Organocatalysis

DOI: 10.1002/anie.201205878

# Umpolung by N-Heterocyclic Carbenes: Generation and Reactivity of the Elusive 2,2-Diamino Enols (Breslow Intermediates)**

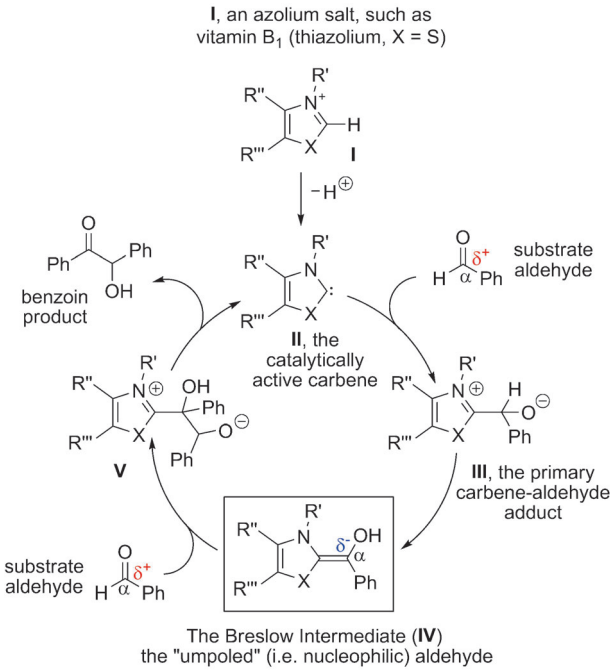
*Albrecht Berkessel,* Silvia Elfert, V. Reddy Yatham, Jörg-M. Neudörfl, Nils E. Schlörer, and J. Henrique Teles*

*Dedicated to Professor Ronald Breslow*

In biochemistry, reactions such as pyruvate decarboxylation and benzoin-type condensations that are catalyzed by vitamin $B_1$ dependent enzymes were considered some of the mechanistically most "mysterious" transformations, until in 1958 Breslow proposed that all these reactions hinge on the formation of an N-heterocyclic carbene (NHC) as the catalytically active entity (Scheme 1).[1–3] The azolium salt **I** (e.g. X = S, in thiamine) is deprotonated to form thiazolin-2-ylidene **II**, the catalytically active species. Nucleophilic attack of carbene **II** onto an aldehyde generates the primary carbene–aldehyde adduct **III**. A subsequent protonation/deprotonation affords amino enol **IV**.

Amino enol **IV** acts as an acyl anion equivalent, and reacts with the carbonyl group of a second aldehyde molecule, thereby generating addition product **V**. A second proton transfer follows, and the elimination of the benzoin product regenerates the carbene catalyst **II**. In honor of his groundbreaking work, the nucleophilic amino enol **IV** has been addressed as the "Breslow intermediate" ever since. It represents the assumed chemical entity crucial for all biochemical and organocatalytic umpolung reactions. Dozens of excellent publications on new applications of carbene umpolung catalysis appear each year, and they all invoke Breslow intermediates as the crucial intermediates.[4,5]

Despite its central importance in bio- and organocatalysis, no unambiguous generation and characterization of Breslow intermediates, that is, 2,2-diamino enols, has been reported to date. Rovis and co-workers recently disclosed that the reversible addition of triazolylidene carbenes to iminium ions furnishes 1,2,2-triaminoethenes.[6,7] However, these aza analogues of 2,2-diamino enols do not show the expected reactivity of a Breslow intermediate, that is, formation of a cross-benzoin product in the presence of an aldehyde.



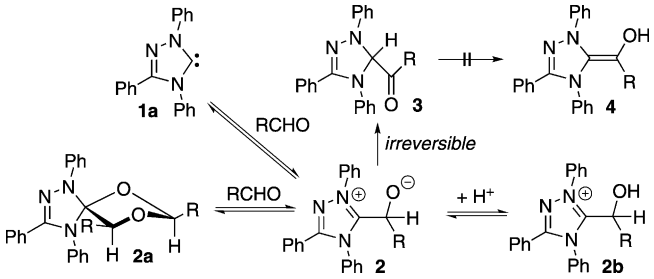

***Scheme 1.*** Catalytic cycle of the benzoin condensation as proposed by Breslow.[1,2]

Herein, we describe our own approach, which ultimately led to the generation of a number of 2,2-diamino enols (Breslow intermediates), their unambiguous characterization by NMR spectroscopy, and the proof of their reactivity in cross-benzoin reactions. Thus, we could provide evidence for the existence of Breslow intermediates, for their accessibility from N-heterocyclic carbenes and aldehydes, and for their postulated acyl anion reactivity.

Our own previous studies were aimed at generating Breslow intermediates based on 1,2,4-triazolylidene carbenes, such as **1a**, as they are readily accessible and highly reactive umpolung catalysts (Scheme 2).[8,9] We reported earlier that in the presence of excess aldehyde the primary carbene–aldehyde adduct **2** is reversibly converted into the spiro-dioxolane **2a**, the resting state of the catalytic system in the case of aliphatic aldehydes.[10] The addition of acid results in intermediate **2** being reversibly protonated to give (isolable) **2b**.[9] Alternatively, intermediate **2** can irreversibly isomerize to ketone **3**. The latter is catalytically incompetent and thus a "dead end" in the catalytic system.[10]

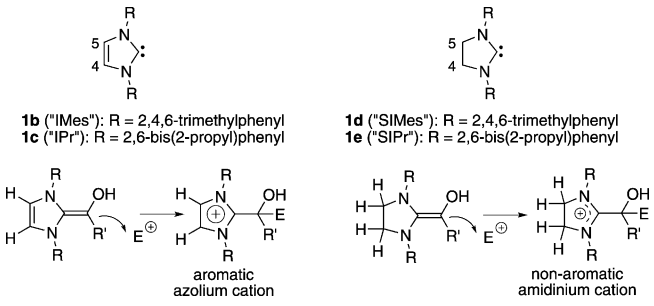
[*] Prof. Dr. A. Berkessel, S. Elfert, V. R. Yatham, Dr. J.-M. Neudörfl, Dr. N. E. Schlörer
Cologne University, Department of Chemistry
Greinstrasse 4, 50939 Cologne (Germany)
E-mail: berkessel@uni-koeln.de
Homepage: http://www.berkessel.de
Dr. J. H. Teles
BASF SE, GCS/X-M311
67056 Ludwigshafen (Germany)

[**] Support by the Fonds der Chemischen Industrie and by BASF SE is gratefully acknowledged. We thank Felix Klauck for providing samples of $^{13}$C-labeled 2,4-bis(trifluoromethyl)benzaldehyde.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205878.




***Scheme 2.*** Formation of spiro-dioxolane (**2a**) and ketone (**3**) in the reaction of a 1,2,4-triazolylidene with an aldehyde.

Our attempts to induce tautomerization of ketones **3** to their reactive enol form **4** (by numerous acids, bases, silylating agents) met with frustration—with decomposition or the formation of isomeric silyl enol ethers as the typical outcome. As gauged by DFT calculations (see the Supporting Information), the enol form **4** (Scheme 2) is about 50 kJ mol$^{-1}$ higher in energy than the corresponding ketone (for R = Ph). Our calculations revealed, however, that the introduction of electron-withdrawing substituents should make the enol form more readily accessible (e.g. for R = 2,4-bis(trifluoromethyl)phenyl: $\Delta\Delta G$ ca. 20 kJ mol$^{-1}$, Gibbs free energies at 298 K in the gas phase). Unfortunately, treatment of carbene **1a** with 2,4-bis(trifluoromethyl)benzaldehyde still gave ketone **3** exclusively—with no tautomerization to enol form **4**. We therefore turned our attention to "tuning" the carbene moiety. N-Heterocyclic carbenes can generally be subdivided into those in which the heterocycle can become an aromatic azolium ion, and those in which saturation at C4,5 precludes aromatization (Scheme 3). In view of the expected lower reactivity/higher stability of Breslow intermediates derived from saturated N-heterocyclic carbenes, we focused our study on the interaction of aldehydes with dihydro-IMes (SIMes, **1d**) and the related dihydro-IPr (SIPr, **1e**). Our reasoning was also supported by an elegant kinetic study by Mayr and coworkers,[11] who recently analyzed the reactivity of 2-benzylidene derivatives (i.e. "desoxy-Breslow intermediates", which lack the enol-hydroxy function[12]) of IMes (**1b**) and SIMes (**1d**), and also of the 1,2,4-triazolylidene carbene **1a**, with benzhydrylium ions as the electrophiles. These results confirmed a quite significantly higher ($k_{unsat.}/k_{sat.}$ ca. 1000) reactivity of the IMes (**1b**) and triazolylidene (**1a**) derivatives relative to the one derived from saturated SIMes (**1d**).




***Scheme 3.*** 4,5-Unsaturated (**1b,c**) and saturated (**1d,e**) N-heterocyclic carbenes.

To our extreme delight, NMR spectroscopic analysis revealed the clean formation—within a few minutes—of the 2,2-diamino enols **5d** and **6e** when the carbenes SIMes (**1d**) and SIPr (**1e**) were combined with benzaldehyde and 2,4-bis(trifluoromethyl)benzaldehyde, respectively, at room temperature in [D$_8$]THF under rigorous exclusion of oxygen. Figure 1 (top) shows the $^1$H NMR spectrum of the 2,2-diamino enol **6e**. The use of $^{13}$C-labeled 2,4-bis(trifluoromethyl)benzaldehyde ($^{13}$CHO) revealed the expected $^{13}$C-OH/C couplings and thus additionally confirmed the chemical

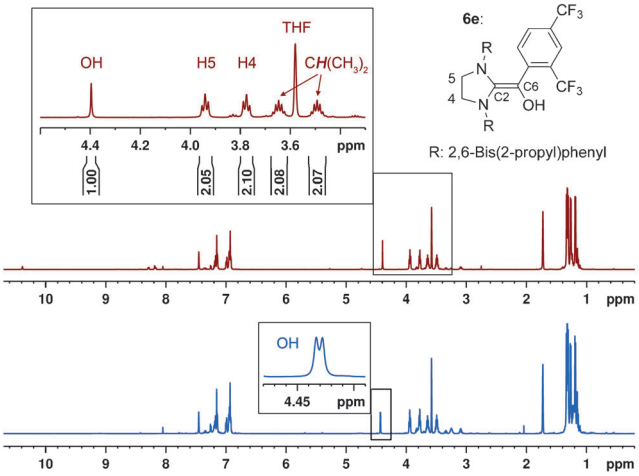



***Figure 1.*** Top: $^1$H NMR spectrum ([D$_8$]THF, 600 MHz) of the reaction of SIPr (**1e**) with 2,4-bis(trifluoromethyl)benzaldehyde (1 equiv) which results in the formation of the 2,2-diamino enol **6e**. Bottom: 2,2-diamino enol **6e**, $^{13}$C label at C6.

shift assignments of enol **6e**: $\delta = 4.40$ ppm (d, $^2J_{COH} = 3.23$ Hz, see Figure 1, bottom); $\delta = 145.8$ ppm (d, $^1J_{C6\text{-}C2} = 106.4$ Hz, C2), $\delta = 142.5$ ppm (d, $^1J_{C6\text{-}Car} = 69.8$ Hz, $C_{ar}$). The labeled C atom (C6) itself resonates at $\delta = 109.5$ ppm (see the Supporting Information for the $^{13}$C NMR spectra). Most characteristic is the resonance at $\delta = 4.40$ ppm which is assigned to the hydroxy proton of 2,2-diamino enol **6e**, supported by its rapid H/D exchange upon addition of [D$_4$]MeOH (see the Supporting Information for spectra). Another characteristic feature of the enol OH proton is the pronounced temperature dependency of its chemical shift (Figure 2). The variable-temperature $^1$H NMR spectra shown in Figure 2 also revealed coalescence of the enol's imidazolidine (C4,C5) protons ($\delta$ ca. 3.7–4.0 ppm at 25 °C) at approximately −55 °C. The underlying conformational behavior of the 2,2-diamino enol **6e** will be the subject of future studies. Note that identical $^1$H NMR spectra were recorded before and after cooling the solution to −95 °C (Figure 2, top and bottom red traces).

By simple combination of a saturated carbene with one equivalent of aldehyde, we were able to generate cleanly the 2,2-diamino enols **5d**, **5e**–**10e** shown in Figure 3. NMR spectroscopy did not indicate any degradation of the 2,2-diamino enols over several hours under rigorous exclusion of oxygen. Instantaneous decomposition occurs upon admission of air. As exemplarily tested with $^{13}$C-labeled enol **5e** (label at C6), exposure of the mixture to acid (acetic acid, 2 equiv)

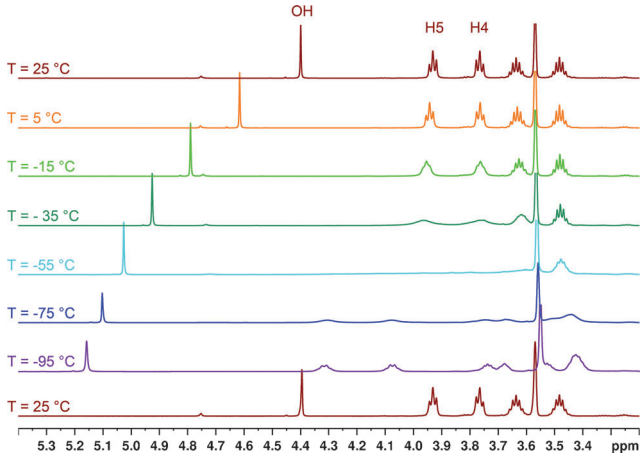



***Figure 2.*** Variable-temperature $^1$H NMR spectra ([D$_8$]THF, 600 MHz, 25 °C to −95 °C) of the 2,2-diamino enol **6e**. At $T$ = 25 °C, the OH proton of the enol resonates at $\delta$ = 4.40 ppm.

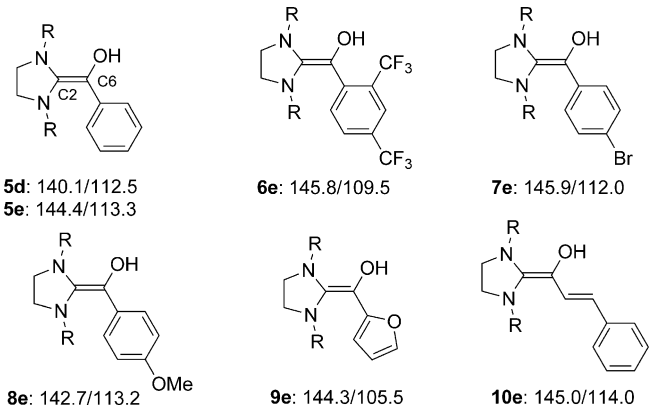



***Figure 3.*** $^{13}$C NMR shifts [ppm] of C2/C6 of the 2,2-diamino enols **5d**, **5e**–**10e** ([D$_8$]THF, 25 °C); **5d**: R = 2,4,6-trimethylphenyl, **5e**–**10e**: R = 2,6-bis(2-propyl)phenyl.

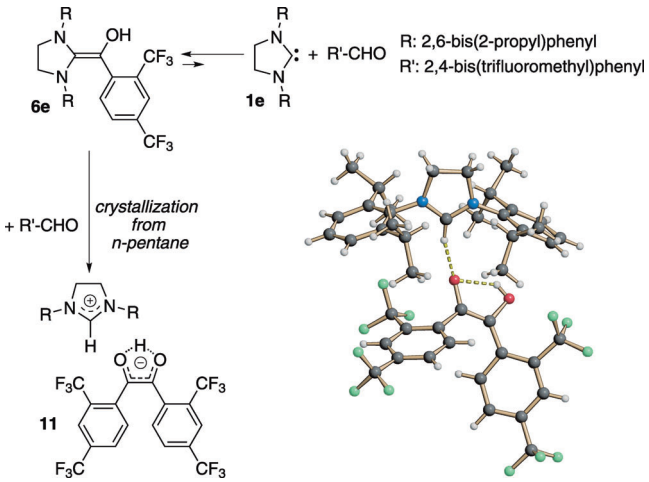



***Figure 4.*** Formation of the benzoin-azolium salt **11** from SIPr (**1e**) and 2,4-bis(trifluoromethyl)benzaldehyde, and its X-ray crystal structure.[13]

results in clean fission to the corresponding aldehyde and azolium salt.

The smooth formation of 2,2-diamino enols proves the accessibility of the Breslow intermediate from aldehydes and N-heterocyclic carbenes. By using Ph-C$^2$HO and $^1$H/$^2$H NMR spectroscopy we could show that the source of the hydroxylic proton/deuteron in the 2,2-diamino enol product is indeed the aldehydic H/$^2$H atom (see the Supporting Information for $^1$H and $^2$H NMR spectra).

NMR spectroscopic studies in [D$_8$]THF revealed that SIPr (**1e**) still formed the 2,2-diamino enol **6e** when treated with an excess (10 equiv) of 2,4-bis(trifluoromethyl)benzaldehyde. The use of $^{13}$C-labeled aldehyde ($^{13}$CHO) confirmed that no homobenzoin formation took place. However, crystallization of the benzoin-azolium salt **11** (Figure 4) occured when *n*-pentane was used as the solvent (1 equiv of aldehyde). In other words, the 2,2-diamino enol is the energetically most favorable state of the equilibrating catalytic system in homogeneous solution. Shifting the equilibria by crystallization, however, allows benzoin formation to proceed (Figure 4).

With this in mind, we examined the reaction of the benzaldehyde-derived and presumably more nucleophilic 2,2-diamino enol **5e**. Traces of homobenzoin were at best formed in the presence of excess benzaldehyde (10 equiv). However, when diamino enol **5e** was exposed to the more electrophilic 2,4-bis(trifluoromethyl)benzaldehyde, NMR spectroscopic analysis first of all revealed a comparatively rapid equilibration between the benzaldehyde-derived diamino enol **5e** and the 2,2-diamino enol **6e** derived from 2,4-bis(trifluoromethyl)benzaldehyde (Figure 5), thus proving the reversibility of the 2,2-diamino enol formation. Simultaneously, the expected cross-benzoin product **12** was produced slowly from the 2,2-diamino enol **5e**. The identity of the cross-benzoin product **12** was proven by independent synthesis (see the Supporting Information). Neither its isomer **13**, nor significant amounts of the two possible homobenzoin products were formed.

Clearly, the reaction manifold shown in Figure 5 can also be accessed from compound **6e**: The formation of **12** was also observed when **6e** was generated from carbene **1e** and $^{13}$CHO-labeled 2,4-bis(trifluoromethyl)benzaldehyde [that is, $^{13}$C label at C6 (C-OH) in **6e**] and exposed to benzaldehyde (1:1).

We furthermore succeeded in preparing 2,2-diamino enol ethers of type **15**. As shown in Scheme 4, we reasoned that these methyl enol ethers should be accessible by alkylation of N-heterocyclic carbenes such as IMes (**1b**), IPr (**1c**) or SIMes (**1d**) with MOM chloride (MOM: methoxymethyl), followed by deprotonation. The alkylation of the carbene (**1b** and **1c**) azolium salts with *t*BuOK and MOM-Cl proceeded smoothly in THF at room temperature, thereby affording the salts **14b** and **14c** in almost quantitative yields (see the Supporting Information for experimental details and the X-ray crystal structure of the azolium salt **14c**).[13]

Treatment of suspensions of salts **14b**,**c** in [D$_8$]THF with *t*BuOK (1.1 equiv) resulted in deprotonation, as evident by rapid dissolution. NMR spectroscopic examination of the

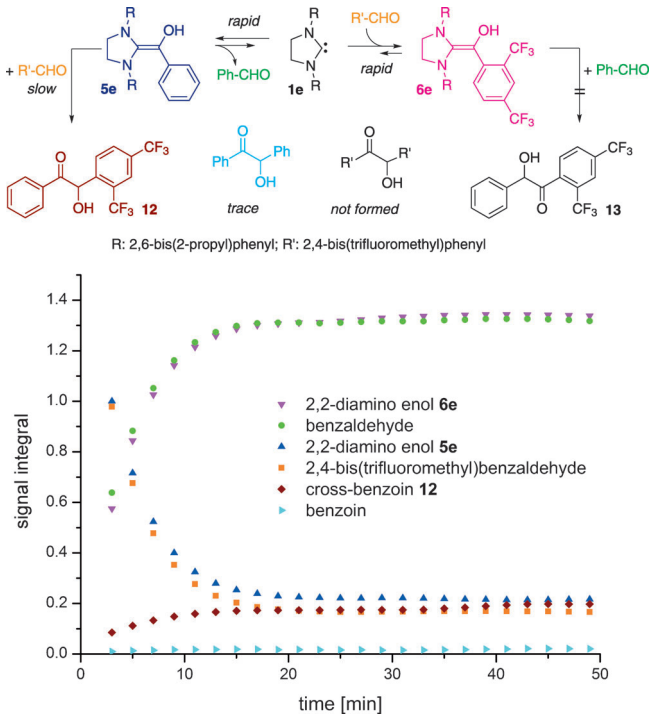
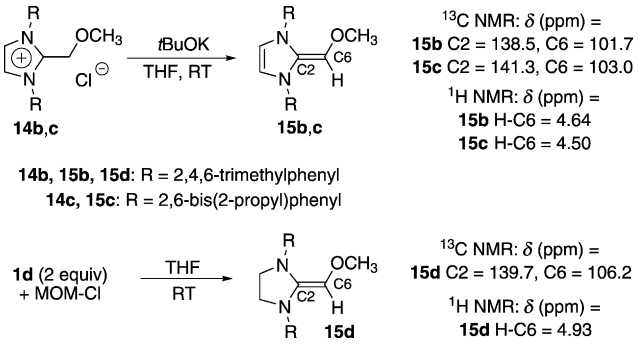



***Figure 5.*** Top: Reaction manifold involving the 2,2-diamino enols **5e** and **6e**, benzaldehyde, and 2,4-bis(trifluoromethyl)benzaldehyde. Bottom: Time course ($^1$H NMR spectroscopy in [D$_8$]THF) of the reaction of the 2,2-diamino enol **5e** with 2,4-bis(trifluoromethyl)benzaldehyde (1 equiv), which results in the rapid formation of the diamino enol **6e** and the slow production of the cross-benzoin **12**. The first measurement was at 3 min; the signal integral of 2,2-diamino enol **5e** is set to 1.0.




***Scheme 4.*** Preparation of the methylated Breslow intermediates **15b–d**. NMR data: [D$_8$]THF, 500/400 MHz.

resulting solutions revealed the clean formation of the enol ethers **15b** and **15c**, respectively, as the sole products. The most characteristic $^1$H and $^{13}$C NMR shifts are included in Scheme 4 (see Supporting Information for one- and two-dimensional NMR spectra of **15b,c**). The imidazolidine-derived enol ether **15d** was prepared simply by treating MOM-Cl with two equivalents of SIMes (**1d**). As in the case of the 2,2-diamino enols **5d** and **5e–10e** (Figure 3), the $^{13}$C resonances of the 2,2-diamino enol ether moiety are all found in the typical regions of $\delta = 138$–$146$ (C2) and 100–115 (C6) ppm. It is noteworthy that no 2,2-diamino enol could be generated cleanly from the unsaturated carbene IMes (**1b**) and aldehyde, whereas the *O*-methylated (i.e. protected) enol **15b** was readily obtained by the route outlined in Scheme 4.

Upon removal of the THF solvent, both enol ethers **15b** and **15d** could be crystallized from *n*-pentane, and their crystal structures are shown in Figure 6. The crystal structures

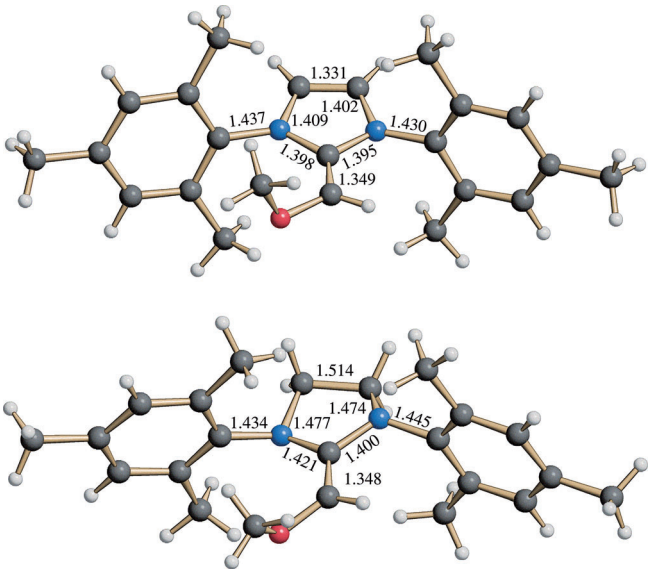



***Figure 6.*** X-ray crystal structures of the methylated Breslow intermediates **15b** (top) and **15d** (bottom).[13]

of the methyl enol ethers **15b** and **15d** clearly reflect the saturated (**15d**) versus unsaturated (**15b**) character of the heterocycles. The C=C bond of the 2,2-diamino enol ether moiety, however, is virtually the same length in both compounds. Consequently, a zwitterionic resonance form involving an aromatic azolium does not appear to contribute significantly to the structural features of the 2,2-diamino enol ether **15b**. This is in line with X-ray data obtained by Mayr and co-workers on the related 2-benzylidene IMes ($d_{C=C} =$ 1.361 Å) and 2-benzylidene SIMes ($d_{C=C} = 1.354$ Å).[11]

The 2,2-diamino enol ethers **15b,c** are readily alkylated at C6 by methyl iodide (see the Supporting Information for NMR spectra). No reaction was observed when **15c** was exposed, at room temperature, to aldehydes such as benzaldehyde or 2,4-bis(trifluoromethyl)benzaldehyde. The methylated Breslow intermediates **15b–d** were almost indefinitely stable in solution under rigorous exclusion of oxygen. The admission of air, however, results in rapid oxidation to afford the corresponding heterocyclic ureas (see the Supporting Information for the X-ray crystal structure of the IMes- and the IPr-urea).[13]

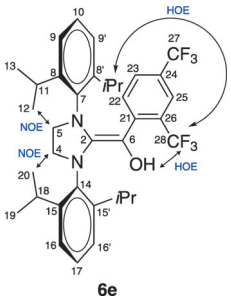
In summary, we have reported the generation and NMR spectroscopic characterization of 2,2-diamino enols (Breslow intermediates) from N-heterocyclic carbenes and aldehydes. We furthermore showed that these 2,2-diamino enols can react as acyl anion equivalents with additional aldehydes to provide benzoins. In addition, we have generated *O*-methy-

lated 2,2-diamino enols and characterized them, inter alia, by X-ray crystallography.

## Experimental Section

**6e**: In a glovebox, an NMR tube was charged with SIPr **1e** (20 mg, 51 μmol, 1.0 equiv) in [$D_8$]THF and sealed with a septum. 2,4-Bis(trifluoromethyl)benzaldehyde (8.4 μL, 51 μmol, 1.0 equiv) was added by means of a syringe and the reaction was followed by NMR spectroscopy. The $^1$H NMR spectrum recorded 3 min after addition of the aldehyde revealed full conversion of the carbene **1e** into the 2,2-diamino enol **6e**. $^1$H NMR (600 MHz, [$D_8$]THF): $\delta = 7.44$ (br s, 1H; H25), 7.18 (t, $^3J_{HH} = 7.3$ Hz, 1H; H17), 7.14 (d, $^3J_{HH} = 7.3$ Hz, 2H; H16, H16′), 6.98 (dd, $^3J_{HH} = 8.2$ Hz, $^4J_{HH} = 1.2$ Hz, 1H; H23), 6.95 (t, $^3J_{HH} = 7.0$ Hz, 1H; H10), 6.92 (d, $^3J_{HH} = 8.2$ Hz, 1H; H22), 6.92 (d, $^3J_{HH} = 7.0$ Hz, 2H; H9, H9′), 4.40 (s, 1H; OH), 3.93 (t, $^3J_{HH} = 7.6$ Hz, 2H; H5), 3.77 (t, $^3J_{HH} = 7.6$ Hz, 2H; H4), 3.64 (sept, $^3J_{HH} = 6.8$ Hz, 2H; H18, H18′), 3.48 (sept, $^3J_{HH} = 6.8$ Hz, 2H; H11, H11′), 1.32 (d, $^3J_{HH} = 6.8$ Hz, 6H; H19, H19′), 1.30 (d, $^3J_{HH} = 6.8$ Hz, 6H; H20, H20′), 1.26 (d, $^3J_{HH} = 6.8$ Hz, 6H; H13, H13′), 1.18 ppm (d, $^3J_{HH} = 6.8$ Hz, 6H; H12, H12′); $^{13}$C NMR (150 MHz, [$D_8$]THF): $\delta =$ 148.3 (2C; C15, C15′), 147.4 (2C; C8, C8′), 145.8 (1C; C2), 142.5 (1C; C21), 141.9 (1C; C14), 140.7 (1C; C7), 131.6 (1C; C22), 127.9 (1C; C10), 127.7 (1C; C17), 126.4 (1C; C26), 126.3 (1C; C23), 125.0 (1C; C27), 124.9 (1C; C28), 124.5 (2C; C9, C9′), 124.4 (1C; C24), 124.3 (2C; C16, C16′), 124.1 (1C; C25), 109.5 (1C; C6), 54.1 (1C; C5), 52.4 (1C; C4), 29.5 (2C; C18, C18′), 28.9 (2C; C11, C11′), 26.9 (2C; C13, C13′), 25.2 (2C; C19, C19′), 24.0 (2C; C20, C20′), 22.9 ppm (2C; C12, C12′); $^{19}$F NMR (376 MHz, [$D_8$]THF): $\delta = -63.25$ (s, 3F; C27-$F_3$), −60.15 ppm (s, 3F; C28-$F_3$).




Received: July 23, 2012
Revised: August 31, 2012
Published online: October 18, 2012

**Keywords:** Breslow intermediates · carbenes · NMR spectroscopy · reaction mechanisms · umpolung

[1] R. Breslow, *J. Am. Chem. Soc.* **1957**, *79*, 1762 – 1763.
[2] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726.
[3] Review: R. Kluger, K. Tittmann, *Chem. Rev.* **2008**, *108*, 1797 – 1833.
[4] Recent reviews: a) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320 – 332; *Angew. Chem. Int. Ed.* **2012**, *51*, 314 – 325; b) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; c) T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094 – 7107; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940 – 6952; d) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, 2295 – 2309.
[5] For the characterization of acyl azolium intermediates in conjugate umpolung reactions, see J. Mahatthananchai, P. Zheng, J. W. Bode, *Angew. Chem.* **2011**, *123*, 1711 – 1715; *Angew. Chem. Int. Ed.* **2011**, *50*, 1673 – 1677.
[6] D. A. DiRocco, K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 6143 – 6145.
[7] D. A. DiRocco, T. Rovis, *Angew. Chem.* **2012**, *124*, 6006 – 6008; *Angew. Chem. Int. Ed.* **2012**, *51*, 5904 – 5906.
[8] D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem.* **1995**, *107*, 1119 – 1122; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021 – 1023.
[9] J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61 – 83.
[10] a) A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles, *Angew. Chem.* **2010**, *122*, 7275 – 7279; *Angew. Chem. Int. Ed.* **2010**, *49*, 7120 – 7124; b) for a subsequent computational study, see O. Hollóczki, Z. Kelemen, L. Nyulászi, *J. Org. Chem.* **2012**, *77*, 6014 – 6022.
[11] a) B. Maji, M. Horn, H. Mayr, *Angew. Chem.* **2012**, *124*, 6335 – 6339; *Angew. Chem. Int. Ed.* **2012**, *51*, 6231 – 6235; b) after acceptance of this paper, a related publication appeared, describing the generation and reactivity of other methyl diaminoenol ethers: B. Maji, H. Mayr, *Angew. Chem.* **2012**, *124*, 10554 – 10558; *Angew. Chem. Int. Ed.* **2012**, *51*, 10408 – 10421.
[12] a) C. E. I. Knappke, J.-M. Neudörfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2010**, *8*, 1695 – 1705; b) C. E. I. Knappke, A. J. Arduengo III, H. Jiao, J.-M. Neudörfl, A. Jacobi von Wangelin, *Synthesis* **2011**, 3784 – 3795.
[13] CCDC 892932 ()**11**, 892933 (**14c**), 892934 (**15b**), 892935 (**15d**), 892936 (IMes-urea), 892937 (IPr-urea) 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.