

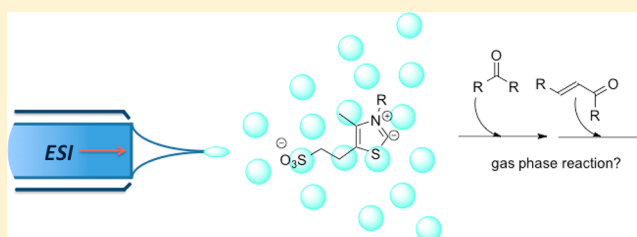
Gas Phase Studies of N-Heterocyclic Carbene-Catalyzed Condensation Reactions

Yuan Tian and Jeehiun K. Lee*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08901, United States

S Supporting Information

ABSTRACT: N-Heterocyclic carbenes (NHCs) catalyze *Umpolung* condensation reactions of carbonyl compounds, including the Stetter reaction. These types of reactions have not heretofore been examined in the gas phase. Herein, we explore the feasibility of examining these reactions in the absence of solvent. A charge-tagged thiazolylidene catalyst is used to track the reactions by mass spectrometry. We find that the first *Umpolung* step, the addition of the NHC catalyst to a carbonyl compound to form the “Breslow intermediate”, does not readily proceed in the gas phase, contrary to the case in solution. The use of acylsilanes in place of the carbonyl compounds appears to solve this issue, presumably because of a favorable Brook rearrangement. The second addition reaction, with enones, does not occur under our gas phase conditions. These reactions do occur in solution; the differential reactivity between the condensed and gas phases is discussed, and calculations are used to aid in the interpretation of the results.

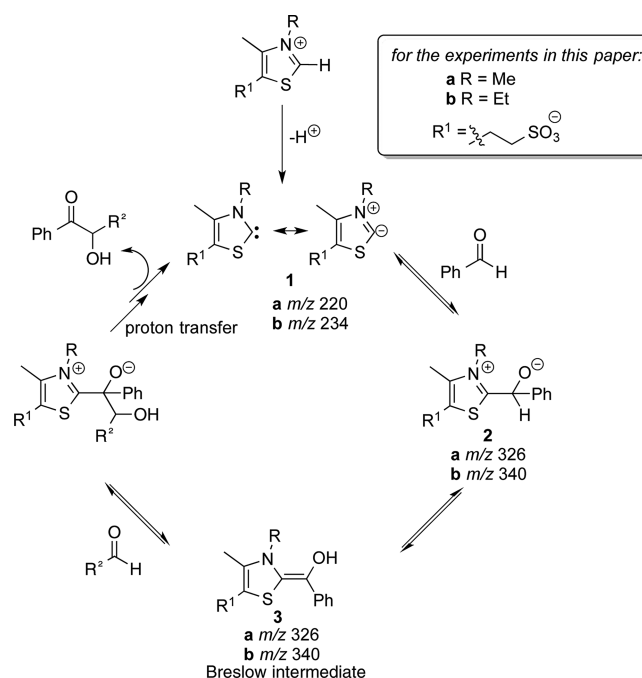


INTRODUCTION

A particularly intriguing class of reactions in organic synthesis involves the reversal of the polarity of a functional group (*Umpolung*).¹ The classic example is the benzoin condensation, first reported by Wöhler and Liebig in 1832 with a mechanism proposed by Lapworth in 1903; cyanide catalyzes the dimerization of two benzaldehyde units.² In 1943, Ukai and co-workers discovered that thiazolium salts can also catalyze the condensation.³ Several years later, Breslow proposed the deprotonated thiazolium, the thiazolylidene (which can also be considered a thiazolium zwitterion), as the catalytic species.^{3–6} His proposed mechanism (Scheme 1) involves deprotonation of the thiazolium to yield thiazolylidene/thiazolium zwitterion, which nucleophilically adds to a benzaldehyde, followed by a proton transfer to form the “Breslow intermediate”, which possesses the *Umpolung* reactivity (the aldehyde becomes nucleophilic rather than electrophilic). The Breslow intermediate then adds to a second benzaldehyde. This reaction, as well as its related counterpart, the Stetter reaction (in which the second addition involves an enone), has seen a renaissance in the past decade, with enantioselective versions catalyzed by a variety of N-heterocyclic carbenes (NHCs; thiazolylidenes, imidazolylidenes, and triazolylidenes).^{7–25}

The Breslow mechanism is commonly accepted for the benzoin condensation. Many attempts over the years had been made to isolate the Breslow intermediate, which had proven to be elusive until 2012, when both a nitrogen analogue and the intermediate itself were observed and characterized spectroscopically; studies of the nucleophilicity of related deoxy and methoxy analogues have also been conducted.^{26–30} Mechanisms involving a thiazolylidene dimer (first proposed by Lemal) have also been suggested; data both in support of and against such mechanisms exist.^{31–43} Much less mechanistic

Scheme 1



isms involving a thiazolylidene dimer (first proposed by Lemal) have also been suggested; data both in support of and against such mechanisms exist.^{31–43} Much less mechanistic

Received: May 13, 2015

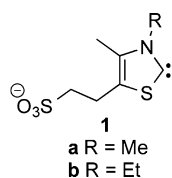
Published: June 12, 2015

work exists for the Stetter reaction. The mechanism is generally assumed to be similar to that of the benzoin, as they share the same first step (addition of NHC to aldehyde), although possibly with different concertedness and rate-determining steps.^{44–47}

Because of the ever-growing prevalence and synthetic utility of reactions catalyzed by ylidenes, we sought to explore the potential of studying the gas phase counterpart of this reaction, in the absence of solvent. Because the intermediates are not charged, the reaction is potentially difficult to track using mass spectrometry. The solution phase reaction has been studied using ESI-MS, first by Glorius and co-workers, who examined an imidazolylidene-catalyzed conjugate *Umpolung* reaction to form a lactone.⁴⁸ They took advantage of the protonation of intermediates in the electrospray process, allowing the use of positive ion mass spectrometry for detection. We also examined the solution phase reaction, but using negative ion mass spectrometry; in our case, we synthesized a novel thiazolium with a sulfonate charge tag.⁴⁹ This synthesized compound was used to catalyze the benzoin condensation in solution, and intermediates were detected using negative ion ESI-MS. In this work, by contrast, we seek to examine these condensation reactions in the gas phase, for the first time. The two prior mass spectrometric studies of these types of reactions have involved conducting the reactions in solution and using ESI-MS to track reaction progress. By contrast, we are attempting the reactions directly in the gas phase. Such studies are potentially useful, because intrinsic reactivity in the absence of solvent can be useful for understanding the role of solvent in the analogous condensed phase reactions.

RESULTS AND DISCUSSION

Charge-Tagged Catalyst. The intermediates in these reactions are uncharged. To detect relevant species in the gas phase reaction, we synthesized two thiazolium species, each with a sulfonate “charge tag” (**1a** and **1b**). The sulfonate serves as a nonreactive moiety that, because it is charged, can be detected using mass spectrometry.



First Step: Formation of the Breslow Intermediate.

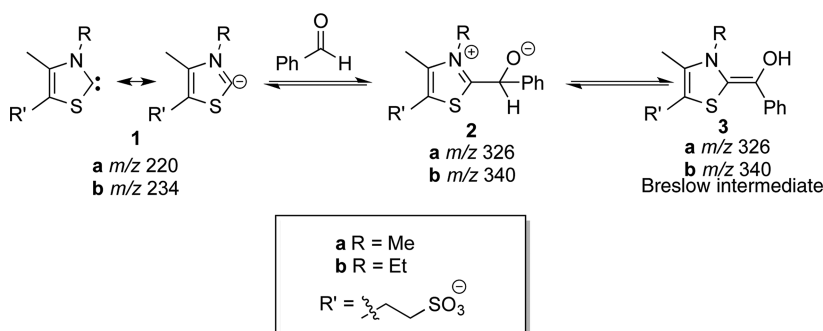
The charge-tagged catalyst **1a** was electrosprayed and isolated in the mass spectrometer. We then introduced benzaldehyde to

ascertain whether the catalyst would add to the aldehyde *in vacuo* (Scheme 2). The resultant intermediate [either oxyanion **2a** or Breslow intermediate **3a** (Scheme 2)] would have an *m/z* ratio of 326. This is a step that occurs readily in solution,^{3,5,6} however, under our gas phase conditions, no signal corresponding to *m/z* 326 was observed.⁵⁰ We also tried the addition of catalyst **1b** to benzaldehyde (expected ion at *m/z* 340), but again, no signal corresponding to initial addition (to form **2b** and/or **3b**) was observed. No other ions are observed, either; we see only the *m/z* ratio corresponding to the catalyst.

There is always the possibility that the entire catalytic cycle is taking place, with short-lived charged intermediates, and neutrals that we cannot observe. If the entire reaction in Scheme 1 takes place, we would simply regenerate the catalyst, *m/z* 220 or 234. This is a possibility that we can never discount; however, we thought that perhaps another reason we may not detect **2** or **3** in this gas phase reaction could be due to the difficult proton transfer to form **3** from **2**. The formation of Breslow intermediate **3** from oxyanion intermediate **2** requires a 1,2-proton shift. By orbital symmetry rules, one would expect an intramolecular, direct 1,2-proton shift to be highly unfavorable.^{44,51,52} If the solvent is protic, then presumably the solvent can shuttle the proton.^{5,53} However, the solvent is often aprotic, leading to other proposals for how this proton transfer is effected. Hawkes and Yates studied the Stetter reaction mechanism and proposed that the proton transfer would occur intermolecularly, with another molecule of **2** doing the “shuttling”.⁴⁴ Using calculations, Gronert also suggested intermolecular protonation by a second molecule, but rather than **2**, he suggested the *N*-alkyl group of the thiazolium catalyst.^{54,55} A later experimental study by Rovis and co-workers established that for their reaction in toluene, the proton transfer is likely effected by an ether substituent on their substrate.⁴⁵

Our reaction is in the gas phase, where there is no solvent to aid in the proton transfer. Reaction with a second molecule of the catalyst is unlikely; the catalysts are both negatively charged, and also, the low relative concentration of catalyst ions disfavors collision and reaction. Rovis and co-workers showed proton transfer with a substituent on the substrate; however, our substrates are much simpler, and this is not a possibility. We therefore hypothesized that under our conditions, in the absence of solvent, the initial tetrahedral intermediate would not be particularly stable and formation of the Breslow intermediate was not possible because of the unfavorable 1,2-proton transfer. We calculated the gas phase energetics for the addition of **1a** to benzaldehyde to form **2a** and then **3a**, via intramolecular proton transfer (Figure 1). The initial addition is

Scheme 2



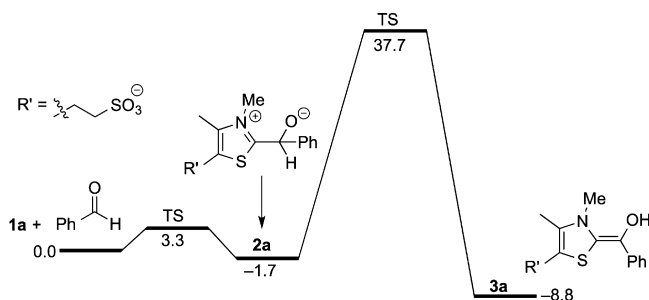


Figure 1. Calculated [B3LYP/6-31+G(d)] enthalpies (298 K) for gas phase reaction of catalyst **1a** with benzaldehyde.

calculated to have a small enthalpy of activation (3.3 kcal/mol), but the 1,2-proton transfer has a barrier of 39 kcal/mol (from the tetrahedral intermediate **2a**). This is consistent with related calculations on this 1,2-shift.^{44,45,51,53,55–57}

So how are we to overcome this high-energy 1,2-proton shift? We were drawn to the fact that the 1,2-shift should be facile for a silyl group, which had been shown by Brook several decades ago (thus resulting in an eponymously named rearrangement).⁵⁸ Heathcock first invoked the possibility of this pathway for an *Umpolung* reaction in 1981, in his studies of fluoride-catalyzed conversions of acylsilanes to aldehydes and ketones.⁵⁹ Degl'Innocenti followed up on this with fluoride- and cyanide-catalyzed conjugate additions of acylsilanes to enones.⁶⁰ In 2003, Linghu and Johnson utilized acylsilanes in the cyanide-catalyzed benzoin condensation, to circumvent the product mixture limitations of the reaction.⁶¹ In the benzoin condensation, the reaction of two different aldehydes results in four possible products. Linghu and Johnson found that coupling an acylsilane and aldehyde resulted in just one product.⁶² He later expanded this chemistry to metal-phosphite catalysts, with enantioselectivity.⁶³

In 2004, Scheidt and co-workers reported the successful use of thiazolium salts (as opposed to charged cyanide or fluoride species) as the nucleophilic catalyst precursors in the Stetter reactions of acylsilanes with enones.⁶⁴ The Stetter reaction often incurs benzoin side products (with the aldehyde self-condensing), but Scheidt showed that the use of acylsilanes as acyl anion precursors solves this problem, as the sterically congested acylsilane is not a good electrophile.⁶⁵

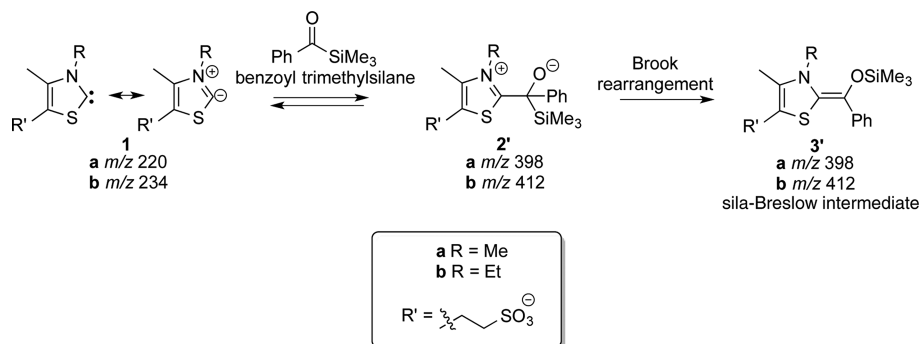
Because the direct, intramolecular 1,2-silyl shift (Brook rearrangement) should be facile, we thought that the use of acylsilanes might allow us to form the silyl version of the Breslow intermediate in the absence of solvent (Scheme 3).⁵⁸

We conducted calculations to ascertain the feasibility of this plan. Schumacher and Goldfuss had previously calculated energetics for the *Umpolung* reactions of acylsilanes with various catalysts in THF solvent and found the Brook rearrangement step to have a low barrier.⁵⁶ We hoped to find the same in the gas phase. The gas phase addition of catalyst **1a** to the silyl analogue of benzaldehyde (benzoyltrimethylsilane) has a calculated barrier slightly higher than that of benzaldehyde, as might be expected from the greater steric bulkiness and decreased electrophilicity of the acylsilane (Figure 2). At 5.4 kcal/mol, however, the barrier for the first addition is still low. The subsequent Brook rearrangement to form the “sila-Breslow” intermediate **3a'** has a barrier of only 0.4 kcal/mol (compared to a barrier of >35 kcal/mol for the non-silyl version!). Therefore, we were hopeful that the use of acylsilanes could help in the forward progress of the gas phase benzoin condensation.

We now turned our attention back to the experiments. The reaction of carbene catalysts **1a** and **1b** with benzaldehyde yielded no observable reaction. In contrast, the reaction of catalyst **1a** with the silyl analogue of benzaldehyde [benzoyltrimethylsilane (Scheme 3)] does yield *m/z* 398, which corresponds to both the initial oxyanion (**2a'**) and the sila-Breslow intermediate (**3a'**) (Figure 3). Likewise, we find that catalyst **1b** with benzoyltrimethylsilane yields a product with a *m/z* ratio of 412, which corresponds to the addition product [**2b'** or **3b'** (Scheme 3)].

By mass spectrometry, we cannot be certain whether we have oxyanion **2'** or Breslow-like intermediate **3'** [because they have the same *m/z* ratio (Scheme 3)]. The gas phase addition of the carbene catalysts and the nonsilylated benzaldehyde yields no reaction, which is consistent with calculations; intermediate **2** is not particularly stable, and the barrier to proton transfer to move the reaction forward is prohibitively high (Figure 1). By contrast, the carbene catalysts readily produce a detectable adduct signal when allowed to react with benzoyltrimethylsilane (Figure 3), also in agreement with calculations (Figure 2), which indicate the favorability of the Brook rearrangement and support the presence of structure **3'**. To probe further whether we have **2'** or **3'**, we conducted collision-induced dissociation (CID) experiments. CID of *m/z* 398 [**2a'** or **3a'** (Scheme 3)] yields *m/z* 383, corresponding to loss of a methyl group (Scheme 4). CID of *m/z* 412 (**2b'** or **3b'**) results in a *m/z* ratio corresponding to the loss of an ethyl group (Scheme 4). These results imply that for both *m/z* 398 and 412, CID results in loss of the *N*-alkyl substituent (Scheme 4, paths A). This result seems to be more consistent with the sila-Breslow intermediate structure **3'**. Oxyanion structure **2'** would presumably

Scheme 3



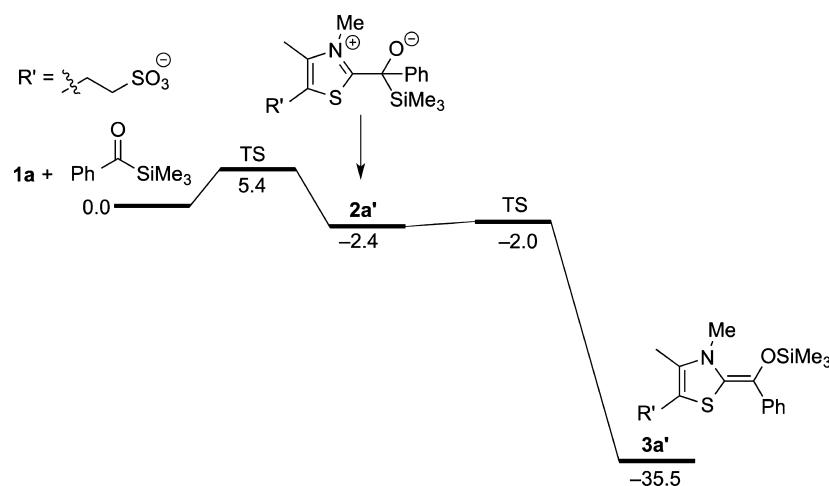


Figure 2. Calculated [B3LYP/6-31+G(d)] enthalpies (298 K) for the gas phase reaction of catalyst **1a** with benzoyltrimehylsilane.

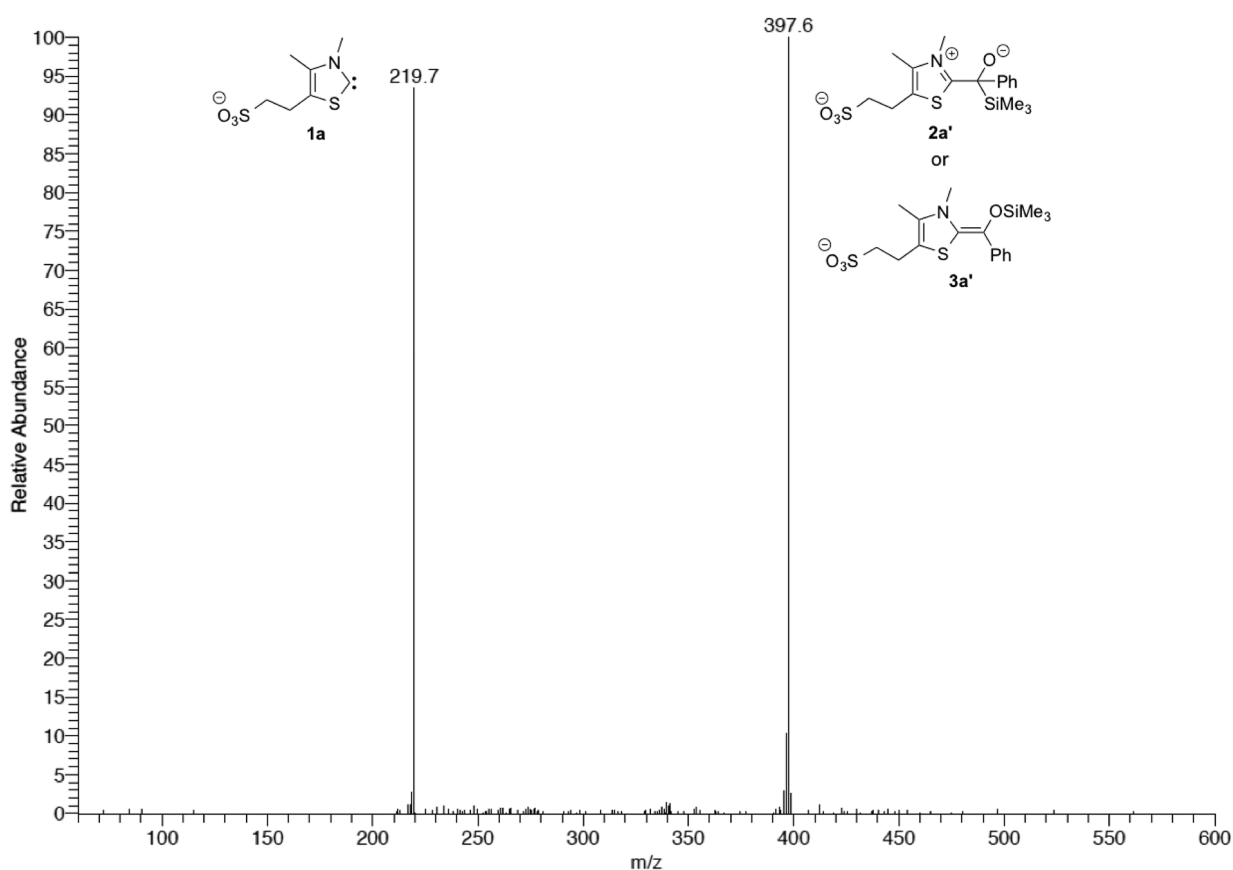


Figure 3. Mass spectrum of reaction progress for **1a** with benzoyltrimehylsilane.

dissociate back to catalyst **1** and benzoyltrimehylsilane upon CID (Scheme 4, paths B). Although this is not definitive evidence of structure **3'**, it is certainly supportive. These CID data, along with the successful reaction between the catalyst and benzoyltrimehylsilane versus the unsuccessful reaction with benzaldehyde, support the Brook rearrangement to form **3'** having taken place (Scheme 3).

Second Addition. The second addition in these *Umpolung* reactions involves either an aldehyde (benzoin-type condensation) or enone (Stetter reaction). We focused on the Stetter reaction because of the seminal work by Scheidt and co-workers, who have comprehensively studied the condensed

phase reactions of NHCs with acylsilanes and enones.^{64–66} We started with methyl vinyl ketone (MVK), which Scheidt found to be quite reactive.⁶⁴ We first isolated m/z 398 (**2a'**/**3a'**) and then added MVK (Scheme 5). Scheme 5 shows possible paths of reaction. Enone addition results in intermediate **4'**. This intermediate could presumably undergo [1,4] O to C silyl migration (red path) or [1,6] O to O silyl migration (blue path). We do not see any ions corresponding to any of the intermediates or products shown in Scheme 5. Thus, under our gas phase conditions, no reaction is observed. We also tried acrolein but saw no reaction.

Scheme 6

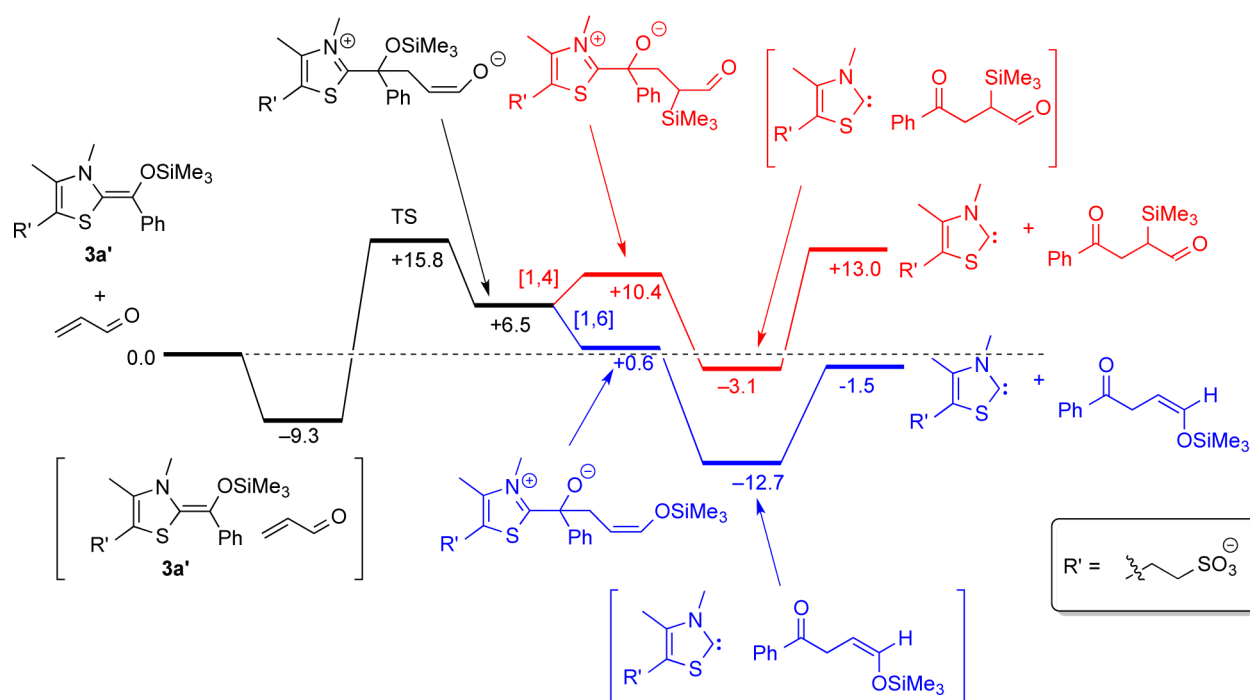
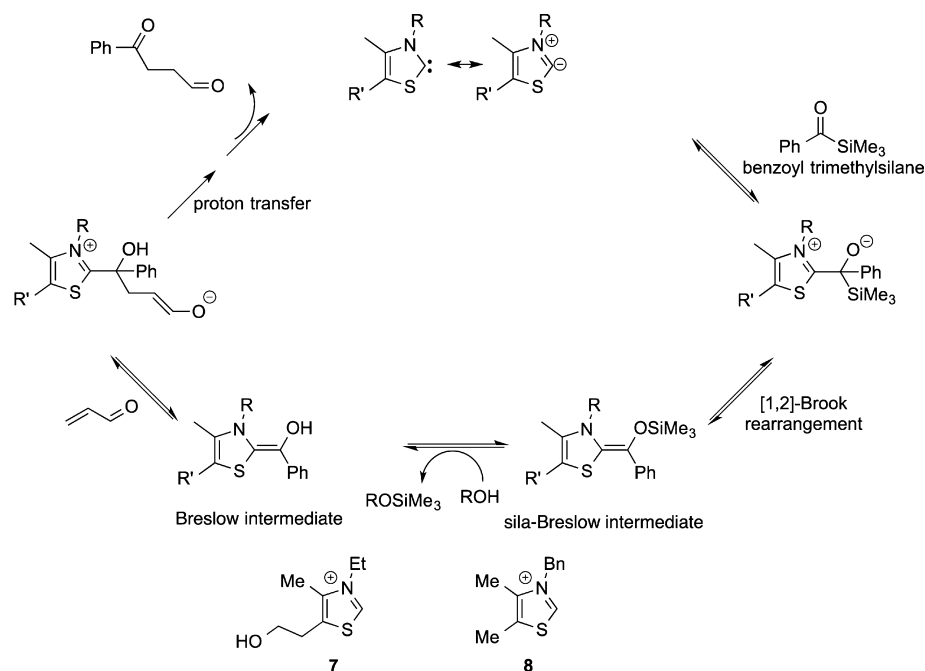


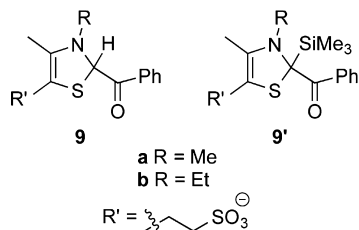
Figure 4. Possible pathways for the sila-Stetter. The [1,4] O to C trimethylsilyl migration is colored red and the [1,6] O to O trimethylsilyl migration blue. Transition structures for the [1,4] and [1,6] migrations were not calculated. Calculations conducted at the B3LYP/6-31+G(d) level of (ΔH , 298 K).

observed: in a competition between dissociating back to the separated reactants (+9.3 kcal/mol) and addition (+25.1 kcal/mol), dissociation is the most likely path. Entropy also favors dissociation; this has been studied extensively in the gas phase, particularly for substitution reactions.^{70–72} In Figure 4, we show both [1,4] O to C (in red) and [1,6] O to O silyl migration (in blue). The pathway involving [1,4] O to C silyl migration is overall endothermic (red path), while the path for the [1,6] O to O silyl transfer (blue path) is exothermic by -1.5 kcal/mol.

However, the reaction probably never proceeds beyond the first TS (labeled “TS”). Thus, the calculations support the experimental observations, showing the absence of reaction.

One last possibility we considered is that rather than an oxanion **2'** or Breslow intermediate **3'** structure, we have the ketone structure **9'**, which would also not be prone to further reaction. In a 2010 condensed phase study attempting to isolate the Breslow intermediate, Berkessel and co-workers found instead a ketone structure.^{28,73} Subsequent gas phase

calculations by us confirmed the stability of ketone **9a** was greater than that of Breslow intermediate **3a** (by 7 kcal/mol).⁴⁹ To assess the possibility of a ketone structure, we calculated the relative stability of sila-analogue **9a'** compared to that of its isomer, the corresponding Breslow intermediate **3a'**. We find that ketone structure **9a'** is 23 kcal/mol less stable than Breslow intermediate **3a'**. That is, unlike proton analogue **9a**, **9a'** is not more stable than the corresponding Breslow intermediate. Sila-Breslow intermediate **3a'** is therefore the most stable calculated structure for *m/z* 398, and the lack of subsequent reaction may in fact be due to the unfavorability of the second addition.



CONCLUSIONS

We report herein the first study of the gas phase *Umpolung* reaction of N-heterocyclic carbenes with carbonyl compounds. Although these types of reactions occur readily in solution, they do not appear to do so in the gas phase. Our experiments provide evidence to support the computational prediction that the first step to form the Breslow intermediate requires “shuttling” of the proton; a direct 1,2-proton transfer is not favorable. We overcome this issue by using an acylsilane. Direct 1,2-silyl transfer (Brook rearrangement) should occur, and computations indeed predict a low barrier to form the sila-Breslow intermediate. Our experimental results are consistent with sila-Breslow intermediate formation. Attempts to effect the Stetter reaction by adding enones are unsuccessful. Our computational and experimental results support Scheidt’s hypothesis that desilylation of the sila-Breslow intermediate must occur for reaction to proceed. With this initial study in hand, we can now focus on developing methods, including instrument and experimental modifications, to examine further these types of NHC-catalyzed reactions in the gas phase.

EXPERIMENTAL SECTION

Mass Spectrometric Experiments. Most substrates are commercially available and were used as received. The sulfonate-tagged thiazolium and benzoyltrimethylsilane are both known compounds and were synthesized according to literature procedures.^{49,74} Mass spectrometric experiments were conducted using a house-modified quadrupole ion trap mass spectrometer as previously described.⁷⁵ Charge-tagged thiazolylidene ions were generated by electrospray ionization (ESI) from a 0.1 mM solution of the synthesized thiazolium in methanol with 0.1% ammonium hydroxide. An electrospray needle voltage of 2.7 kV and a flow rate of 20 $\mu\text{L}/\text{min}$ were used, with a capillary temperature of 190 °C. Neutral substrates were added via leak valves, with the helium gas flow. Reactions were tracked for up to 10 s. Spectra were an average of 10 scans.

Computational Method. Calculations were conducted at the B3LYP/6-31+G(d) level of theory using Gaussian09; the geometries were fully optimized, and frequencies were calculated.^{76–80} All the values reported are at 298 K. No scaling factor was applied.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates for all calculated species. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01069.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jee.lee@rutgers.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Javier de Alaniz Read for extremely insightful and helpful discussions. Yijie Niu also provided valuable insights, for which we are grateful. We also thank Rixin Wang (Pennsylvania State University, University Park, PA) for his synthesis of the benzoyltrimethylsilane. We thank the National Science Foundation for financial support.

REFERENCES

- (1) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258.
- (2) Wohler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249–282.
- (3) Ukai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296–300; *Chem. Abstr.* **1951**, *1945*, 5148.
- (4) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995–1005.
- (5) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
- (6) Mizuhara, S.; Handler, P. *J. Am. Chem. Soc.* **1954**, *76*, 571–573.
- (7) Stetter, H. *Angew. Chem.* **1976**, *88*, 695–704.
- (8) Stetter, H.; Raemsch, R. Y.; Kuhlmann, H. *Synthesis* **1976**, *11*, 733–735.
- (9) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407–496.
- (10) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217–1221.
- (11) de Alaniz, J. R.; Rovis, T. *Synlett* **2009**, *8*, 1189–1207.
- (12) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632–2634.
- (13) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.
- (14) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *291*, 77–144.
- (15) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989–3991.
- (16) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066–14067.
- (17) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872–10874.
- (18) Um, J. M.; DiRocco, D. A.; Noey, E. L.; Rovis, T.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 11249–11254.
- (19) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402–10405.
- (20) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2391–2394.
- (21) Jousseume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410–1414.
- (22) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782–11785.
- (23) Holmes, J. M.; Gravel, M. In *Comprehensive Organic Synthesis II*; Molander, G. A., Knochel, P., Eds.; Elsevier: Amsterdam, 2014.
- (24) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.
- (25) Flanigan, D. M.; Romanav-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, DOI: 10.1021/acs.chemrev.5b00060.
- (26) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143–6145.
- (27) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schläpfer, N. E.; Teles, J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12370–12374.
- (28) Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7120–7124.

- (29) Maji, B.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 10408–10412.
- (30) Maji, B.; Horn, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6231–6235.
- (31) Lemal, D. M.; Lovald, R. A.; Kawano, K. I. *J. Am. Chem. Soc.* **1964**, *86*, 2518–2519.
- (32) Chen, Y.-T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714–7722.
- (33) Castells, J.; Lopez-Calahorra, F.; Domingo, L. *J. Org. Chem.* **1988**, *53*, 4433–4436.
- (34) Castells, J.; Domingo, L.; Lopez-Calahorra, F.; Marti, J. *Tetrahedron Lett.* **1993**, *34*, 517–520.
- (35) Chen, Y.-T.; Jordan, F. *J. Org. Chem.* **1991**, *56*, 5029–5038.
- (36) Castells, J.; Lopez-Calahorra, F.; Geijo, F.; Perez-Dolz, R.; Bassetas, M. *J. Heterocycl. Chem.* **1986**, *23*, 715–720.
- (37) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699–702.
- (38) Lopez-Calahorra, F.; Rubires, R. *Tetrahedron* **1995**, *51*, 9713–9728.
- (39) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241–8242.
- (40) Ma, Y.; Wei, S.; Lan, J.; Wang, J.; Xie, R.; You, J. *J. Org. Chem.* **2008**, *73*, 8256–8264.
- (41) Sakaki, S.; Musashi, Y.; Ohkubo, K. *J. Am. Chem. Soc.* **1993**, *115*, 1515–1519.
- (42) van den Berg, H. J.; Challa, G. *J. Mol. Catal.* **1989**, *51*, 1–12.
- (43) Metzger, J.; Larive, H.; Dennilauler, R.; Baralle, R.; Gauret, C. *Bull. Soc. Chim. Fr.* **1964**, 2857–2867.
- (44) Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, 5563–5570.
- (45) Moore, J. L.; Silvestri, A. P.; Read de Alaniz, J.; DiRocco, D. A.; Rovis, T. *Org. Lett.* **2011**, *13*, 1742–1745.
- (46) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 1514–1522.
- (47) Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192–197.
- (48) Schrader, W.; Handayani, P. P.; Burstein, C.; Glorius, F. *Chem. Commun.* **2007**, 716–718.
- (49) Zeng, H.; Wang, K.; Tian, Y.; Niu, Y.; Greene, L.; Hu, Z.; Lee, J. K. *Int. J. Mass Spectrom.* **2014**, *369*, 92–97.
- (50) In solution, the reaction mixture is often heated, whereas our reaction mixtures are at room temperature.
- (51) Goldfuss, B.; Schumacher, M. *J. Mol. Model.* **2006**, *12*, 591–595.
- (52) Kemp, D. S. *J. Org. Chem.* **1971**, *36*, 202–204.
- (53) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124–5131.
- (54) Gronert's mechanism also involved a spiroepoxide intermediate (formed from **2**), which had first been proposed by Jordan et al.³²
- (55) Gronert, S. *Org. Lett.* **2007**, *9*, 3065–3068.
- (56) Schumacher, M.; Goldfuss, B. *Tetrahedron* **2008**, *64*, 1648–1653.
- (57) Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrler, E.; Harder, W.; Brode, S. *Helv. Chim. Acta* **1996**, *79*, 61–83.
- (58) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84.
- (59) Schinzer, D.; Heathcock, C. H. *Tetrahedron Lett.* **1981**, *22*, 1881–1884.
- (60) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645–648.
- (61) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534–2536.
- (62) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833–1840.
- (63) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070–3071.
- (64) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315.
- (65) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715–5724.
- (66) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932–4933.
- (67) Squires, R. R.; DePuy, C. H. *Org. Mass Spectrom.* **1982**, *17*, 187–191.
- (68) DePuy, C. H.; Damrauer, R.; Bowie, J. H.; Sheldon, J. C. *Acc. Chem. Res.* **1987**, *20*, 127–133.
- (69) Gronert, S. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 845–848.
- (70) DePuy, C. H.; Bierbaum, V. M. *Acc. Chem. Res.* **1981**, *14*, 146–153.
- (71) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219–4228.
- (72) Gronert, S. *Chem. Rev.* **2001**, *101*, 329–360.
- (73) Holloczki, O.; Kelemen, Z.; Nyulaszi, L. *J. Org. Chem.* **2012**, *77*, 6014–6022.
- (74) Picard, J. P.; Calas, R.; Dunogues, J.; Duffaut, N.; Gervai, J.; Lapouyade, P. *J. Org. Chem.* **1979**, *44*, 420–424.
- (75) Liu, M.; Chen, M.; Zhang, S.; Yang, I.; Buckley, B.; Lee, J. K. *J. Phys. Org. Chem.* **2011**, *24*, 929–936.
- (76) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision A.01; Gaussian, Inc.: Wallingford, CT, 2009.
- (77) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974–12980.
- (78) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
- (79) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- (80) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.