Organocatalysis

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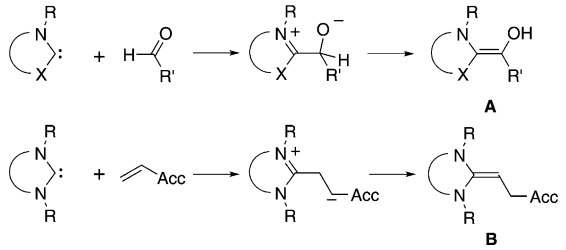
Nucleophilic Reactivities of Deoxy Breslow Intermediates: How Does Aromaticity Affect the Catalytic Activities of N-Heterocyclic Carbenes?**

*Biplab Maji, Markus Horn, and Herbert Mayr**

Dedicated to Professor George A. Olah on the occasion of his 85th birthday

N-Heterocyclic carbenes[1] (NHCs, **1**) are widely used as umpolung reagents[2] in organocatalysis.[3] In benzoin condensations[4] and Stetter reactions[5] the initially formed Breslow intermediate **A**,[6] a nucleophilic acyl anion equivalent, reacts with an aldehyde or Michael acceptor to give 1,2- or 1,4-functionalized products. Recently, Fu, Matsuoka, and Glorius independently reported the umpolung of the β-position of Michael acceptors, where 1,1-diaminoalkenes **B** act as key intermediates.[7] Since the structure of **B** is closely related to **A**, it has been named "deoxy Breslow intermediate" (Scheme 1).[7c,8]

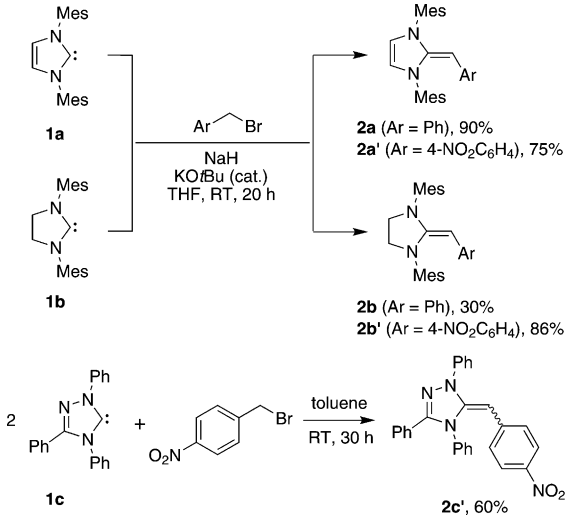


Scheme 1. Reactions of NHCs with aldehydes and Michael acceptors to give intermediates **A** and **B**, respectively.

Most suitable for these reactions were 1,2,4-triazol-5-ylidenes, 1,3-thiazol-2-ylidenes, and imidazol-2-ylidenes, while imidazolidin-2-ylidenes are not effective as umpolung reagents.[3,8] This observation is surprising, because in recent work we have shown that the imidazol-2-ylidene **1a** and imidazolidin-2-ylidene **1b** have almost the same nucleophilicities and Lewis basicities, while Enders's carbene **1c** reacted 10^3 times more slowly and 55 kJ mol^{-1} less exothermic with C-electrophiles.[9]

As the different catalytic activities of unsaturated and saturated carbenes thus cannot be assigned to the different properties of the carbenes themselves, the question arose whether it is due to the different reactivities of the corresponding Breslow intermediates. While characterizations of Breslow intermediates by spectroscopic and theoretical methods have been reported,[10] we are not aware of any kinetic investigations comparing the reactivities of 1,1-diaminoethenes derived from different classes of NHCs. Therefore, we have now synthesized compounds **2**[11] and determined the kinetics of their reactions with electrophiles.

The reactions of **1a** and **1b** with benzyl or 4-nitrobenzyl bromide, and subsequent deprotonation of the resulting amidinium ions with NaH in the presence of a catalytic amount of KO*t*Bu in THF afforded **2a**–**2b′** in yields of 30–90% (Scheme 2). While **2a** and **2a′** could also be generated



Scheme 2. Synthesis of deoxy Breslow intermediates **2**.

with stoichiometric amounts of KO*t*Bu in the absence of NaH,[8] this procedure did not allow the synthesis of **2b** and **2b′**. Attempts to synthesize **2c′** analogously resulted in complex reaction mixtures. However, **2c′** was synthesized in 60% yield from 4-nitrobenzyl bromide and 2 equivalents of **1c** in toluene, the second molecule of **1c** acting as the base. For details of the synthetic procedures see the Supporting Information.

In order to quantify the nucleophilic reactivities of **2** we have studied the kinetics of their reactions with the benzhy-

[*] M. Sc. B. Maji, Dr. M. Horn, Prof. Dr. H. Mayr
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13 (Haus F), 81377 München (Germany)
E-mail: herbert.mayr@cup.uni-muenchen.de
Homepage: http://www.cup.lmu.de/oc/mayr

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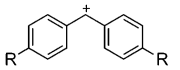
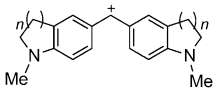
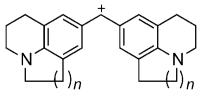
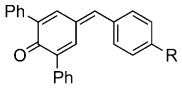
Table 1: Benzhydrylium ions **3a–f** and quinone methides **3g**, **h** employed as reference electrophiles in this work.

Electrophile			E[a]
	R = NMe_2	**3a**	−7.02
	R = $N(CH_2)_4$	**3b**	−7.69
	n = 2	**3c**	−8.22
	n = 1	**3d**	−8.76
	n = 2	**3e**	−9.45
	n = 1	**3f**	−10.04
	R = OMe	**3g**	−12.18
	R = NMe_2	**3h**	−13.39

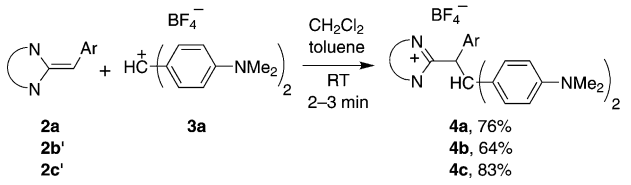
[a] Electrophilicity parameters E for **3a–f** from Ref. [12a], for **3g**,**h** from Ref. [12b].

drylium ions **3a–f** and the quinone methides **3g**,**h** (Table 1) which have been used as reference electrophiles for characterizing the reactivities of manifold structurally variable nucleophiles.[12]

$$\log k = s_N(N + E) \quad (1)$$

Equation (1) has been demonstrated to reliably predict second-order rate constants k for a wide range of electrophile–nucleophile combinations. In this approach, electrophiles are assigned a solvent-independent electrophilicity parameter E, whereas nucleophiles are characterized by a pair of solvent-dependent parameters (N, s_N).[13]

Representative product studies (Scheme 3) revealed that the benzhydrylium ion **3a** attacks the exocyclic olefinic carbon atoms of the deoxy Breslow intermediates **2** to give the azolium salts **4a–c** which were isolated and fully characterized (**4c** by X-ray crystallography; for details see the Supporting Information).[14]



Scheme 3. Reactions of **2a**, **2b′**, and **2c′** with the reference electrophile **3a**.

The kinetics of the reactions of **2** with **3** were followed photometrically in THF or DMSO at 20 °C by monitoring the disappearance of the absorbances of **3** using conventional or stopped-flow spectrophotometers. Pseudo-first-order conditions were established by using a high excess of **2**. The first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the decay of the absorbances of **3** to the function $A_t = A_0 \exp(-k_{obs}t) + C$. The slopes of the linear plots of k_{obs} against the concentrations of **2** (see Figure S4 and pp. S14–S24 in the Supporting Information) gave the second-order rate constants k listed in Table 2.

Table 2: Second-order rate constants k ($M^{-1}s^{-1}$) for the reactions of the deoxy Breslow intermediates **2** with the reference electrophiles **3** at 20 °C.

Nucleophile	Solvent	N, s_N[a]	Electrophile	k [$M^{-1}s^{-1}$]
2a	THF	17.12, 0.80	**3e**	1.33×10^6
			3f	4.50×10^5
	DMSO	17.41, 0.74	**3e**	8.80×10^5
			3f	2.30×10^5
			3g	6.10×10^3
			3h	1.05×10^3
2a′	THF	14.45, 0.71	**3c**	2.96×10^4
			3d	7.89×10^3
			3e	5.16×10^3
			3f	1.16×10^3
2b	THF	13.91, 0.64	**3b**	9.60×10^3
			3c	5.95×10^3
			3d	1.53×10^3
			3e	8.88×10^2
			3f	3.01×10^2
2b′	THF	11.42, 0.70	**3a**	1.10×10^3
			3b	4.35×10^2
			3c	1.74×10^2
			3d	6.83×10^1
2c′	THF	12.75, 0.71	**3b**	4.00×10^3
			3d	5.91×10^2
			3f	8.68×10^1

[a] N, s_N as defined by Equation (1).

When values of log k were plotted against the corresponding electrophilicity parameters E of **3**, linear correlations were obtained (Figure 1). Equation (1) can therefore be used to evaluate the N and s_N parameters of the deoxy Breslow intermediates **2** (third column of Table 2).[12] Table 2 and Figure 1 show that the reactions are only slightly slower in DMSO than in THF (by a factor of 1.6).

The order of the nucleophilic reactivities of compounds **2** differs dramatically from the reactivity order of the corresponding precursor carbenes **1** (Scheme 4): While the carbene **1a** was found to be 2.5 times less reactive than **1b**,[9] the benzylidene imidazole **2a** reacts 10^3 times faster than its

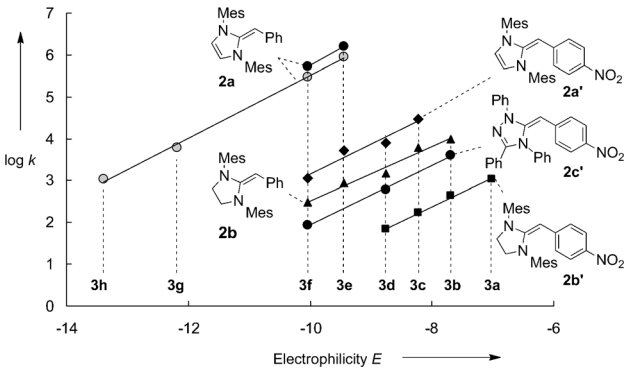
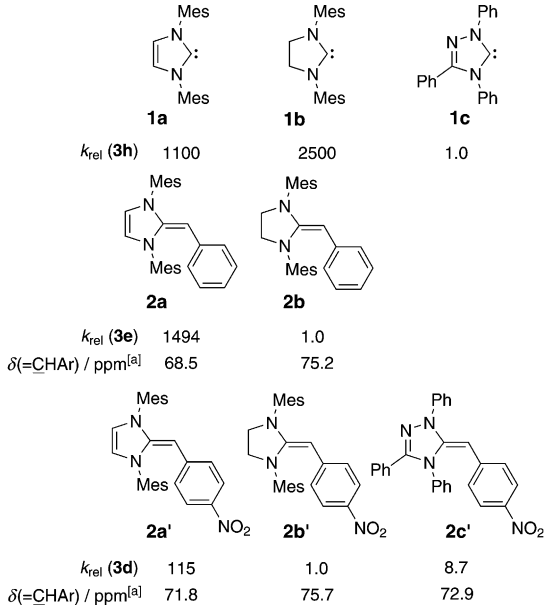


Figure 1. Plot of log k for the reactions of **2** with the electrophiles **3** (THF, 20 °C) versus the corresponding electrophilicity parameters E. Open circles: DMSO solvent.



Scheme 4. Relative reactivities of the NHCs **1** towards benzhydrylium ions (taken from Ref. [9]) and comparison with the corresponding reactivities of deoxy Breslow intermediates **2** (THF, 20 °C). [a] In C_6D_6.

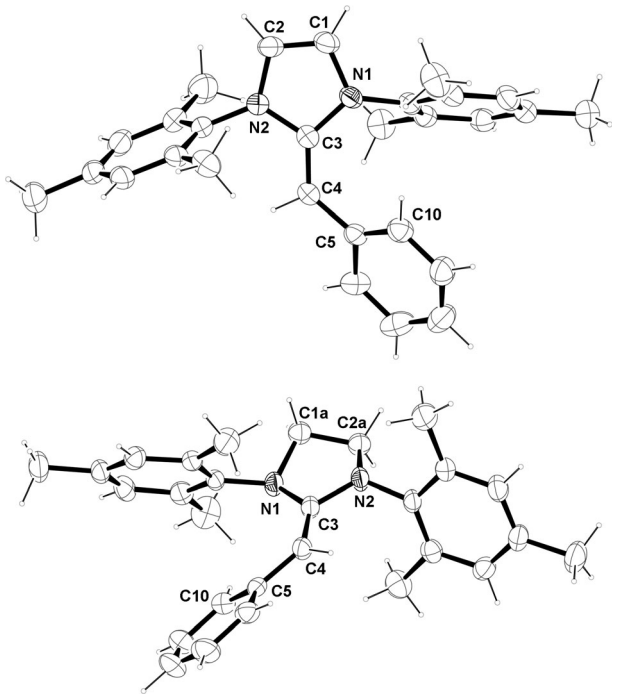
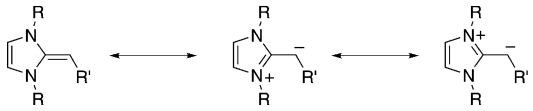


Figure 2. Crystal structures of **2a** (top) and **2b** (bottom). Only one position of the disordered atoms C1 and C2 is shown for **2b**. Selected bond lengths [pm] and angles [°]: **2a**: C3-C4 136.1, N1-C3-C4-C5 9.9, C3-C4-C5-C10 32.1; **2b**: C3-C4 135.4, N1-C3-C4-C5 11.6, C3-C4-C5-C10 26.7.

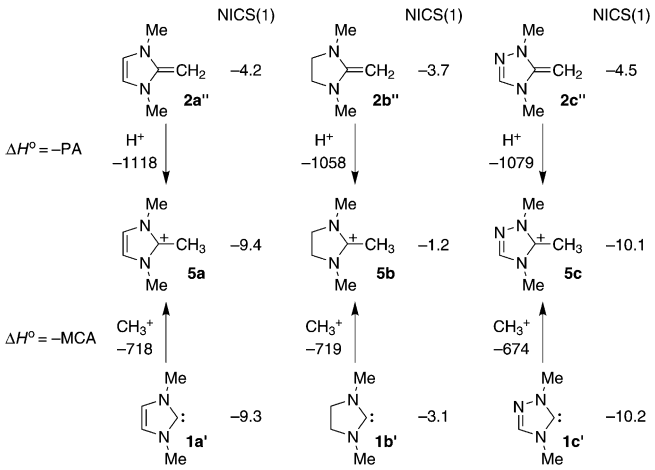
saturated analogue **2b**. The attenuating effect of the nitro group reduces the reactivity ratio $k_{2a'}/k_{2b'}$ to 10^2, and even the triazole-derived olefin **2c′** is one order of magnitude more reactive than the imidazolidine derivative **2b′**.

The reactivity orders **2a** ⋙ **2b** and **2a′** > **2c′** > **2b′** are in line with the relative charge densities at the nucleophilic carbon atoms which can be derived from the corresponding ^{13}C NMR chemical shifts (Scheme 4) as well as from quantum chemical calculations (Scheme S1 in the Supporting Information).

How can one explain the high reactivity ratio k_{2a}/k_{2b} = 1494 which contrasts the relative nucleophilicities of the precursor carbenes k_{1a}/k_{1b} = 0.44? In the X-ray structures of **2a** and **2b** (Figure 2)[14] one can observe that the exocyclic double bond in **2a** is only slightly longer than that in **2b** (Δ = 0.7 pm), indicating that the resonance structures with aromatic rings have only little significance for the ground state of **2a** (Scheme 5).



Scheme 5. Resonance structures for 2-alkylidene imidazoles.



Scheme 6. Comparison of the proton affinities (PA) of the diaminoethylenes **2** with the methyl cation affinities (MCA, from Ref. [9]) of the corresponding carbenes **1** (in kJ mol^{-1}, MP2/6-31 + G(2d,p)//B98/6-31G(d)) and the NICS(1) values of **1**, **2**, and **5** (B3LYP/6-311 + G(d)).

In order to compare the thermodynamics of these reactions, gas-phase proton affinities of the 1,1-diaminoethylenes **2a″**, **2b″**, and **2c″** were calculated on the MP2/6-31 + G(2d,p)//B98/6-31G(d) level of theory using the Gaussian 09 program package.[15] Scheme 6 shows that the proton affinity of **2b″**, derived from the saturated Arduengo carbene **1b′**, is 60 kJ mol^{-1} lower than that of **2a″**. Compound **2b″** is an even weaker Brønsted base than the triazole-derived olefin **2c″** which includes an electronegative nitrogen atom (ΔPA = 21 kJ mol^{-1}). The nucleophilicity order **2a′** > **2c′** > **2b′** (Scheme 4, bottom line) thus mirrors the proton affinity order **2a″** > **2c″** > **2b″** (Scheme 6, top). Analogously, the completely different nucleophilicity order of the NHCs **1a** ≈ **1b** ⋙ **1c** (Scheme 4, top row) is also reflected by the order of methyl cation affinities **1a′** ≈ **1b′** ⋙ **1c′** (Scheme 6, bottom).[9] As shown in Table S29 in the Supporting Information,

analogous results are obtained for 1,1-diaminoethylenes where the methyl groups of **2a″**–**2c″** are replaced by *tert*-butyl, phenyl, and mesityl groups, respectively.

As the carbenes **1** are attacked by electrophiles at the nonbonding lone pair in the plane of the heterocyclic ring, the π system is not affected and the different reactivities of the NHCs **1** can be explained by inductive effects.[9] In contrast, electrophilic additions to **2** occur at the conjugated π system, and resonance effects become important.

From the comparable NICS(1)[16] values of **2a″**, **2b″**, and **2c″** one can deduce that aromaticity is not important for the ground states of these compounds, as evident from the X-ray structures of **2a** and **2b** (Figure 2, Scheme 5). Electrophilic additions to the nonaromatic **2a″** and **2c″** give rise to the formation of the aromatic azolium ions **5a** and **5c** (large NICS(1) values, Scheme 6) and thus account for the high proton affinities of **2a″** and **2c″**, respectively.[17]

In contrast, the NICS(1) values in Scheme 6 show that the aromatic character will not be changed when **5a** and **5c** are formed through methyl cation addition to the precursor carbenes **1a′** and **1c′**. For that reason neither do the unsaturated carbenes **1a′** and **1c′** have greater Lewis basicity than the saturated carbene **1b′** (Scheme 6) nor do **1a** and **1c** have greater nucleophilicity than **1b** (Scheme 4). Calculations of $NICS(0)_{\pi zz}$ values[18a] led to similar conclusions.[18b]

We thus conclude that the different catalytic activities of saturated (e.g. **1b**) and unsaturated NHCs (e.g. **1a**,**c**) cannot be explained by the intrinsic properties of the carbenes, but that one of the subsequent steps must account for this difference. In this work we have shown that Breslow intermediates derived from unsaturated NHCs (e.g. **2a**) are significantly more nucleophilic than those derived from saturated NHCs (e.g. **2b**). The development of aromaticity by electrophilic attack at Breslow intermediates derived from unsaturated NHCs is, therefore, considered to be an important reason for the preferred use of such carbenes as umpolung catalysts. In coordination and transition-metal chemistry, on the other hand, where the σ-donor ability of the carbenes plays the dominant role, saturated as well as unsaturated NHCs have been reported to be suitable ligands.[19]

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[13] For a comprehensive listing of nucleophilicity parameters *N*, electrophilicity parameters *E*, and s_N, see http://www.cup.lmu.de/oc/mayr/DBintro.html.

[14] CCDC 879115 (**2a**), 879114 (**2b**), and 879116 (**4c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] Gaussian 09, Revision A.02, M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2009**.

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