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N-Heterocyclic Carbenes in Organocatalysis

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Since the initial discoveries of stable carbenes by Arduengo¹ and Bertrand,² there has been a huge international focus on the chemistry and applications of these compounds. Members of the N-heterocyclic carbene (NHC) family 1-4 (Figure 1) are established as excellent ligands for metal-based catalysis, and have recently emerged as versatile and efficient organocatalysts for a plethora of synthetic transformations.³ Despite their widespread use in organocatalysis, the product distributions of

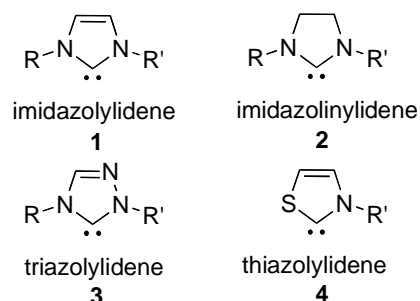


Figure 1 N-heterocyclic carbene catalyst families

reaction processes catalysed by NHCs differ dramatically with variation of catalyst family. As a result, considerable confusion exists over the difference in reactivity of NHCs derived from (for example) imidazolium or triazolium salt precatalysts.^{4,5} At the moment, direct comparison between the reactivity of NHC structural classes is precluded by the use of structurally different catalysts and most importantly through a lack of detailed mechanistic studies of these processes.

Organocatalytic reactions catalysed by NHCs derived from azolium salts typically involve multi-step sequences. Common to all these transformations are: the initial deprotonation of an azolium salt to generate the NHC; nucleophilic addition of the NHC to an electrophile that initiates a bond-forming sequence; regeneration of the NHC for turnover. As part of an overall structure-reactivity investigation of the comparative behaviour of NHCs as organocatalysts in the benzoin and Stetter reactions, we have determined the conjugate acid pK_a values in water of 27 N-heterocyclic carbenes based on the catalyst families in Figure 1. The resulting values were found to span over 15 pK units. The effect of the following factors on acidity were considered: the number of heterocycle ring nitrogens, the carbene NCX bond angle (X=N or S), the number of alkyl versus aryl N-substituents, steric and inductive substituent effects, C4-C5 saturation in the heterocycle and the nature of the counterion in the azolium salt precursor.

¹ A. J. Arduengo *et al*, *J. Am. Chem. Soc.* **1991**, *113*, 361.

² A. Igau *et al*, *J. Am. Chem. Soc.* **1988**, *110*, 6463.

³ (a) N. Marion *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (b) D. Enders *et al*, *Chem. Rev.* **2007**, *107*, 5606.

⁴ J. R. Struble, J. Kaeobamrung and J. W. Bode, *Org. Lett.*, **2008**, *10*, 957.

⁵ C. Campbell, N. Duguet, K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. C. O'Donoghue and A. D. Smith, *Chem. Comm.*, **2008**, *27*, 5044.