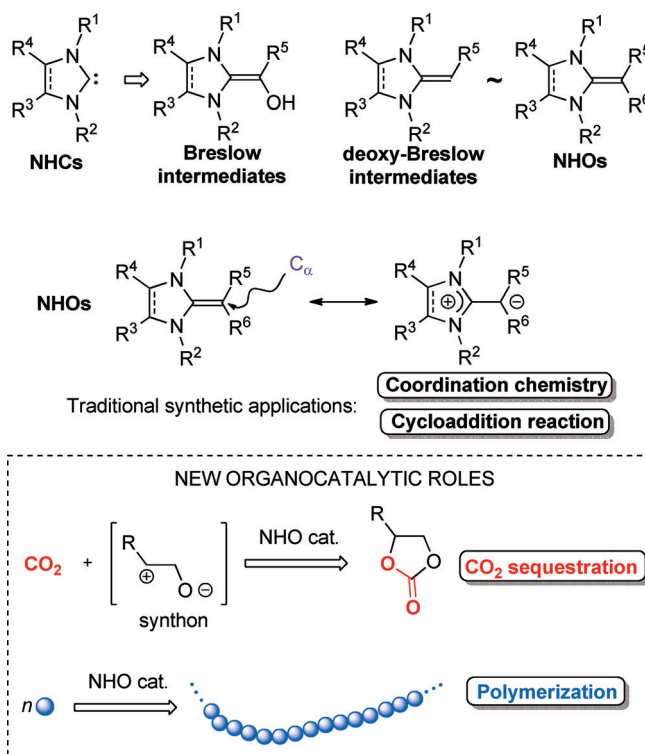
zoles, and pyrazoles.[8] They can also be used as dienophiles in inverse-electron-demand Diels–Alder and other cycloaddition reactions.[8] Due to the strong nucleophilicity of the α-carbon, NHOs are often stronger Lewis bases than their parent NHCs,[9] leading to several applications of NHOs as end-on ligands[10] in transition metal coordination and catalysis,[7,9,10a–g] as well as stabilization of the metalloid boron and silicon in borenium ions[10h,i] and silylenes.[10j] Very recently, NHOs have elicited great interest among synthetic chemists for their intriguing new roles as organocatalysts in important chemical transformations, such as CO_2 sequestration[11,12] and polymerization reactions (Figure 1).[4,13,14] With suitable structural design, NHOs can serve as a new class of Brønsted/Lewis base organocatalysts for a wide range of chemical reactions. This Concept article gives a general overview of the aforementioned recent synthetic applications of NHOs (Figure 1) and provides an outlook for the future of N-heterocyclic olefins in organic chemistry.

CO_2 Sequestration Reactions

The sequestration of CO_2, 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.[11] To date, most of the efficient $CO_2 \rightarrow$ organic product transformations have involved complicated coordination chemistry with transition metal catalysts. There have also been a number of studies reporting the application of NHCs in CO_2 sequestration.[15] In 2013, Lu and co-workers published an elegant breakthrough in which they used the strongly nucleophilic N-heterocyclic olefins to capture

[a] 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
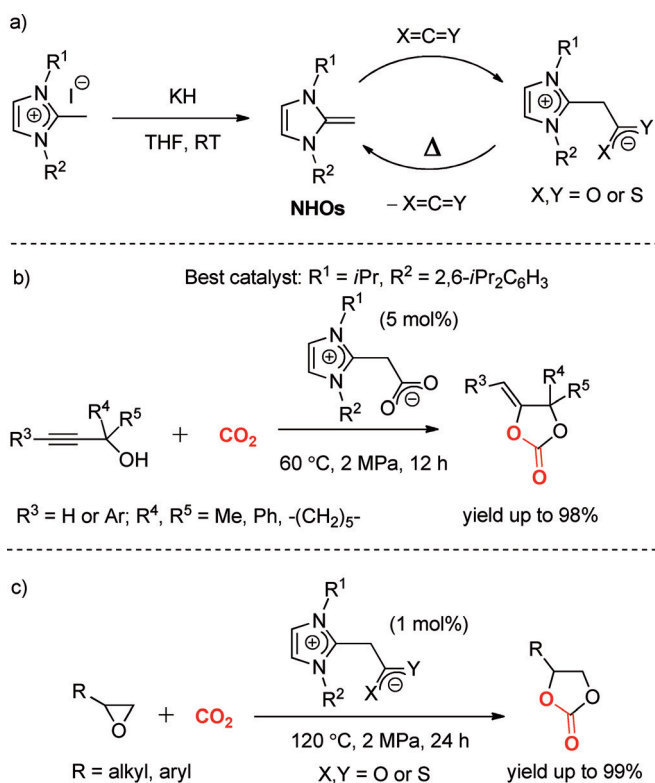
Scheme 1. NHO–CXY adducts as organocatalysts for CO_2 sequestration.

CO_2 and activate it for further transformations (Scheme 1a).[11] This work involved a simple procedure to produce NHO–CO_2 adducts and the utilization of these adducts as organocatalysts for the carboxylative cyclization of propargylic alcohols. The zwitterionic NHO–CO_2 adducts were presumably formed by 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 in solid state, so the authors could obtain X-ray crystallographic data of these compounds. The newly formed C_α–C_{CO_2} bonds were longer than their analogous bonds in the known NHC–CO_2 adducts,[11] hinting that NHOs might actually be better than NHCs in capturing/releasing CO_2. Indeed, Lu and co-workers found out that the thermolytic decarboxylation of NHO–CO_2 adducts could be carried out significantly more easily than that of NHC–CO_2 or other organocatalyst–CO_2 adducts.[16] This encouraged the authors to utilize NHO–CO_2 adducts as organocatalysts for CO_2 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–CO_2 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–CS_2 adducts[12] for comparison to their previously synthesized NHO–CO_2 catalysts. These new catalytic systems were used to promote coupling reactions of CO_2 with epoxides (Scheme 1c). The adducts appeared to increase in catalytic efficiency in the order NHO–CS_2 < NHO–COS < NHO–CO_2, with the latter two being able to smoothly promote the fixation of CO_2 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_α–C_{CO_2} bond in the NHO–CXY (X, Y = O or S) organocatalysts. Although thiocarbonate esters are also compounds of significant synthetic interest, Lu and co-workers did not report the similar catalyzed addition of COS or CS_2 themselves to propargylic alcohol or epoxide substrates. Most inspiringly, the authors 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_2 adduct as organocatalyst in the same reaction afforded comparable product yield.[12]

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 could be used as nucleophilic Lewis bases in conjunction with strong Lewis acids for similar applications to frustrated Lewis pairs (FLPs).[13] In a study reported in 2014, Lu and co-workers used NHOs, in combination with $Al(C_6F_5)_3$, to initiate the polymerization of several acrylate ester monomers (Scheme 2a).[13] The approach was based on the prior concept of the closely related NHC/Al Lewis pairs.[17] Thus, the monomers were pre-activated by mixing with $Al(C_6F_5)_3$ (0.13–0.50 mol%); and the polymerization reactions generally proceeded to completion within minutes after the
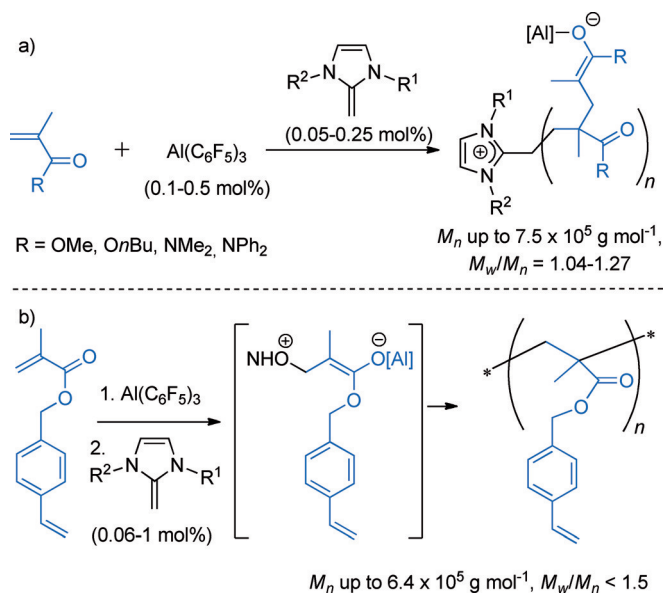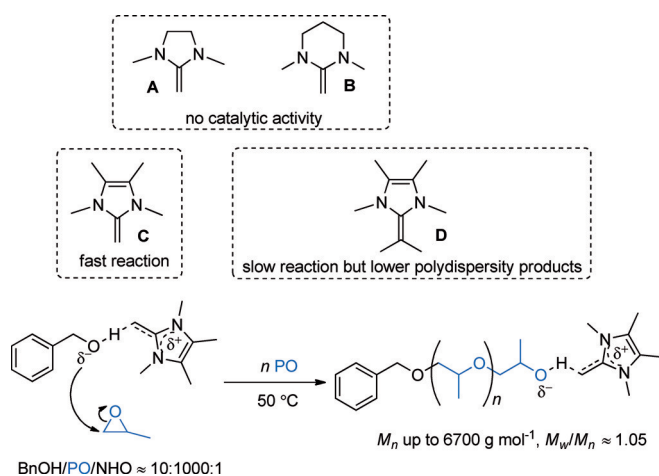

Scheme 2. NHOs as Lewis base organocatalysts for Lewis-pair-mediated polymerization reactions.

addition of the NHO Lewis base catalysts (0.05–0.25 mol %). Interestingly, the pre-formed NHO–Al(C$_6$F$_5$)$_3$ Lewis pairs were ineffective for this transformation, which can be attributed to their high stability. Replacement of Al(C$_6$F$_5$)$_3$ with aluminum halides or B(C$_6$F$_5$)$_3$ also led to unsatisfactory results. The polymers from NHO–Al(C$_6$F$_5$)$_3$ catalyzed reactions were generally high in molecular weight with relatively narrow molar mass distributions The statistical copolymerization of two different acrylate ester monomers also worked well but sequential block copolymerization, however, could not be obtained using these Lewis pairs, probably owing to side reactions occurring with the growing aluminum–enolate species (Scheme 2a), which can undergo different termination reactions, hence disfavoring the sequential block copolymerization.[18]

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$_6$F$_5$)$_3$ pairs (Scheme 2b).[14] 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.[14] By using similar procedures to their previous work,[13] 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.

In a very recent study, Naumann, Thomas, and Dove further extended the synthetic potential of NHO organocatalysts in polymerization chemistry.[4] 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,[4] af-

fording 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 Brønsted base, coordinated to the alcohol to form an alkoxide-like complex. This complex added to propylene oxide to initiate the polymerization process (Scheme 3). As Lu and co-workers had to use aluminum Lewis acids as co-catalysts in their reactions, Naumann, Thomas, 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),[13, 14] which is in stark contrast to the "anionic" transformations reported by Naumann, Thomas, and Dove.[4] Nonetheless, in all of 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).

Future Directions and Challenges for N-Heterocyclic Olefins in Organocatalysis

Although lacking the "carbene"-valent availability of NHCs, NHOs are considered better Brønsted/Lewis bases than their parent NHC compounds (Scheme 4a).[5a, 7] NHOs are also

Scheme 3. NHOs as "anionic" organocatalysts for polymerization of PO.
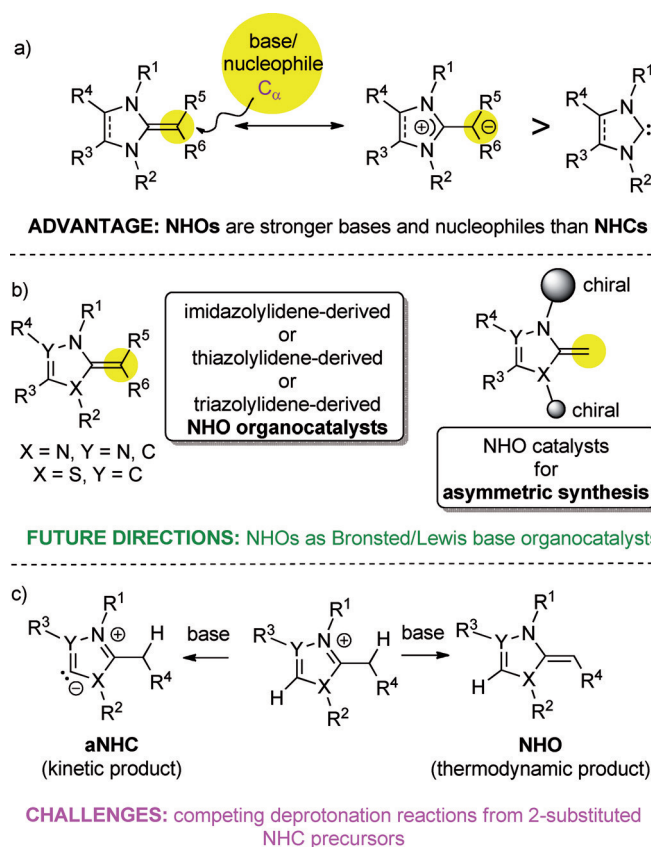
Scheme 4. Future directions and challenges for NHOs in organocatalysis.

known to be stronger nucleophiles than NHCs.[11] Hence, NHOs are likely to have a very bright future in organocatalysis chemistry, whereby they can be used to promote a very wide range of Brønsted[19] or Lewis[20] base-mediated chemical reactions. Such reactions 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 evident that the structures of NHOs 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 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 in this field include the co-existence of abnormal NHCs (aNHCs)[21] 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 exocylic α-carbon, aNHCs can be the kinetic side-products with NHOs being the thermodynamic ones.[22] Therefore, it should always be confirmed that NHOs are being formed exclusively in any in situ catalyst generation for NHO-mediated reactions. 4,5-disubstituted N-heterocyclic precursors are ideal substrates, as there is no competing side-reaction associated with the deprotonation of these compounds. Furthermore, NHO catalysts with extremely high Brønsted/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, elegant studies from Lu and co-workers[11–14] and from Naumann, Thomas, and Dove[4] have demonstrated the great synthetic potential of N-heterocyclic olefins in promoting CO_2 fixation and polymerization processes. With their highly ylidic characters and inherently tunable structures, as observed with the parent NHC species, it is expected that NHOs will soon emerge as versatile organocatalysts for a much broader range of important Lewis/Brønsted base-catalyzed reactions.

Acknowledgements

[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*, 9307–9387.

[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* (Ed.: 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; *Angew. Chem.* **2012**, *124*, 6335–6339; 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**, 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. Fürstner, M. Alcarazo, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 3210–3214; *Angew. Chem.* **2008**, *120*, 3254–3258.

[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. Glöckner, 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, *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*, 1375–1389.

[17] For examples, see: Y. Zhang, G. M. Miyake, E. Y.-X. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 10158–10162; *Angew. Chem.* **2010**, *122*, 10356–10360; 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: *Controlled and Living Polymerizations* (Eds.: A. H. E. Müller, K. Matyjaszewski), Wiley-VCH, Weinheim, **2009**.

[19] For a recent review of Brønsted base catalysis, see: A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus in *Topics in Current Chemistry, Vol. 291* (Ed.: B. List), Springer, Berlin, **2009**, pp. 201–232.

[20] For a recent review of Lewis base catalysis, see: S. E. Denmark, G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638; *Angew. Chem.* **2008**, *120*, 1584–1663.

[21] For a recent review on aNHCs, see: M. Melaimi, M. Soleihavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 8810–8849; *Angew. Chem.* **2010**, *122*, 8992–9032.

[22] O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.* **2009**, *109*, 3445–3478.