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# Influence of the N-Substituents on the Nucleophilicity and Lewis Basicity of N-Heterocyclic Carbenes

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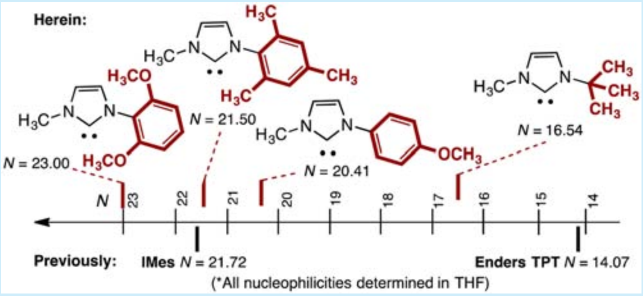
Supporting Information

**ABSTRACT:** The ability to modulate the nucleophilicity and Lewis basicity of N-heterocyclic carbenes is pivotal to their application as organocatalysts. Herein we examine the impact of the N-substituent on the nucleophilicity and Lewis basicity. Four N-substituents popular in NHC organocatalysis, namely, the *N*-2,6-$(CH_3O)_2C_6H_3$, *N*-Mes, *N*-4-$CH_3OC_6H_4$, and *N*-*tert*-butyl groups, have been examined and found to strongly affect the nucleophilicity. Thus, the *N*-2,6-$(CH_3O)_2C_6H_3$ group provides the most nucleophilic imidazolylidene NHC reported and the *N*-*tert*-butyl group one of the least. This difference in nucleophilicity is reflected in the catalyst efficiency, as observed with a recently reported trienyl ester rearrangement.



N-Heterocyclic carbene (NHC) catalysis provides access to a diverse range of intermediates for reaction discovery.[1] Among others, the acyl anion equivalent,[2] homoenolates,[3] acyl azoliums[4] and acyl azolium enols/enolates[5] are now routinely exploited in increasingly sophisticated reaction designs. While other Lewis base catalysts can access some of these classes of intermediates, few access all.[6] Although the versatility of NHC organocatalysis is striking, practical application requires highly judicious catalyst selection. This can involve variation of the heterocycle, with imidazole, triazole, and thiazole NHC catalysts being common, although increasingly prevalent is N-substituent modification to deliver optimal catalytic activity for a given reaction design.[7] In the context of acyl anion-mediated reactions, the role of the N-substituent has been investigated.[7b,c,8] In contrast, an examination of NHC nucleophilicity as a function of the N-substituent, to our knowledge, is yet to be reported. Hence, catalyst design remains largely empirical.

Since 2009 we have reported a series of transformations involving enol esters and enolic anhydrides.[9] In these studies, and those from others using ester substrates, it is clear that the required NHC catalysts are distinct from those suited to acyl anion-mediated reactions.[1g,10,11] While Tolman electronic parameters (TEPs), p$K_a$ values, and $^{13}$C NMR studies give information that is useful for catalyst selection,[12] measures of nucleophilicity are more scarce. Recently, as part of our studies on reactivity scales for nucleophiles and electrophiles, we reported the nucleophilicities of three common NHCs (SIMes, IMes, and TPT; Figure 1).[13,14] While this study addressed the role of the heterocycle in nucleophilicity, the impact of the N-substituent was not addressed. Herein, the dependence of the nucleophilicity on the N-substituent is examined, with the nucleophilicity, as well as the Lewis basicity, of NHCs bearing the *N*-2,6-$(CH_3O)_2C_6H_3$ (**1a**), *N*-Mes (**1b**), *N*-4-$CH_3OC_6H_4$ (**1c**), and *N*-*tert*-butyl groups (**1d**) determined. These N-substituents have been exploited in recent discoveries in NHC catalysis,[9h,15−18] particularly using ester substrates. The studies herein demonstrate that the N-substituent plays a significant role in defining the catalyst nucleophilicity, with 3 orders of magnitude rate difference between **1a** and **1d**. Thus, the impact of the N-substituent is at least as significant as the nature of the azolium moiety in determining NHC nucleophilicity.

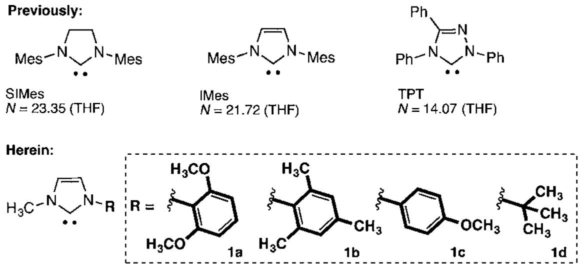


**Figure 1.** Overview of the study.

A series of *p*-quinone methide electrophiles (i.e., **2**, **3**, and **4**) were previously used to determine the nucleophilicity parameters (*N*) of SIMes, IMes, and TPT (Figure 1). This was achieved by exploiting the observation that the rate of addition of nucleophiles to Michael acceptors or carbocations can be predicted by eq 1:[19]

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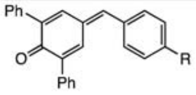
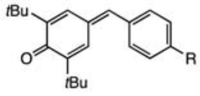
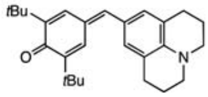
$$\log k_{20°\mathrm{C}} = s_{\mathrm{N}}(N + E) \tag{1}$$

In this equation, nucleophiles are characterized by a solvent-dependent nucleophilicity parameter $N$ and a sensitivity parameter $s_N$, while electrophiles are characterized by a solvent-independent electrophilicity parameter $E$. To date, this relationship has been used to examine 1039 nucleophiles and 272 electrophiles.[20a]

To determine the effect of the N-substituent on the nucleophilicity, studies began with the preparation of the required NHCs by deprotonation of the corresponding imidazolium salts **1a**−**d**·HI with KO*t*-Bu. Although triazolylidenes are more commonly exploited in NHC catalysis, the impact on the nucleophilicity of changing between a triazolylidene and an imidazolylidene has been previously studied (vide supra), thus allowing trends to be extrapolated. Since the nucleophilicities of the four new NHCs **1a**−**d** are likely to be within the range of those already reported, the reference electrophiles **2a**−**c**, **3a**−**d**, and **4** used previously were employed in this study (Table 1). These references are easily handled, have absorption maxima monitorable in the presence of various NHCs, and cover a suitable range of electrophilicities.

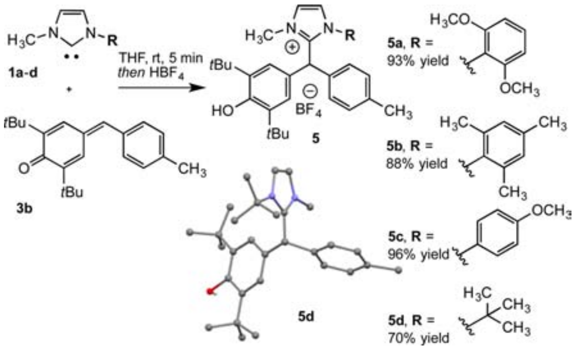
**Table 1. Reference *p*-Quinone Methides 2−4**

| electrophile (E) | | R | $E^a$ |
|---|---|---|---|
|  | **2a** | H | −11.87 |
| | **b** | $OCH_3$ | −12.18 |
| | **c** | $N(CH_3)_2$ | −13.39 |
|  | **3a** | $NO_2$ | −14.36 |
| | **b** | $CH_3$ | −15.83 |
| | **c** | $OCH_3$ | −16.11 |
| | **d** | $N(CH_3)_2$ | −17.29 |
|  | **4** | - | −17.90 |

[a] Electrophilicity parameters for **2**−**4** from refs 20b and 20c.

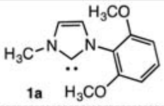
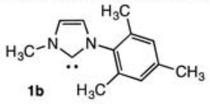
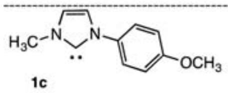
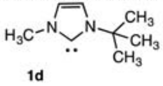
To demonstrate that the outcome of the reaction of NHCs **1a**−**d** with the reference electrophiles are the expected Michael adducts (i.e., **5a**−**d**), preparatory studies were undertaken (Scheme 1). Paralleling earlier reports, the reactions of NHCs **1a**−**d** with *p*-quinone methide **3b** gave the adducts **5a**−**d** in high yields as the only isolable products. Structural confirmation was obtained through regular spectroscopic methods as well as with single-crystal X-ray diffraction for **5d**. Having confirmed the formation of the expected adducts, attention was directed toward the rates of these reactions.

**Scheme 1. Synthesis of 5a−d and X-ray Structure of 5d**



The reactions of NHCs **1a**−**d** with the reference *p*-quinone methides **2**−**4** were studied in THF at 20 °C by photometric monitoring of the disappearance of the colored quinone methides in the presence of a large excess of the NHC to achieve pseudo-first-order conditions. Least-squares fitting of the exponential function $A = A_0 \exp(-k_{\mathrm{obs}}t) + C$ to the observed time-dependent absorbances $A$ of the quinone methide provided the first-order rate constants $k_{\mathrm{obs}}$. The slopes of the linear correlations between $k_{\mathrm{obs}}$ and the concentrations of **1** correspond to the second-order rate constants $k_2$ listed in Table 2. The rate constants $k_2$ were then used in association with the electrophilicity parameters of **2**−**4** to construct correlation lines for the four NHCs (Figure 2). As can be seen, in all cases good fits were obtained, which allowed the nucleophilicity parameters to be accurately determined.

**Table 2. Second-Order Rate Constants and Nucleophilicity Parameters for the Reactions of NHCs 1a−d with Reference Electrophiles 2−4 in THF at 20 °C**

| NHC **1a-d** | E | $k_2$ [L mol$^{-1}$ s$^{-1}$] | $N$, ($s_N$) |
|---|---|---|---|
|  **1a** | **2b** | $1.16 \times 10^5$ | 23.00 |
| | **2c** | $2.11 \times 10^4$ | (0.46) |
| | **3c** | $1.62 \times 10^3$ | |
| | **4** | $2.27 \times 10^2$ | |
|  **1b** | **2a** | $3.46 \times 10^4$ | 21.50 |
| | **2b** | $1.52 \times 10^4$ | (0.45) |
| | **2c** | $3.02 \times 10^3$ | |
| | **3a** | $5.62 \times 10^3$ | |
| | **3b** | $5.01 \times 10^2$ | |
| | **3c** | $3.15 \times 10^2$ | |
| | **3d** | $6.34 \times 10^1$ | |
| | **4** | $5.86 \times 10^1$ | |
|  **1c** | **2b** | $6.70 \times 10^3$ | 20.41 |
| | **2c** | $1.37 \times 10^3$ | (0.46) |
| | **4** | $1.41 \times 10^1$ | |
|  **1d** | **2b** | $1.46 \times 10^2$ | 16.54 |
| | **2c** | $2.42 \times 10^1$ | (0.47) |
| | **3c** | 3.10 | |
| | **4** | $2.10 \times 10^{-1}$ | |

The nucleophilicities of these newly characterized carbenes can be compared with those of other NHCs and nucleophilic

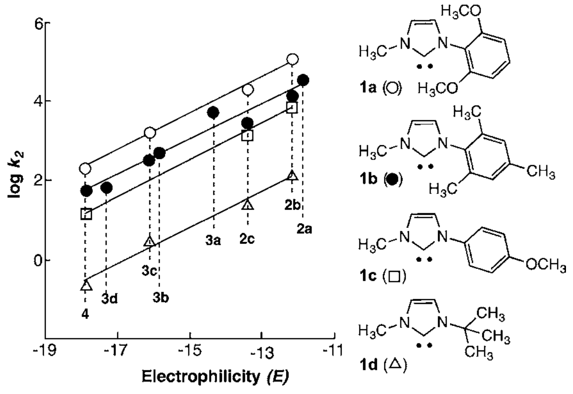


**Figure 2.** Correlations of log $k_2$ vs electrophilicity parameters for the reactions of NHCs **1a**−**d** with *p*-quinone methides **2**−**4**.

catalysts (Figure 3). From this comparison, it is clear that the nucleophilicity is heavily influenced by the nature of the N-substituent. Thus, the most nucleophilic of the NHCs bears an *N*-2,6-$(CH_3O)_2C_6H_3$ substituent (i.e., **1a**) and is more nucleophilic than IMes. The least nucleophilic is the *N*-*tert*-butyl NHC **1d**, which is only moderately more nucleophilic than the Enders carbene (TPT) and DBU. Interestingly, replacing a single mesityl substituent with a methyl group has little impact on the nucleophilicity of the catalyst (IMes, cf. **1b**). Finally, a *para* electron-donating substituent gives an NHC that is less nucleophilic than either the *N*-Mes NHC **1b** or the *N*-2,6-$(CH_3O)_2C_6H_3$ NHC **1a**.

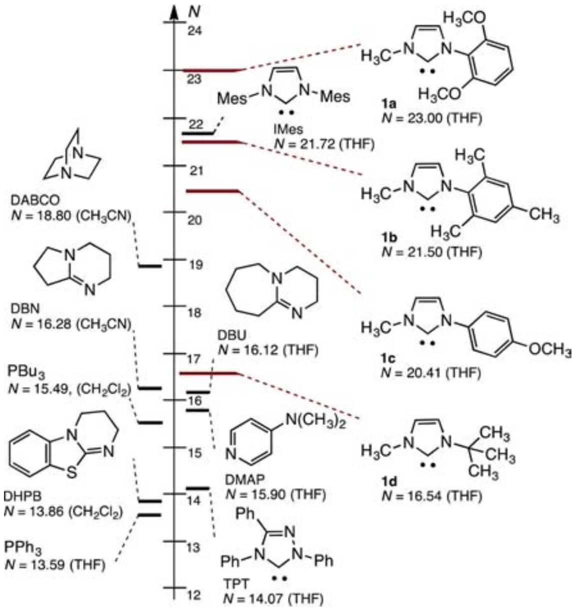


**Figure 3.** Nucleophilicities of **1a**−**d** and other catalysts.

In previous studies, the Lewis basicities of NHCs have been studied computationally because of an inability to determine equilibrium constants from their interactions with *p*-quinone methides. This is a result of their exceptionally high Lewis basicity. To allow Lewis basicity to be determined in this study, methyl cation affinities (MCAs), as defined in Figure 4, have been calculated for NHCs **1a**−**d** employing MP2/6-31+G-(2d,p)//B86/6-31G(d), a method previously shown to result in reliable MCAs.[13,21]

Most strikingly, we found that the *N*-2,6-$(CH_3O)_2C_6H_3$ substituent in **1a** led to the most Lewis basic catalyst, with an MCA some 28 kJ mol$^{-1}$ higher than that of the variant bearing a single mesityl group (**1b**). Interestingly, the MCA of **1b** was 23 kJ mol$^{-1}$ lower than that of IMes (MCA = 767 kJ mol$^{-1}$),[13] indicating that replacement of a mesityl group with a methyl group decreases the Lewis basicity while having little bearing on the nucleophilicity. In contrast, switching from a methyl substituent to a *tert*-butyl substituent has very little impact on the Lewis basicity (719 kJ mol$^{-1}$ vs 718 kJ mol$^{-1}$ for R = $CH_3$; Figure 4).[13] The dihedral angle between the imidazole and the aromatic N-substituent indicates significant twisting out of plane in both carbenes **1a** and **1b** (80.5° and 83.7°) and methyl imidazoles **6a** and **6b** (69.5° and 88.9°). While some planarization (**1a** → **6a**) is observed, it is not sufficient to allow through-space interactions of the *ortho* group and the azolium.

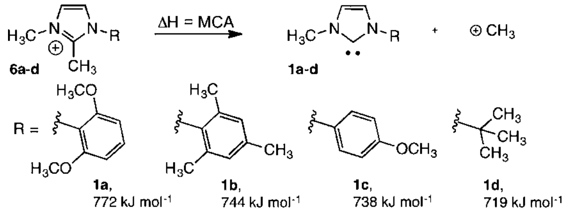


**Figure 4.** Gas-phase methyl cation affinities (MCAs) calculated at the MP2/6-31+G(2d,p)//B98/6-31G(d) level of theory.

Studies from our group on NHC-catalyzed (4 + 2) annulations show significant sensitivity to the N-substituent.[9d−f] To further examine this sensitivity, the conversion of triene **7** to cycloadduct **8** was monitored over time using NHCs bearing the four N-substituents examined herein (Figure 5). Preliminary studies on imidazolium-derived NHCs were hampered by kinetic difficulties due to very high reaction rates. In contrast, monitoring with the triazolium series of NHCs demonstrated that the reaction is successful with the most nucleophilic triazolium-derived catalysts **9a** and **9b** and fails with N-substituents associated with the least nucleophilic NHCs. These results are consistent with our observations that NHC addition to esters is significantly more challenging than that to aldehydes. The success or failure of this reaction is correlated with the catalyst nucleophilicity and not its Lewis basicity, with catalyst **9b** likely to display similar Lewis basicity to **9c** but giving a significantly different reaction outcome.

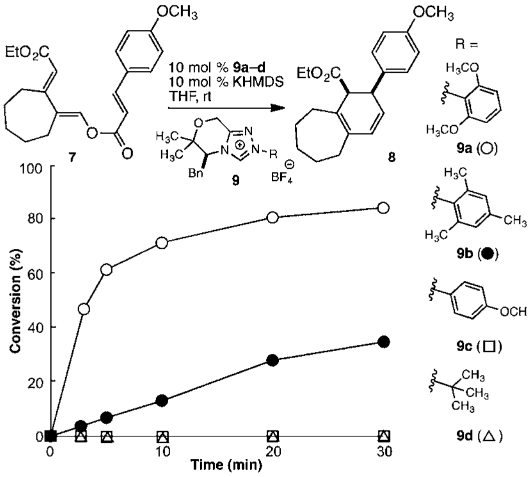


**Figure 5.** Conversion of ester **7** to diene **8** with catalysts **9a**−**d**.

The capacity of NHCs to enable reactions that are unattainable with other nucleophilic catalysts is associated with their unique Lewis basicity and nucleophilicity profiles. As applications of NHCs in organocatalysis develop, the capacity to modulate these properties takes on increasing importance. In recent years, the N-substituents examined in this report have allowed new discoveries in NHC catalysis. Herein we report that the *N*-2,6-$(CH_3O)_2C_6H_3$ substituent gives one of the most nucleophilic and Lewis basic NHC catalysts, while the impact of remote electron-donating groups on the NHC properties is modest. Finally, hindered alkyl groups give one of the least nucleophilic and Lewis basic NHCs.

The studies reported herein demonstrate that the N-substituent plays a significant role in defining catalyst nucleophilicity. Together with the known role of heterocycle selection in nucleophilicity,[13] these studies demonstrate that significant variation in catalyst properties is possible by manipulation of these two parameters.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01525.

Procedures and additional data (PDF)

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### Notes

The authors declare no competing financial interest.

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