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Kinetic and Structure-Activity Studies of the Triazolium Ion-Catalyzed Intramolecular Stetter Reaction

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Mechanistic studies of the triazolium ion-catalyzed intramolecular Stetter reaction using initial rates analysis in $NEt_3/NEt_3 \cdot HCl$ buffered methanol showed the reaction to be first-order in catalyst and zero-order in aldehyde over a broad range of aldehyde concentrations. The observed reaction rate is higher for catalysts bearing N-aryl substituents with electron-withdrawing groups. A concurrent, NHC-independent substrate isomerization was also observed and found to demonstrate a first-order dependence on aldehyde concentration. The reported data are consistent with deprotonation to form the Breslow intermediate being turnover-limiting in this process.

Introduction

First reported in 1973, the Stetter reaction is considered closely related mechanistically to the more commonly employed benzoin reaction.[1] For both of these processes, the reaction is widely accepted to proceed via umpolung activation of an aldehyde **3** using catalysts such as nucleophilic heterocyclic carbenes (NHCs). For example, triazolium salts such as **1** can be deprotonated in situ to give the corresponding reactive NHC **2**. Addition of the NHC to the aldehyde **3** leads initially to an isolable tetrahedral species **4** before the formation of an enaminol **5** that acts as an acyl anion equivalent that is commonly known as the Breslow intermediate (Figure 1A).[2] While this key intermediate reacts with another equivalent of aldehyde **3** in the benzoin reaction, in the Stetter reaction nucleophilic addition to a Michael acceptor **8** occurs, followed by protonation and catalyst release (Figure 1B). Building upon this mechanistic model, the Stetter reaction has found widespread synthetic use, including the development of effective enantio- and diastereoselective transformations.[3]

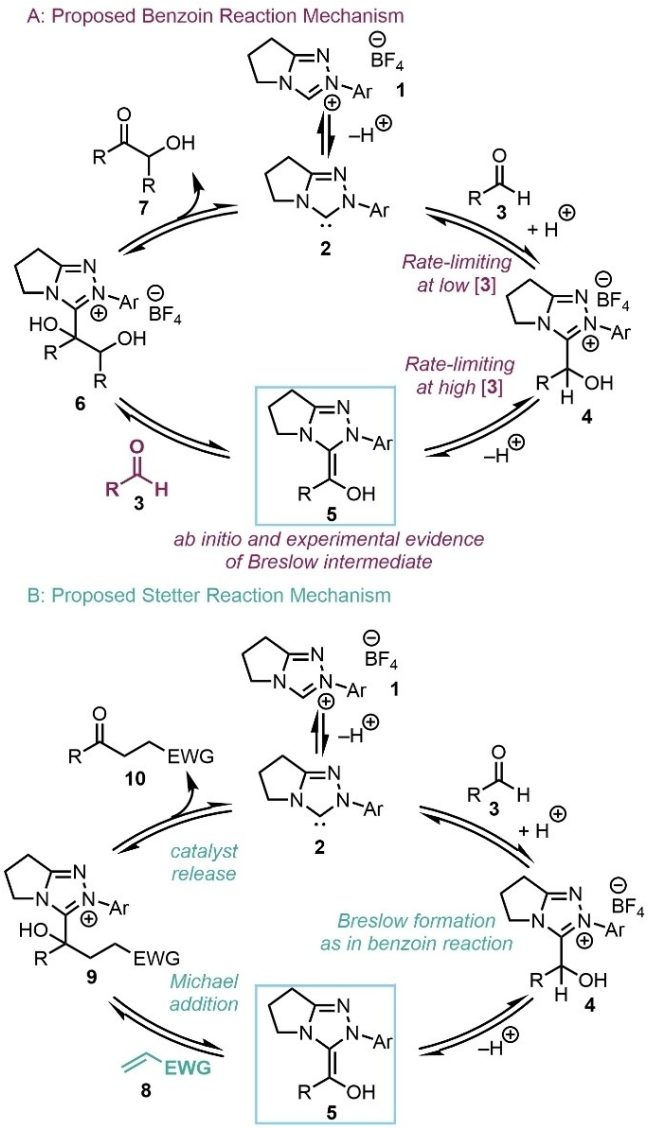

Figure 1. Proposed mechanistic pathway for A: the benzoin reaction and B: the Stetter reaction, via a common Breslow intermediate **5.**

Due to their mechanistic similarity, it is often considered that insight into the mechanism of the Stetter reaction can be intimated from studies of the benzoin reaction. The validity of this general mechanism for the benzoin reaction has been substantiated by computational predictions;[4] identification and characterization of intermediates;[5] the use of intermediates or their analogues in control reactions,[6] and further validated

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through dynamic covalent binding using boronic esters.[7] Despite this combined knowledge, a variety of detailed kinetic analyses of the benzoin reaction of benzaldehyde have given different and often ambiguous results. As an example, specific mechanistic investigations by Leeper into the thiazolium ion-catalyzed benzoin reaction of benzaldehyde in buffered MeOH (NEt_3:NEt_3·HCl 2:1) employed an initial rate method and demonstrated a close to first-order dependence on [benzaldehyde].[8] In contrast, an initial rates analysis of the triazolium ion-catalyzed benzoin reaction of benzaldehyde in a buffered MeOH solution (NEt_3:NEt_3·HCl 2:1) by our groups indicated that reaction order was dependent upon concentration.[9]

At low concentration (< ~0.5 M) in aldehyde, a first-order aldehyde dependence was observed, but at increased concentration (> ~0.5 M) a change to zero-order dependence was observed. At higher benzaldehyde concentrations, the rate is limited by deprotonation to form the Breslow intermediate, but at reduced benzaldehyde concentrations, catalyst addition to form the initial adduct and product-forming steps are considered rate-limiting. The observed variation of reaction mechanism depending on choice of catalyst, or even with change in substrate concentration, highlights the mechanistic complexity of these reactions.

To fully develop the NHC-catalyzed Stetter reaction as a synthetic process, specific studies regarding its reaction mechanism are needed. The Stetter transformation employing compound **11** as starting material is among the most commonly used benchmarks for reactivity and selectivity when reporting new NHC catalysts, particularly for (chiral) triazolium ion-catalyzed processes (Figure 1A).[10] Importantly, this substrate has also been used for mechanistic investigations of the Stetter reaction. For example, in 2011, reports from the Rovis group demonstrated that deprotonation to form the Breslow intermediate is turnover-limiting under two mechanistically different scenarios.[11,12] In the first,[11] in the presence of catechol as an additive and in MeOH as solvent, a primary kinetic isotope effect ($k_H/k_D = 2.7$) was observed (Figure 2A). Further studies using chiral NHC **14** in toluene showed that the reaction process was first-order in both NHC catalyst and aldehyde substrate, with $k_H/k_D = 2.6$.[12] Building upon these results and previous reports from our groups,[13,14] in this manuscript kinetic studies upon the intramolecular Stetter reaction using substrate **11** are reported. The buffered conditions (MeOH, NEt_3:NEt_3·HCl 2:1) initially reported by Leeper for investigation of the thiazolium-catalyzed benzoin reaction,[8] and since used in many analyses of NHC-catalyzed umpolung processes, were chosen for kinetic analysis to enable direct comparison with reported benzoin reaction (Figure 2B).

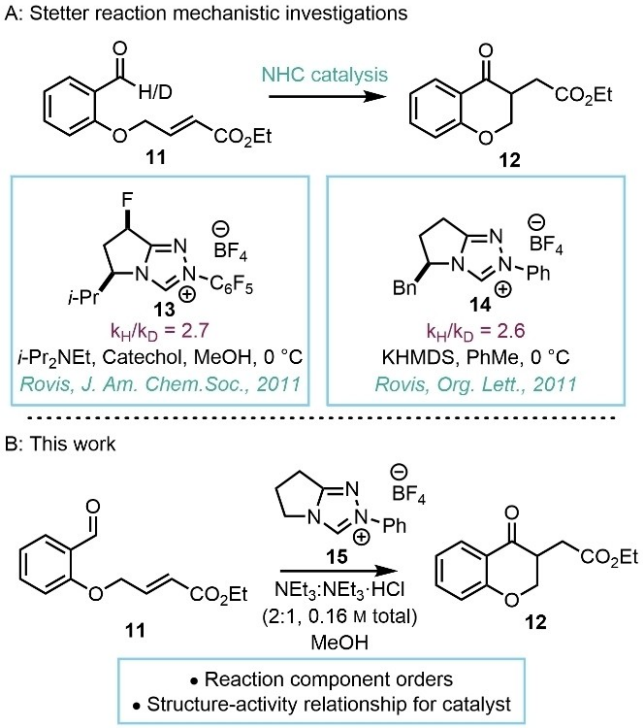

Figure 2. A: Previous mechanistic studies of the NHC-catalyzed Stetter reaction. B: This work: initial rates analysis in buffered MeOH solution (NEt_3:NEt_3·HCl 2:1)

Results and Discussion

Model studies and identification of a NHC-independent isomerization process

Initially, reaction orders were sought. As described by Leeper,[8] potential issues associated with changes in reaction order as substrate concentration changes, combined with catalyst degradation and failure of the assumption of irreversibility at all stages of the reaction, may hamper elucidation of reaction orders in NHC-catalyzed reactions. As a result, an initial rate method at low (< 10%) product formation was employed. To reliably assess the reaction progress at low concentrations of product, timepoint analysis was performed using high-performance liquid chromatography (HPLC).

In an initial experiment, aldehyde **11** and triazolium salt **15** were dissolved in methanol at 35 °C under argon and a buffer solution of NEt_3 and NEt_3·HCl (2:1 in methanol) was added, initiating the reaction (Figure 3A). Aliquots were removed from the reaction every hour and, after quenching, analyzed by HPLC (Figure 1B). Starting material **11** and a 50:50 mixture of both enantiomers of racemic Stetter product **12** were identified by HPLC analysis on a chiral stationary phase.[15] Interestingly, two by-products were also observed that were identified upon isolation as (*Z*)-**16** and (*E*)-**17**, the products of isomerization of **11**, in an 80:20 ratio. Similar isomerizations have been reported in the literature, both in NHC-catalysis,[16] and in the absence of NHCs.[17] Further control studies were performed to determine if

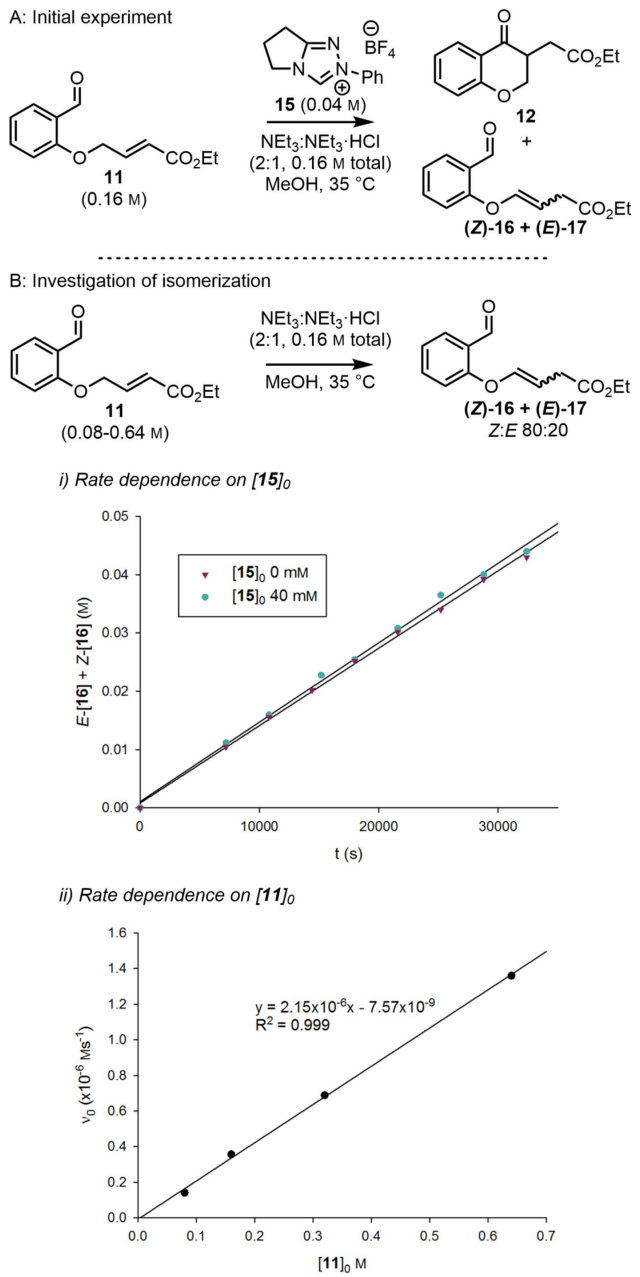

Figure 3. A: Observed isomerization side-reaction under the triazolium **15**-catalyzed Stetter reaction conditions. B: Kinetic analysis of isomerization in buffered methanol (NEt_3:NEt_3·HCl (2:1, 160 mM total)) at 35 °C under argon: i) **11** (0.64 M), **15** (40 mM (teal) or 0 mM (purple)); ii) **11** (0.08–0.64 M), **15** (40 mM).

this isomerization was NHC-catalyzed and therefore potentially interfering with the Stetter reaction. Simply stirring aldehyde **11** in buffered MeOH solution (NEt_3:NEt_3·HCl 2:1) for 72 hours led to the formation of (*Z*)-**16** and (*E*)-**17** in an identical 80:20 ratio, and isolation in 32% yield, suggesting this process occurs independently of the NHC. Performing the reaction both with and without triazolium **15**, and monitoring the rate of formation of the isomerization products, led to essentially identical reaction profiles (Figure 3B).[15] The initial rate for the isomerization process showed a first-order dependence on aldehyde concentration with a first-order rate constant, $k_{isom} = 2.14 \times 10^{-6}\ s^{-1}$ (Figure 3B). Exposing **16** to the reaction conditions (with NHC precursor **15** and buffer) resulted in no further reaction after 12 hours, suggesting that on this timescale this isomerization reaction is irreversible and that the product does not significantly interfere with the NHC-promoted Stetter transformation. Over the range of aldehyde concentrations tested (0.08 M to 0.64 M) the isomerization process is therefore an independent parallel reaction, allowing simultaneous monitoring of the NHC-catalyzed Stetter reaction.

Initial rate studies of the NHC-catalyzed Stetter reaction

The NHC-catalyzed Stetter reaction was then investigated, and reaction orders with respect to NHC **15** and aldehyde **11** were identified. Initial rate analyses of the reaction were performed at aldehyde **11** concentrations of 0.08 M, 0.16 M, 0.32 M and 0.64 M, and triazolium **15** concentrations of 0.01 M, 0.02 M and 0.04 M. Despite the wide range of aldehyde concentrations probed, the reaction rate was independent of aldehyde concentration (zero-order in aldehyde) across all those tested (Figure 4). A plot of initial rates against initial triazolium salt concentration (0.01 M, 0.02 M and 0.04 M) shows a clear first-order dependence on catalyst concentration[18] with an estimated first-order rate constant of $k_{obs} = 2.21 \times 10^{-5}\ s^{-1}$ (Figure 4).

The zero-order dependence on aldehyde concentration is distinct from the first-order dependence observed in toluene carried out by Rovis, indicating the kinetic importance of the different solvents and reaction conditions employed in these investigations. Applying the steady-state approximation to the concentration of the Breslow intermediate,[15] the absence of the aldehyde from the rate equation can be rationalized assuming that the initial equilibrium (Figure 5A) between aldehyde **11** and triazolium **1** significantly favors 3-(hydroxybenzyl)azolium salt **19**. In previous work from our groups using N-aryl triazolium salt precatalysts, we have shown that NHC addition to a range of substituted benzaldehydes to give isolable tetrahedral hydroxy adducts (*c.f.* **4**, Figure 1) is rapid and reversible, and favors adduct formation (*e.g.* for Ar = Ph, $K_{exp} = 27$ in CH_2Cl_2, Figure 5A).[14] Significantly, *ortho*-alkoxy substitution on the benzaldehyde (as present in **11**) resulted in a significant increase in the rate and equilibrium constants for adduct formation. As aldehyde concentration is significantly higher than triazolium precatalyst concentration in the present study ([**11**] > [**15**]), this equilibrium is expected to substantially favor the tetrahedral hydroxy adduct. In addition, the observed zero-order dependence on [**11**] in the context of the current catalytic conditions is consistent with adduct-formation from triazolium **1** not being turnover-limiting (Figure 5B). Experiments at lower initial aldehyde concentrations (to test whether aldehyde dependence could be observed) did not give reliable data due to difficulty in measuring small concentration changes accurately under the initial rates regime (< 10% product formation). It was proposed that k_{BI} (deprotonation to form the Breslow

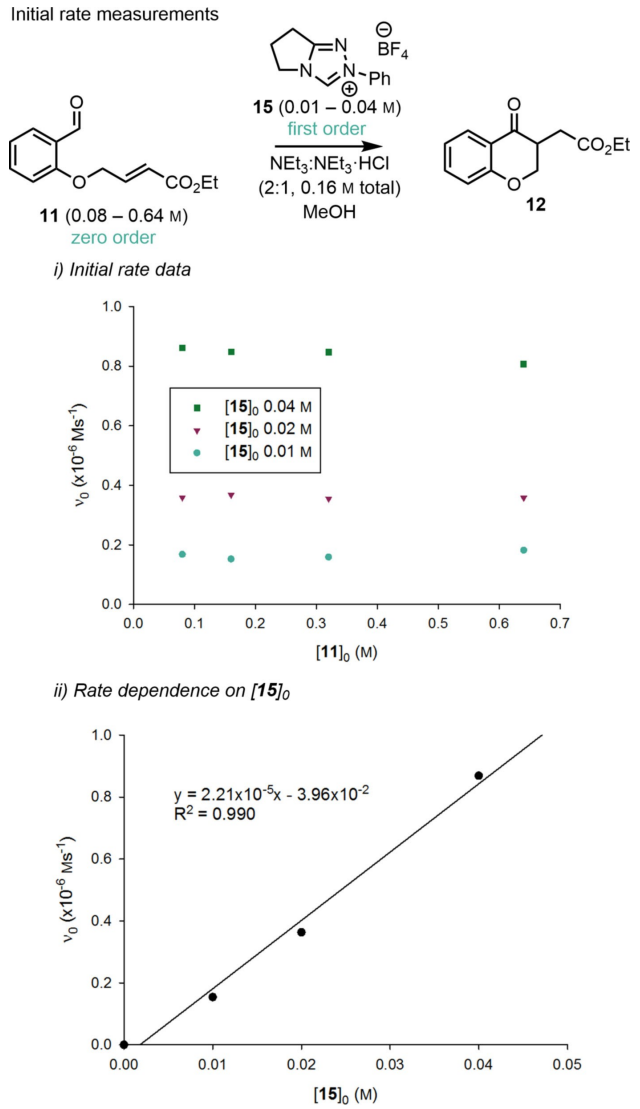

Figure 4. Initial rates analysis of **15**-catalyzed Stetter reaction in buffered methanol (NEt_3:NEt_3·HCl (2:1 0.16 M total)) at 35 °C under argon: i) initial rates at [**11**] = 0.08 M, 0.16 M, 0.32 M and 0.64 M; and [**15**] = 0.04 M (green),0.02 M (purple) and 0.01 M (teal); ii) v_0 for each $[\mathbf{15}]_0$ taken from the respective y-intercept in i).

intermediate **19**) and k_{intra} (intramolecular Michael addition of the acyl anion equivalent to give **20**) could be differentiated based on the electronic requirements of each step (Figure 5B).[19]

Both steps, if turnover limiting, would be expected to result in a zero-order dependence on aldehyde concentration. Previous reports have shown that deprotonation to form the Breslow intermediate is affected by through-bond electronic effects, with an increase in the rate of C(α)-H/D exchange of methylated adducts observed for compounds containing electron-withdrawing N-aryl substituents (Figure 5A).[13] If deprotonation is turnover-limiting in this reaction, a similar trend in overall reaction rate would be predicted. Conversely, the Michael addition would be expected to be accelerated by electron-donating N-aryl substituents due to an increase in the

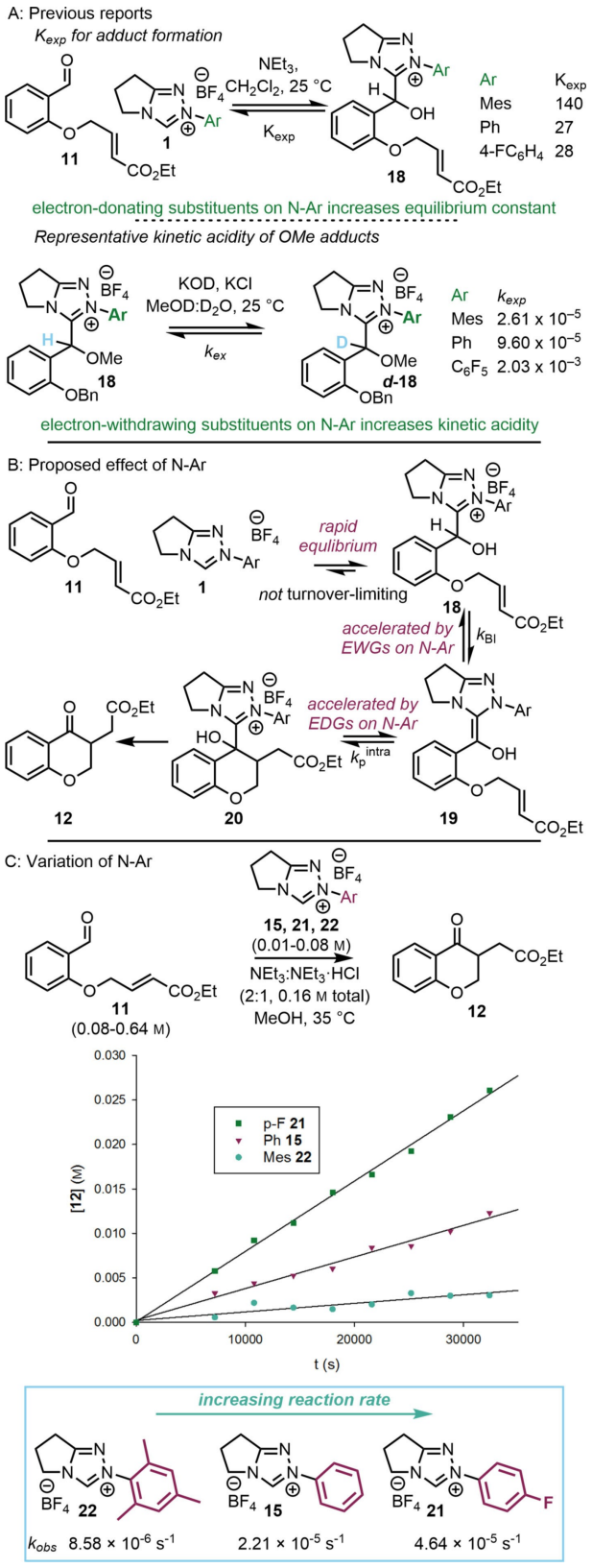

Figure 5. A: Reported effects of N-aryl substituents on NHC-mediated processes. B: Predicted effects of N-aryl substituents on the NHC-catalyzed Stetter reaction. C: Initial rate data for Stetter reactions with $[\mathbf{11}]_0$ = 0.32 M in buffered methanol (NEt_3 and NEt_3·HCl (2:1, 0.16 M total)) at 35 °C under argon catalyzed by: **21** (green), **15** (purple) and **22** (teal) at 0.02 M catalyst loading.

nucleophilicity of the acyl anion equivalent (Figure 5B). Comparable reactions with catalysts **21** and **22** were therefore performed and their first-order rate constants compared with that for **15** (Figure 5C).[20] The rates of product formation for the reactions catalyzed by **15**, **21** and **22** indicate enhanced rates when the NHC N-Ar substituent incorporates an electron-withdrawing group (EWG): **21** (*N*-(*p*-F-Ph)) > **15** (*N*-Ph) > **22** (*N*-Mes) (Figure 5C).[19] Significantly, the reaction catalyzed by *N*-Mes **22** required a higher catalyst concentration (20–80 mM) than either *N*-(*p*-F-Ph) **21** or *N*-Ph **15** (10–40 mM) due to the slow rate of Stetter product formation compared with isomerization in this case. This trend, along with the reaction orders and observed rate constant, is consistent with deprotonation to form the Breslow intermediate (k_2) being turnover-limiting rather than the Michael addition step.

The first-order rate constant measured herein, $k_{obs} = 2.21 \times 10^{-5}\ s^{-1}$, based on the observed Stetter initial rate dependence on triazolium **15** concentration at 35 °C, can be compared to the analogous value for the benzoin reaction of benzaldehyde **3** (R = Ph) using the same catalyst **15**, buffer and solvent (albeit at the higher reaction temperature of 50 °C). In the case of the benzoin reaction, a clear change in dependence of initial rate on benzaldehyde concentration from first- to zero-order was observed at higher aldehyde concentrations according to Equation 1. At high $[PhCHO]_0$ when $k_p[PhCHO] \gg k_{-BI}$, values for ν_{max} approach $k_{BI}[\mathbf{4}]$ (*c.f.* k_{BI} [**18**] in Figure 5B).

$$\nu = \frac{k_p \nu_{max}[PhCHO]}{k_{-BI} + k_p[PhCHO]} = \frac{k_p k_{BI}[4][PhCHO]}{k_{-BI} + k_p[PhCHO]} \quad (1)$$

As the nucleophilic addition of the acyl anion equivalent to benzaldehyde is intermolecular in the benzoin process, only a turnover-limiting Breslow intermediate-forming step could explain the zero-order dependence on aldehyde in this case. This was again supported by the rate dependence of different triazoliums with higher ν_{max} plateau values observed for electron-withdrawing N-aryl substituents. The dependence of ν_{max} on triazolium concentration for the benzoin reaction catalyzed by **15** yielded $k_{obs} = 7.48 \times 10^{-5}\ s^{-1}$, which is ~3-fold higher than for the Stetter reaction with *ortho*-alkoxy aldehyde **11**. Although some of this difference can be attributed to the different temperatures used, the remainder is also consistent with a decrease in k_{obs} for a more electron-donating *ortho*-alkoxy substituent and turnover-limiting Breslow intermediate formation.

Conclusion

In conclusion, an initial rates analysis of the NHC-catalyzed intramolecular Stetter reaction in $NEt_3/NEt_3 \cdot HCl$ buffered methanol has been investigated. A concurrent, NHC-independent isomerization of **11** was observed and found to have a first-order dependence on aldehyde concentration. Mechanistic analysis of the Stetter process showed the reaction to be first-order in catalyst and zero-order in aldehyde over a broad range of aldehyde concentrations. Consistent with previous reports, the reaction rate was higher for catalysts with electron-withdrawing N-aryl substituents within the triazolium skeleton. The data reported are consistent with deprotonation to form the Breslow intermediate being turnover-limiting in this reaction.[21]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Breslow intermediate · Initial rates analysis · NHC · Stetter reaction · Triazolium

[1] a) H. Stetter, *Angew. Chem. Int. Ed.* **1976**, *15*, 639; b) H. Stetter, M. Schreckenberg, *Angew. Chem. Int. Ed.* **1973**, *12*, 81.
[2] a) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719; b) R. Breslow, R. Kim, *Tetrahedron Lett.* **1994**, *35*, 699; c) M. Pareek, Y. Reddi, R. B. Sunoj, *Chem. Sci.* **2021**, doi.org/10.1039/D1SC01910D.
[3] a) D. A. DiRocco, T. Rovis, *Asymmetric Organocatalysis 1: Lewis Base and Acid Catalysts* (Ed.: B. List), Georg Thieme Verlag KG, Stuttgart, 2011, pp. 619–635; b) S. R. Yetra, A. Patra, A. T. Biju, *Synthesis* **2015**, *47*, 1357; c) X. Chen, H. Wang, Z. Jin, Y. R. Chi, *Chin. J. Chem.* **2020**, *38*, 1167.
[4] a) T. Dudding, K. N. Houk, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5770; b) B. Goldfuss, M. Schumacher, *J. Mol. Model.* **2006**, *12*, 591; c) J. Martí, F. López-Calahorra, J. M. Bofill, *J. Mol. Struct.* **1995**, *339*, 179.
[5] a) W. Schrader, P. P. Handayani, C. Burstein, F. Glorius, *Chem. Commun.* **2007**, 716–718; b) A. Berkessel, S. Elfert, V. R. Yatham, J. M. Neudorfl, N. E. Schlorer, J. H. Teles, *Angew. Chem. Int. Ed.* **2012**, *51*, 12370; c) M. Paul, P. Sudkaow, A. Wessels, N. E. Schlorer, J. M. Neudorfl, A. Berkessel, *Angew. Chem. Int. Ed.* **2018**, *57*, 8310.
[6] a) B. Maji, H. Mayr, *Angew. Chem. Int. Ed.* **2012**, *51*, 10408; b) D. A. DiRocco, K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 6143; c) A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles, *Angew. Chem. Int. Ed.* **2010**, *49*, 7120.
[7] a) V. Dhayalan, S. C. Gadekar, Z. Alassad, A. Milo, *Nat. Chem.* **2019**, *11*, 543; b) S. C. Gadekar, V. Dhayalan, A. Nandi, I. L. Zak, S. Barkai, M. S. Mizrachi, S. Kozuch, A. Milo, doi.org/10.26434/chemrxiv.13061717.v1.
[8] M. J. White, F. J. Leeper, *J. Org. Chem.* **2001**, *66*, 5124.
[9] R. S. Massey, J. Murray, C. J. Collett, J. Zhu, A. D. Smith, A. C. O'Donoghue, *Org. Biomol. Chem.* **2021**, *19*, 387.
[10] For representative examples, see: a) T. Lu, L. Gu, Q. Kang, Y. Zhang, *Tetrahedron Lett.* **2012**, *53*, 6602; b) T. Soeta, Y. Tabatake, Y. Ukaji, *Tetrahedron* **2012**, *68*, 10188; c) Z. Rafiński, A. Kozakiewicz *J. Org. Chem.* **2015**, *80*, 7468; d) Z. Rafiński, A. Kozakiewicz, K. Rafińska, *ACS Catal.* **2014**, *4*, 1404; e) Z. Rafiński, *ChemCatChem* **2016**, *8*, 2599; f) M.-Q. Jia, Y. Li, Z.-Q. Rong, S.-L. You, *Org. Biomol. Chem.* **2011**, *9*, 2072.
[11] D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 10402.
[12] J. L. Moore, A. P. Silvestri, J. R. de Alaniz, D. A. DiRocco, T. Rovis, *Org. Lett.* **2011**, *13*, 1742.
[13] C. J. Collett, R. S. Massey, O. R. Maguire, A. S. Batsanov, A. C. O'Donoghue, A. D. Smith, *Chem. Sci.* **2013**, *4*, 1514.
[14] C. J. Collett, R. S. Massey, J. E. Taylor, O. R. Maguire, A. C. O'Donoghue, A. D. Smith, *Angew. Chem. Int. Ed.* **2015**, *54*, 6887.
[15] See electronic supporting information for details.
[16] For representative examples, see: a) S. Wei, X.-G. Wei, X. Su, J. You, Y. Ren, *Chem. Eur. J.* **2011**, *17*, 5965; b) M. M. Ahire, S. B. Mhaske, *ACS Omega* **2017**, *2*, 6598.
[17] For representative examples, see: a) S. K. Guha, A. Shibayama, D. Abe, M. Sakaguchi, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2147;

b) K. Sunitha, K. K. Balasubramanian, *Tetrahedron* **1987**, *43*, 3269; c) B. Harish, M. Subbireddy, O. Obulesu, S. Suresh, *Org. Lett.* **2019**, *21*, 1823.
[18] Data is shown for [**11**] = 0.032 M but the same trend was observed at [**11**] = 0.008 M, 0.016 M, and 0.064 M.
[19] Catalyst release was ruled out as the turnover-limiting step based on earlier findings that adduct [**20**] was not observed and so its decay is likely rapid.
[20] Due to an extremely rapid reaction to give product, reliable initial rate data could not be obtained for *N*-2,4,6-Cl_3-C_6H_2 or *N*-C_6F_5-substituted triazolium ion-precatalysts.
[21] The research data supporting this publication can be accessed at https://doi.org/10.17630/7b18dcdd-72a3-4b26-909b–25ccd31cd58c.

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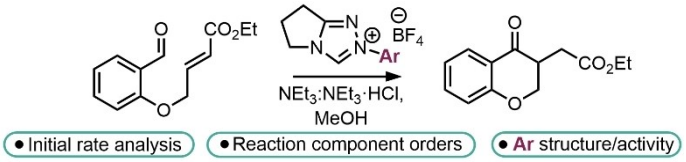

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