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N-Heterocyclic Carbenes | Hot Paper

# Formation of Breslow Intermediates from N-Heterocyclic Carbenes and Aldehydes Involves Autocatalysis by the Breslow Intermediate, and a Hemiacetal

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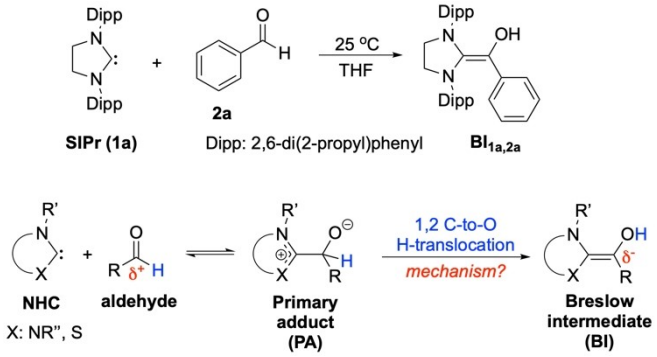
**Abstract:** Under aprotic conditions, the stoichiometric reaction of N-heterocyclic carbenes (NHCs) such as imidazolidin-2-ylidenes with aldehydes affords Breslow Intermediates (BIs), involving a formal 1,2-C-to-O proton shift. We herein report kinetic studies (NMR), complemented by DFT calculations, on the mechanism of this kinetically disfavored H-translocation. Variable time normalization analysis (VTNA) revealed that the kinetic orders of the reactants vary for different NHC-to-aldehyde ratios, indicating different and ratio-dependent mechanistic regimes. We propose that for high NHC-to-aldehyde ratios, the H-shift takes place in the primary, zwitterionic NHC-aldehyde adduct. With excess aldehyde, the zwitterion is in equilibrium with a hemiacetal, in which the H-shift occurs. In both regimes, the critical H-shift is auto-catalyzed by the BI. Kinetic isotope effects observed for R-CDO are in line with our proposal. Furthermore, we detected an H-bonded complex of the BI with excess NHC (NMR).




***Scheme 1.*** Formation of Breslow intermediates (BIs) from N-heterocyclic carbenes (NHCs) and aldehydes under aprotic conditions; top: reaction of SIPr (**1a**) with benzaldehyde (**2a**); bottom: the crucial 1,2-C-to-O proton shift in the conversion of the zwitterionic primary adduct (**PA**) to the Breslow intermediate (**BI**).

## Introduction

Umpolung catalysis by *N*-heterocyclic carbenes (NHCs) hinges on the formation of the so-called Breslow intermediates[1,2] [chemically: (di)amino enols; **BI**, Scheme 1, top] in which the genuine polarity of e.g. an aldehyde substrate is inverted from electrophilic to nucleophilic.[3,4] Postulated in 1958,[1,2] the first successful generation of diamino enols from aldehydes and carbenes, and their characterization by in situ NMR was reported by us in 2012,[5] followed by the first X-ray crystal structures of Breslow intermediates in 2013.[6] Key to success in these early experiments was the use of saturated imidazolidin-2-ylidenes as NHC component, such as SIPr (**1a**), which smoothly affords the Breslow intermediate $\mathbf{BI_{1a,2a}}$ when combined with benzaldehyde (**2a**), as shown in Scheme 1, top.[7,8] Later studies from our laboratory extended the range of BIs produced in this way, and characterized by NMR and X-ray crystallography, to unsaturated, aromatic NHCs, including thiazolin-2-ylidenes, the catalytic principle of Nature's Umpolung catalyst thiamin (vitamin B1).[9–11]

As the initial step of BI formation, it is generally assumed that nucleophilic attack of the NHC on the aldehyde results, in equilibrium, in the formation of a zwitterionic primary adduct (**PA**; Scheme 1, bottom).[4,12]] For the completion of the BI formation, a formal 1,2-C-to-O H-shift must follow. Due to their unfavourable transition state geometries, concerted H-shifts of this type are plagued by activation barriers in the order of 30–50 kcal mol$^{-1}$, and therefore have no kinetic relevance under typical experimental condition, i.e. room temperature, both in solution and in the gas phase.[13–15] Under protic conditions, i.e. in Umpolung catalysis effected by

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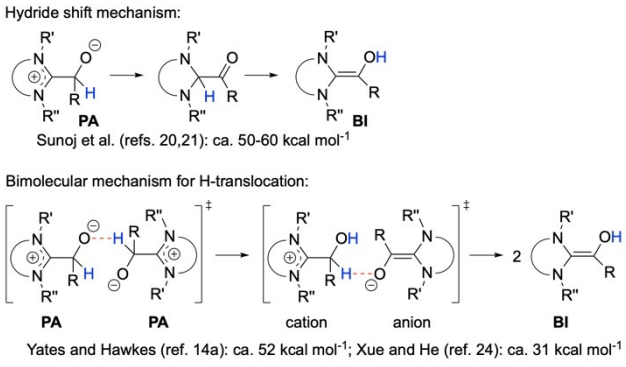
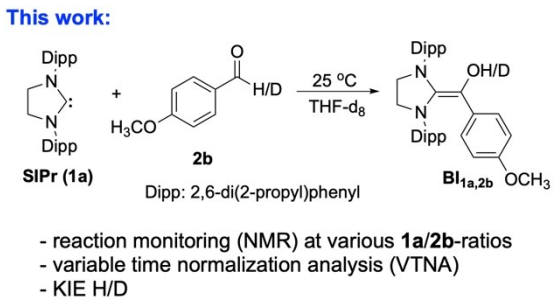
combinations of azolium salts with bases, a concerted 1,2-H-shift may be circumvented by a stepwise O-protonation/C-deprotonation sequence.[16] Similarly, alcohols and phenols are known to facilitate 1,2-C-to-O proton shifts, by making 5-membered (as opposed to 3-membered) transition states accessible.[17,18] Relayed proton transfer by specific substituents on the NHC or aldehyde component has been proposed, too.[19]

Alternatively, a 1,2-hydride shift, affording the keto tautomer of the BI may be envisaged, followed by tautomerization to the enol (Scheme 2, top).[20,21] DFT calculations indicate that such hydride shifts may be possible, while the activation barrier for the enolization of the resulting ketone is again extremely high (50–60 kcal mol$^{-1}$).[20–22]

An alternative pathway for the PA-to-BI conversion has been proposed that involves the interaction of *two* PA entities with one another, and a stepwise transfer of the two protons (Scheme 2, bottom).[14a,24] Clearly, the bimolecular mechanism shown in Scheme 2, bottom, should be distinguishable from intramolecular ones by the kinetic orders of the reactants (NHC, aldehyde). However, to the best of our knowledge, to date no kinetic characterization of the NHC-plus-aldehyde reaction, leading to Breslow intermediates under aprotic conditions, has been reported.




***Scheme 2.*** Top: schematic representation of the hydride shift mechanism, investigated computationally by Sunoj et al.; bottom: bimolecular mechanism for the 1,2-C-to-O proton translocation in **PA**, as proposed by Xue and He[24] and Yates and Hawkes;[14a] including the calculated activation barriers.




***Scheme 3.*** Our experimental/kinetic approaches to the mechanism of Breslow intermediate formation from N-heterocyclic carbenes and aldehydes under aprotic conditions.

## *Results and Discussion*

To experimentally shed light on the mechanism of BI formation from NHCs and aldehydes under aprotic conditions, we set out to thoroughly investigate the kinetics of this intriguing transformation (Scheme 3). For data acquisition, we settled on NMR spectroscopy under strictly anhydrous and anoxic conditions (glove box, $<1$ ppm $O_2$, $<1$ ppm $H_2O$). SIPr (**1a**) was chosen as prototypical NHC component, while anisaldehyde (**2b**) proved ideal for monitoring by $^1$H NMR (Scheme 3; see Supporting Information for details).[25]

An important hurdle that had to be overcome was the preparation of highly pure SIPr (**1a**) on multigram scale, such that large sets of kinetic experiments could be run reproducibly with SIPr (**1a**) from one and the same batch. We found that thermal liberation of SIPr (**1a**) from its $CO_2$-adduct, followed by sublimation (glove box) is best for this purpose (see Supporting Information, S2.1).[26]

When SIPr (**1a**) was mixed with anisaldehyde (**2b**) in a 1:1 ratio in THF-$d_8$, full conversion to $\mathbf{BI_{1a,2b}}$ was reached after ca. 6 h at 298 K (see Supporting Information, S3.2 for concentration/time profiles).[25] Note that at no point in time, accumulation of a reaction intermediate was detectable by NMR monitoring. For kinetic studies, we employed variable time normalization analysis (VTNA), which allows determination of the reaction orders using concentration-time profiles under moderate excess conditions by variable-excess experiments.[27–29] Comparison of same-excess experiments also allows for the interrogation of the reaction system for product inhibition or acceleration. For both sets of experiments (i.e. excess of NHC, and excess of aldehyde), the concentrations of [**1a**] and of [**2b**] are listed in Tables 1 and 2. Additionally, deuterated anisaldehyde (R-CDO, **2b**-$d_1$) was employed under identical conditions, in order to probe the reaction of **1a** with **2b** for kinetic isotope effects.

Comparison of the normalized reaction profiles obtained by NMR with experiments at different excess of SIPr (**1a**) revealed that the reaction orders in **1a** and **2b** were approximately 0.9 and 1.2. Best linear correlations were obtained with those exponents (Table 1, Figure 1, see Supporting Information, S3.4 for details of the kinetic data treatment). Most importantly, product acceleration was found by time-shifting in same-excess experiments. In other words, we could show for the first time that the Breslow intermediate $\mathbf{BI_{1a,2b}}$ acts as an *autocatalyst* in its formation from **1a** and **2b**. This conclusion is further corroborated by

***Table 1:*** Concentrations used in the VTNA of the reaction of SIPr (**1a**) with anisaldehyde **2b**/**2b**-$d_1$, moderate (up to 1.5-fold) excess of SIPr (**1a**).

| Run no.[a] | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **1a**[b] | 0.16 | 0.18 | 0.16 | 0.18 | 0.16[c] | 0.18[c] |
| **2b**/**2b**-$d_1$[b] | 0.14 | 0.12 | 0.12 | 0.14 | 0.12[c] | 0.14[c] |

[a] Experiment numbering as in Figure 1. [b] Concentration [mol L$^{-1}$] in the NMR sample, total volume 600 µL in THF-$d_8$. [c] For this measurement, anisaldehyde-$d_1$ (**2b**-$d_1$) was used.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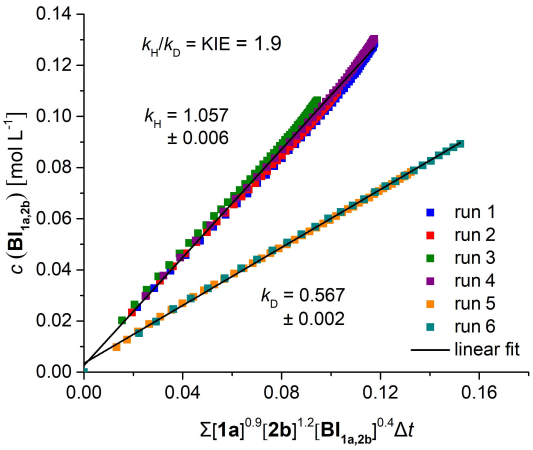


***Figure 1.*** Variable time normalization analysis (VTNA), excess of SIPr (**1a**): reaction order of 0.9 in SIPr (**1a**), 1.2 in anisaldehyde (**2b**) or anisaldehyde-$d_1$ (**2b**-$d_1$), and 0.4 in Breslow intermediate $\mathbf{BI_{1a,2b}}$ gave best overlap ($R^2 = 0.99$). Concentration-time profiles of the reaction of **1a** with **2b** or **2b**-$d_1$ were obtained by $^1$H NMR, (400 MHz, THF-$d_8$, 298 K).

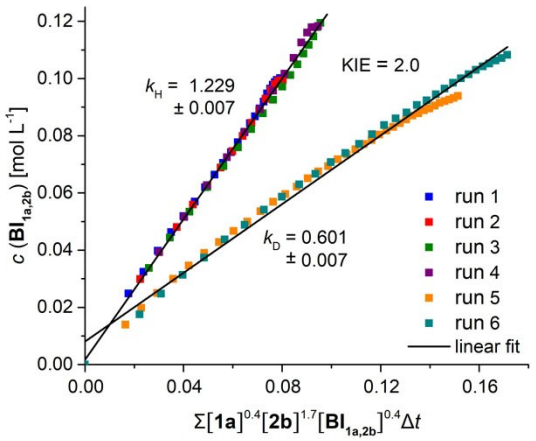


***Figure 2.*** Variable time normalization analysis (VTNA), excess of anisaldehyde (**2b**): reaction order of 0.4 in SIPr (**1a**), 1.7 in anisaldehyde (**2b**) or anisaldehyde-$d_1$ (**2b**-$d_1$), and 0.4 in Breslow intermediate $\mathbf{BI_{1a,2b}}$ gave best overlap ($R^2 = 0.99$). Concentration-time profiles of the reaction of **1a** with **2b** or **2b**-$d_1$ were obtained by $^1$H NMR, (400 MHz, THF-$d_8$, 298 K).

experiments in which $\mathbf{BI_{1a,2b}}$ was deliberately added at $t_0$, and which clearly show its accelerating effect (see Supporting Information, S3.4.3). The mechanistic option of BI autocatalysis has not been considered before—a mechanistic proposal accounting for this new finding will be discussed in Scheme 4. Optimization of line straightness in the normalized reaction profiles yielded a kinetic order of 0.4 in Breslow intermediate (Figure 1). Additionally, the different slopes obtained from using anisaldehyde (**2b**) and its monodeuterated isotopologue (**2b**-$d_1$) revealed a KIE of ca. 1.9 for the reaction of SIPr (**1a**) with the aldehydes **2b**/**2b**-$d_1$.

Under conditions of moderate excess of aldehyde (**2b**, **2b**-$d_1$; Table 2, Figure 2), comparison of the normalized reaction profiles obtained by NMR at different excess of aldehyde (**2b**, **2b**-$d_1$) revealed that the reaction orders in **1a** and **2b** were approximately 0.4 and 1.7, respectively (see Supporting Information, S3.4 for details of the kinetic data treatment). Again, autocatalysis by the Breslow intermediate $\mathbf{BI_{1a,2b}}$ was clearly detectable, again with a kinetic order of ca. 0.4.

From both VTNA studies presented above (Figures 1,2) a KIE of ca. 1.9–2.0 can be calculated when anisaldehyde (**2b**) and its monodeuterated isotopologue (**2b**-$d_1$) were used (ratio of slopes $k_H/k_D$). Alternatively, for KIE determination, an additional normalization factor $f_{KIE}$ can be introduced (Figure 3). When properly chosen, *all* experimental kinetic data points—i.e. those from using both deuterated (**2b**-$d_1$) *and* non-deuterated (**2b**) aldehyde—collapse to one straight line. Application of this method gave a KIE of 1.8 for both kinetic regimes (Figure 3).

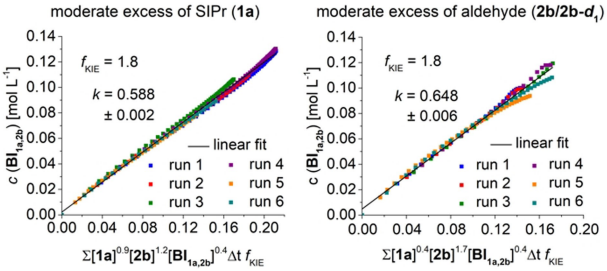


***Figure 3.*** Variable time normalization analysis (VTNA), with additional normalization factor $f_{KIE}$; left: moderate excess of SIPr (**1a**), compare with Figure 1; right: moderate excess of anisaldehyde (**2b**), compare with Figure 2. In both cases, $f_{KIE} = 1.8$ gave best overlap and linearity ($R^2 = 0.99$).

***Table 2:*** Concentrations used in VTNA of the reaction of SIPr (**1a**) with anisaldehyde **2b**/**2b**-$d_1$, moderate (up to 1.8-fold) excess of aldehyde **2b**/**2b**-$d_1$.

| Run no.[a] | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **1a**[b] | 0.10 | 0.10 | 0.12 | 0.12 | 0.10[c] | 0.12[c] |
| **2b**/**2b**-$d_1$[b] | 0.16 | 0.18 | 0.18 | 0.20 | 0.18[c] | 0.20[c] |

[a] Experiment numbering as in Figure 2. [b] Concentration [mol $L^{-1}$] in the NMR sample, total volume 600 µL in THF-$d_8$. [c] For this measurement, anisaldehyde-$d_1$ (**2b**-$d_1$) was used.

Before presenting our mechanistic proposal that accommodates all data (Scheme 4), we will—for the sake of clarity—reiterate the relevant experimental findings:

(i) Under conditions of NHC excess, the kinetic orders of both NHC and aldehyde are close to unity.[30]

(ii) Under conditions of aldehyde excess, the kinetic order of aldehyde increases to almost 2 while the order of NHC significantly decreases to 0.4.

(iii) The results (i) and (ii) above indicate a change in reaction mechanism when moving from an excess of NHC to an excess of aldehyde.

(iv) In both mechanistic regimes, the product, i.e. the Breslow intermediate acts as an autocatalyst, with a kinetic order of ca. 0.4.


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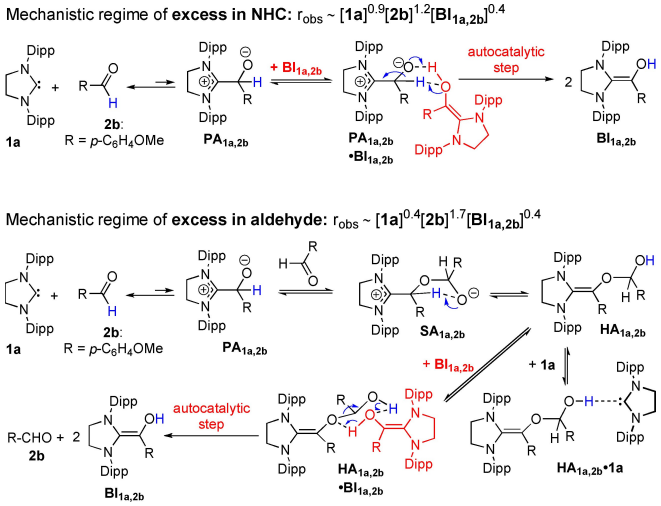
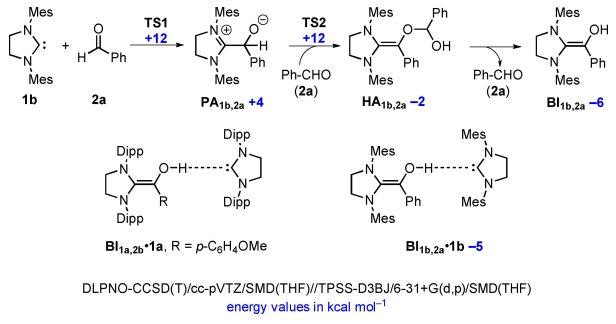
(v) For both mechanistic regimes, a KIE of ca. 1.8–2.0 was found.

For the regime of *NHC excess*, we propose the mechanism summarized in Scheme 4, top. In a first and reversible step, nucleophilic attack of SIPr (**1a**) on the aldehyde **2b** results in the zwitterionic primary adduct ($\mathbf{PA_{1a,2b}}$) in low concentration. According to our DFT calculations on the simpler SIMes (**1b**)—benzaldehyde (**2a**) system shown in Scheme 5, the formation of $\mathbf{PA_{1b,2a}}$ from **1b** and **2a** is endergonic by ca. 4 kcal mol$^{-1}$. In a second step, the crucial 1,2-H-shift in the **PA** is assisted by the Breslow intermediate in autocatalytic fashion, and proceeds via $\mathbf{PA_{1a,2b}}$·$\mathbf{BI_{1a,2b}}$ (Scheme 4, top) through a 5-membered transition state, thus affording two equivalents of the product BI ($\mathbf{BI_{1a,2b}}$). While the DFT characterization of the structurally complex adduct $\mathbf{PA_{1a,2b}}$·$\mathbf{BI_{1a,2b}}$ proved impractical, related scenarios of proton transfer by methanol[17] or even a water molecule have been proposed.[31] It was found that these simple forms of R–OH




***Scheme 4.*** Mechanistic proposal for the reaction of SIPr (**1a**) with anisaldehyde (**2b**) to the Breslow intermediate $\mathbf{BI_{1a,2b}}$ under aprotic conditions. Top: in the presence of excess SIPr (**1a**); bottom: in the presence of excess aldehyde (**2b**).




***Scheme 5.*** Top: calculated energies of the primary zwitterionic intermediate (**PA**), of the hemiacetal (**HA**) and the Breslow intermediate (**BI**) formed from SIMes (**1b**) and benzaldehyde (**2a**). Bottom: calculated energy of the H-bonded complex $\mathbf{BI_{1b,2a}}$·**1b** formed from the Breslow intermediate $\mathbf{BI_{1b,2a}}$ and excess SIMes (**1b**).

can catalyze the crucial proton transfer in primary intermediates derived from thiazolin-2-ylidenes and aldehydes, the latest report by Nandi et al. even unveiling quantum tunneling effects.[31] In the light of these studies, it appears quite reasonable to assume that under *anhydrous* conditions, it is the "OH" of the Breslow intermediate $\mathbf{BI_{1a,2b}}$ that catalyzes proton transfer.

The above mechanism is consistent with the KIE observed for this regime (ca. 1.8–2.0, see Figures 1–3), as the C–H/C–D bond of the aldehyde is broken in the RDS. Additionally, a proton inventory study, carried out at large (7-fold) excess of SIPr (**1a**), identified one (kinetically relevant) H/D translocation in the RDS (see the SI, S.3.3.3). Finally, please note that for autocatalysis to result in sigmoidal conversion/time profiles, the catalytically active reaction product must operate on a large reservoir of substrate, typically the starting material. In the current case, an intermediate of minute stationary concentration is autocatalytically converted to product. As the result, the concentration/time profile deviates from typical 1$^{st}$-order shape only towards the end of the reaction (see Supporting Information, S3.4.3 for examples).[32,33]

Under *excess aldehyde* conditions, the zwitterionic primary adduct ($\mathbf{PA_{1a,2b}}$) can react with a second molecule of aldehyde, reversibly affording the secondary zwitterionic adduct ($\mathbf{SA_{1a,2b}}$, bottom Scheme 4). Intramolecular proton shift via a 5-membered TS converts the latter to the hemiacetal $\mathbf{HA_{1a,2b}}$. Note that in the hemiacetal, the enol structure of the BI product is already present (i.e. the difficult C-to-O H-shift completed). Judging from the closely related transformation shown in Scheme 5, the overall conversion of SIPr (**1a**) with two equivalents of aldehyde **2b** to the hemiacetal $\mathbf{HA_{1a,2b}}$ can be assumed to be almost thermoneutral, with no prohibitive activation barriers along the reaction coordinate. However, now the decomposition of the hemiacetal to the exergonic product $\mathbf{BI_{1a,2b}}$ (plus aldehyde **2b**) has become the bottleneck, as it requires a demanding intramolecular H-shift via a 4-membered TS. We propose that the decomposition of the hemiacetal $\mathbf{HA_{1a,2b}}$ is facilitated by the Breslow intermediate $\mathbf{BI_{1a,2b}}$ in an autocatalytic fashion, via a six-membered TS in $\mathbf{HA_{1a,2b}}$·$\mathbf{BI_{1a,2b}}$ (Scheme 4, bottom). In fact, a most recent DFT-study by Yu et al. also proposes the formation of a hemiacetal intermediate [from SIPr (**1a**) and benzaldehyde (**2a**)], with comparable energetics.[34] In this study, it is proposed that the crucial proton shift is effected, in a stepwise manner, by the primary intermediate ($\mathbf{PA_{1a,2a}}$). While the latter proposal is not supported by our experimental kinetic results, the data by Yu et al. show that a conversion of the hemiacetal to the BI, by catalytic proton transfer, is feasible.

With the decomposition of the hemiacetal $\mathbf{HA_{1a,2b}}$ being catalyzed by the BI product ($\mathbf{BI_{1a,2b}}$), the generation of the former becomes rate-limiting. The kinetic bottleneck—now the H-shift in $\mathbf{SA_{1a,2b}}$ (Scheme 4, bottom)—is reflected in the KIE observed under excess aldehyde condition (see Figures 2, 3). Our proposal of hemiacetal involvement is further supported by our earlier studies on 1,2,4-triazolin-5-ylidene interaction with aldehydes.[23] In that work, spiro-1,3-dioxolane formation—i.e. the cyclization of zwitterions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of the $\mathbf{SA_{1a,2b}}$-type (Scheme 4, bottom) had been observed. For SIMes (**1b**), as a simplified analogue of SIPr (**1a**), our DFT calculations showed thermoneutrality of spiro-dioxolan formation with benzaldehyde (see computational Supporting Information for details). Finally, according to earlier studies by McQuade et al. on the mechanism of the Baylis–Hillman reaction, hemiacetal formation is involved in the latter, too.[15c,d]

The broken kinetic orders found for the two substrates **1a**, **2b** and the BI product ($\mathbf{BI_{1a,2b}}$) require further explanation. At first glance, the mechanism proposed in Scheme 4, top, for an excess of NHC suggests a kinetic order of unity for all three components. The mechanism for an excess of aldehyde (Scheme 4, bottom) suggests a kinetic order of unity for both the NHC **1a** and the BI $\mathbf{BI_{1a,2b}}$, but second order for the aldehyde **2b**. The experimental finding of a reaction order in aldehyde of 1.2 and 1.7, respectively, in the two regimes indicates that both mechanisms can operate simultaneously. In the regime of excess NHC, the reaction involves predominantly one molecule of aldehyde, hence the reaction order is close to unity (1.2). In the regime of excess aldehyde, predominantly two molecules of aldehyde are involved, giving a reaction order close to 2 (1.7).

The observation of a reaction order of 0.4 for the BI autocatalyst indicates that some of it is tied up in an inactive form that has to dissociate first to liberate the free BI, similar to the case observed in some hydroborations involving borane dimers.[35] In fact, our NMR monitoring of the stoichiometric reaction of SIPr (**1a**) with anisaldehyde (**2b**) revealed that the Breslow intermediate $\mathbf{BI_{1a,2b}}$ forms an H-bonded aggregate $\mathbf{BI_{1a,2b}}$·**1a** (see Scheme 5, bottom left) with SIPr (**1a**). The most remarkable NMR signature of the aggregate $\mathbf{BI_{1a,2b}}$·**1a** is a very pronounced broadening of the $^{13}$C resonance of the NHC's carbene-C, i.e. C-2, while the chemical shift of the latter ($\delta = 245$ ppm, THF-$d_8$) remains virtually unaffected (see Supporting Information, S3.5, for NMR spectra).[36] As shown in Scheme 5, bottom right, our DFT calculations on the simplified H-bonded aggregate formed from the Breslow intermediate $\mathbf{BI_{1b,2a}}$ and SIMes (**1b**) demonstrate the mildly exothermic nature ($-5$ kcal mol$^{-1}$) of this complex formation. The reaction order in BI in both regimes is thus approximately one half. In the excess of aldehyde regime, the limiting substrate, the NHC **1a**, is tied up in the same manner by H-bonding to the evolving BI product, reducing its reaction order to approximately one half as well. An alternative H-bonding partner may be seen in the hemiacetal $\mathbf{HA_{1a,2b}}$ (Scheme 4, bottom right). Only in the regime of NHC excess, this effect is less pronounced, leaving most NHC in its free form and hence a reaction order of close to unity (0.9).

## Conclusion

Our study has answered a long-standing question in N-heterocyclic carbene (NHC) chemistry: how are Breslow intermediates formed from NHCs and aldehydes under aprotic conditions? Our kinetic studies revealed that in the presence of excess NHC, the Breslow intermediate itself effects, in autocatalytic fashion, the critical step, i.e. the unfavorable 1,2-C-to-O proton shift in the zwitterionic primary adduct. In the presence of excess aldehyde, the primary adduct is first converted to a hemiacetal. The latter is then cleaved to product through a 1,3-proton shift, again auto-catalyzed by the Breslow intermediate. Note that in particular the second mechanistic regime is pertinent to NHC catalysis, i.e. to reaction conditions in which a large excess of aldehyde substrate is turned over by small amounts of NHC catalyst. Additionally, we identified for the first time H-bonded aggregates of a Breslow intermediate with the NHC that it originated from. It appears reasonable to assume that such species may as well occur in catalytic aldehyde transformations, effected by N-heterocyclic carbenes.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

**Keywords:** Autocatalysis · Breslow Intermediate · Carbenes · NMR · Reaction Mechanisms

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