N-Heterocyclic Carbenes

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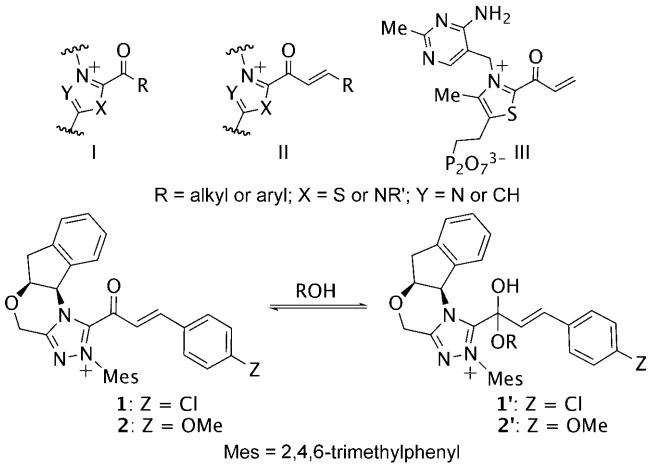
α,β-Unsaturated Acyl Azoliums from N-Heterocyclic Carbene Catalyzed Reactions: Observation and Mechanistic Investigation**

*Jessada Mahatthananchai, Pinguan Zheng, and Jeffrey W. Bode**

Catalytically generated acyl azoliums **I** and their α,β-unsaturated counterparts **II** are thought to be key reactive intermediates in a rapidly growing number of transformations promoted by N-heterocyclic carbene (NHC) catalysts.[1] Acyl azoliums are invoked in the postulated catalytic cycles of nearly all of the new NHC-catalyzed reactions of α-functionalized aldehydes reported since 2004, in which they are generally assumed to possess the reactivity of an activated carboxylic acid, that is, analogous to an activated ester.[2] In NHC-catalyzed processes, they are most often obtained through internal redox reactions of functionalized aldehydes but have also been prepared by oxidations of the Breslow intermediates[3] or additions to ketenes.[4] Acyl azoliums **I** are important intermediates in thiamine pyrophosphate (ThPP) dependent enzymatic reactions.[5] Townsend et al. have recently proposed that unsaturated acyl azolium **III** is the key intermediate in clavulanic acid biosynthesis;[6] despite careful efforts, **III** or its analogues **II** have never been characterized or independently synthesized. Here, we document the observation and characterization of α,β-unsaturated acyl azoliums **1** and **2** (Scheme 1) and demonstrate that their corresponding hemiacetals (**1′** and **2′**) are the kinetically important intermediates in both their acylation and annulation reactions.

Simple acyl azoliums prepared under stoichiometric conditions were extensively studied in a seminal work by Breslow[7] and continued by Daigo,[8] White and Ingraham,[9] Bruice,[10] Lienhard,[11] and Owen.[12] These investigations revealed the unique and rich chemistry of acyl azoliums, including their remarkable reluctance to acylate amines[12,13] and high preference for reactions with water or alcohols. Despite the more than 120 publications since 2004 that feature acyl azoliums, including the rediscovery of their unusual chemoselectivity, there have been no reports of the isolation, detection, or properties of novel acyl azoliums thought to be generated under catalytic conditions.[14]



Scheme 1. Various acyl azoliums and the hemiacetals.

Even at high catalyst loadings, most NHC-catalyzed reactions do not give any detectable intermediates that can be observed with conventional techniques such as UV, IR, NMR spectroscopy,[15] or MS methods.[16] For example, no intermediates could be observed during the redox esterification of cinnamaldehyde, even when the reaction was run with high catalyst loadings or in the absence of base to ensure slow reaction. This is consistent with NMR studies of the redox esterification of ynals by Zeitler, in which the postulated α,β-unsaturated acyl azolium **II** was not observed.[17]

Our recent studies of reactions of ynals catalyzed by azolium salts revealed that the rate-limiting step of the catalytic cycle occurs after the formation of the acyl azolium.[18] These findings strongly suggested that generation of substantial amounts of the α,β-unsaturated acyl azolium intermediate should be possible in the absence of a nucleophile. Careful preparation of a mixture of triazolium **3** and *para*-chlorophenyl ynal **4** in anhydrous $CDCl_3$ gives a clear solution (Figure 1). Upon addition of NaOAc, the solution rapidly becomes yellow, and turns deep red within 20 minutes. The color change was monitored by UV/Vis spectroscopy, and we observed a maximum absorption at 355 nm, with a significantly smaller absorption at 520 nm, for the solution containing acyl azolium **1** (Figure 2). Townsend et al. have speculated that the related protein-bound species **III** (Scheme 1) has a characteristic UV/Vis absorption at 310–320 nm.[6a] Our mixture was further investigated by electrospray ionization–high resolution mass spectrometry (ESI-HRMS), which verified the molecular formula of **1** (Figure 2).

[*] J. Mahatthananchai, Prof. Dr. J. W. Bode
Laboratory for Organic Chemistry, Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology (ETH) Zurich, Wolfgang-Pauli-Strasse 10, 8093 Zurich (Switzerland)
Fax: (+41) 44-633-1235
E-mail: bode@org.chem.ethz.ch
Homepage: http://www.bodegroup.org
Dr. P. Zheng
Department of Chemistry, University of Pennsylvania
231 South 34th Street, Philadelphia, PA 19104 (USA)

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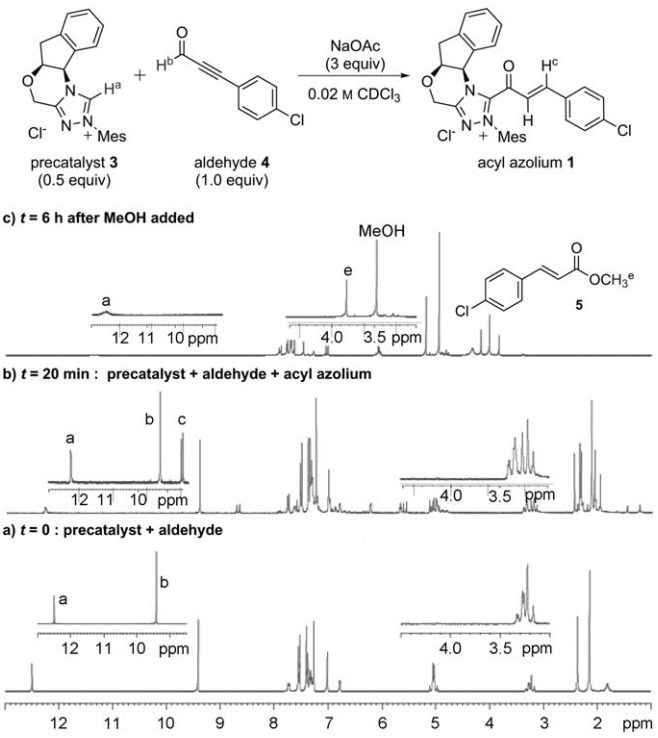
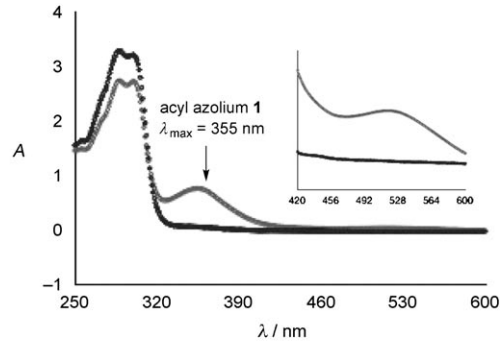
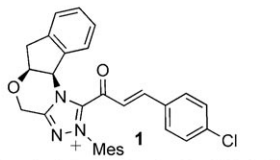


Figure 1. ^{1}H NMR investigation of α,β-unsaturated acyl azolium **1** generated from **3** and **4**, and its methanolysis to **5** (the labeled H atoms correlate to the indicated signals in the spectra).





Chemical Formula: $C_{30}H_{27}ClN_3O_2^+$
***m/z*: 496.1793 (found)**
***m/z*: 496.1792 (calculated)**

Figure 2. UV/Vis and ESI-HRMS characterizations of **1**. Black: precatalyst + aldehyde; gray: acyl azolium.

To confirm the formation of **1**, the reaction was monitored by ^{1}H NMR spectroscopy. Figure 1 shows the ^{1}H NMR spectra of the region from $\delta = 1.0$–13.0 ppm before (Figure 1 a) and after (Figure 1 b) treatment of the mixture of azolium **3** and aldehyde **4** with NaOAc. A new product, characterized by doublets at $\delta = 8.7$ ppm ($^1J = 18.0$ Hz) and at $\delta = 7.6$ ppm ($^1J = 18.0$ Hz), which is consistent with the expected acyl azolium **1**, was detected and grew in intensity over time, reaching a maximum of 30% conversion after about 40 minutes. This new product immediately disappeared upon the addition of MeOH (Figure 1 c), cleanly forming the corresponding unsaturated ester **5** and regenerating the protonated triazolium **3** (C-2 proton peak at $\delta = 12.1$ ppm).[19]

Although this solution could be filtered away from undissolved NaOAc or stored for several hours in the NMR tube, acyl azolium **1** was exceedingly prone to hydrolysis to give *para*-chlorocinnamic acid; all attempts to isolate **1** in pure form were unsuccessful. However, this intermediate was successfully characterized by COSY, HSQC, and HMBC NMR experiments that were performed on the mixture (see the Supporting Information for spectra and details). Correlation spectroscopy (Figure 3) clearly showed

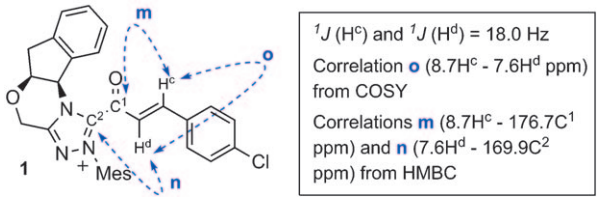
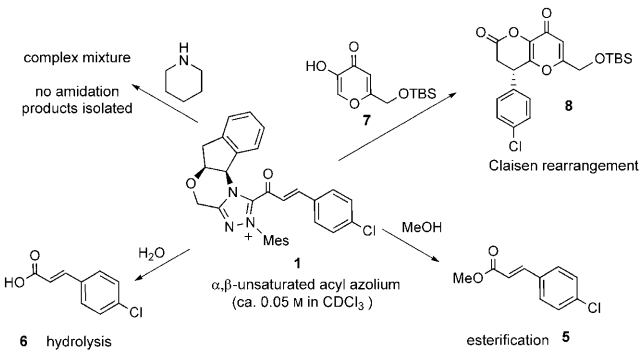


Figure 3. Key NMR correlation assignments of acyl azolium **1**.

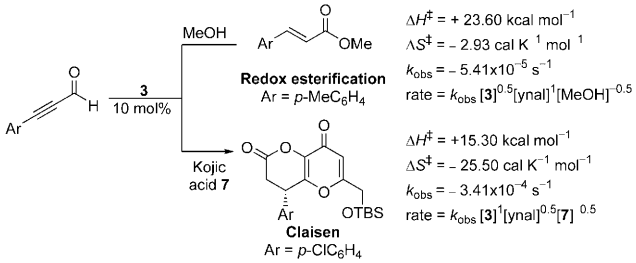
the bond between the acyl group containing an α,β-unsaturated moiety and the triazolium, and ruled out a triazole adduct, which we had previously observed in prior attempts at detecting catalytically generated acyl azoliums with non-anhydrous conditions.[20] ^{1}H NMR experiments were also repeated with *para*-methoxyphenyl ynal, which led to the formation of acyl azolium **2** with higher conversion (about 50%) relative to that of the aldehyde, but was much more susceptible to hydrolysis (see the Supporting Information).

The reactivity of **1**, generated in this pseudo-stoichiometric fashion, paralleled the chemistry observed under catalytic conditions (Scheme 2). It reacts instantaneously with water or MeOH to give acid **6** or ester **5**, but only a complex, unidentifiable mixture was obtained when **1** was treated with piperidine, an observation consistent with the known chemis-



Scheme 2. Reactions of a catalytically generated acyl azolium with various nucleophiles.

try of saturated acyl azoliums and the reluctance of NHC-catalyzed acylations to deliver amide products in the absence of a suitable co-catalyst.[8,12,13] The addition of the kojic acid derivative **7** gives annulation product **8** through a mechanism that we believed to be a Coates–Claisen rearrangement from a hemiacetal intermediate (Scheme 3). Very recent related works by Lupton,[21] Xiao,[22] and Studer,[23] however, invoked a direct 1,4-addition of a nucleophile to the α,β-unsaturated acyl azolium.



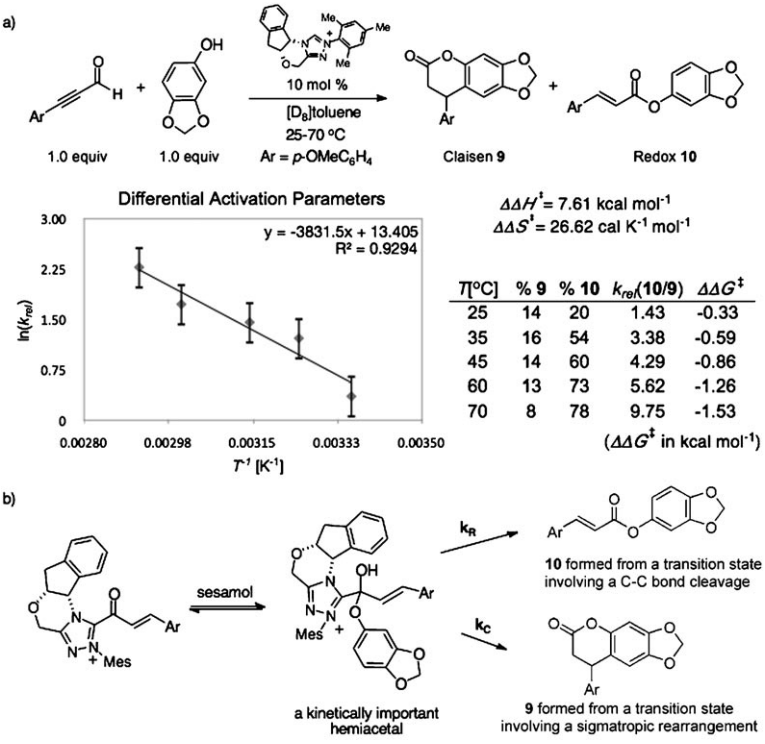
Scheme 3. Activation parameters, rate constants, and rate laws comparison between NHC-catalyzed redox and Claisen reactions.

With the role of the acyl azolium **1** in both the annulation and acylation chemistry established, we sought to further clarify the mechanistic pathways and chemical properties of α,β-unsaturated acyl azoliums by kinetic investigations. In NHC-catalyzed reactions, kinetic studies are often complicated by the complex reaction mechanism and catalyst inhibition events.[15c] Our recent finding that ynals are sufficiently reactive under NHC-catalyzed reactions in the absence of added base[24] simplified the reaction systems and allowed determination of the rate laws and activation parameters for both the esterification and annulation pathways.

This observed rate equation of the redox esterifications reaction is first order in aldehyde, partial order in the triazolium precatalyst, and partial negative order in MeOH (Scheme 3). The negative order in the nucleophile is initially surprising as we had expected that turnover of the acyl azolium to the ester and the NHC would be the rate-determining step. The negative order could be attributed to catalyst inhibition events. The inhibitory effects of the nucleophile were also observed even in the presence of base; the exact nature of this inhibition is not entirely clear.[25] Nonetheless, we were able to rationalize this observed partial rate orders with the derived rate law (see the Supporting Information). From the experimental rate law, we performed an Eyring analysis, which revealed an activation enthalpy ($\Delta H^{\neq}$) of $+23.60\,\mathrm{kcal\,mol^{-1}}$ and an activation entropy ($\Delta S^{\neq}$) of $-2.93\,\mathrm{cal\,K^{-1}\,mol^{-1}}$ for the redox esterification reaction.[26] These activation parameters can be contrasted to those of our recent studies on Coates–Claisen reactions[27] of ynals and enols, in which a large negative $\Delta S^{\neq}$, a lower $\Delta H^{\neq}$, and higher reaction rates with electron-deficient ynals were observed (Scheme 3).

With the role of α,β-unsaturated acyl azolium in the catalytic cycle involving **3** and ynals established, we postulated that the mode of reactivity of NHC-catalyzed reactions of ynals and nucleophilic partner is governed by the pathways available to the corresponding hemiacetal (**1′** or **2′**) derived from the α,β-unsaturated acyl azolium (**1** or **2**). To investigate this hypothesis, we undertook the measurement of the difference in the activation parameters ($\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$)[28] between the Claisen and the redox reactions from the reaction of an ynal with sesamol—a reactant that could undergo both reactions (Scheme 4). We measured a $\Delta\Delta H^{\neq}$ of $7.61\,\mathrm{kcal\,mol^{-1}}$ and a $\Delta\Delta S^{\neq}$ of $26.62\,\mathrm{cal\,K^{-1}\,mol^{-1}}$ from an Eyring analysis of the product ratio ($k_{rel} = \%\mathbf{10}/\%\mathbf{9}$) at five temperatures (see the Supporting Information). These values parallel the data obtained from the rate measurements of the independent processes (Scheme 3) and substantiates our postulate for the role of the kinetically important hemiacetal in the catalytic cycle of both the annulation and esterification reactions. The activation parameters of the competing processes arising for the same hemiacetal intermediate determine the reaction outcome.

Confirmation of the involvement of hemiacetal **V** as the final intermediate in the catalytic cycle of the esterification reaction was obtained by linear free-energy relationship analysis.[29] The Hammett plot revealed that electron-rich ynals underwent esterification faster than their more electrophilic counterparts (Figure 4), an observation consistent with a mechanism featuring the breakdown of hemiacetal **V** as the rate-limiting step in the catalytic cycle (Scheme 5). This



Scheme 4. a) Differential activation parameters measurement from a competition experiment and b) the mechanistic rationale.

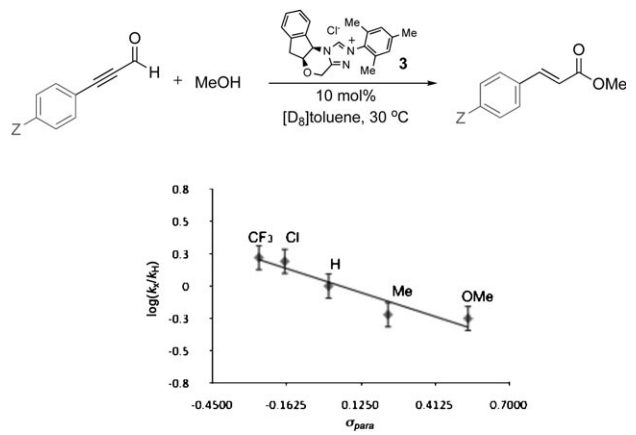
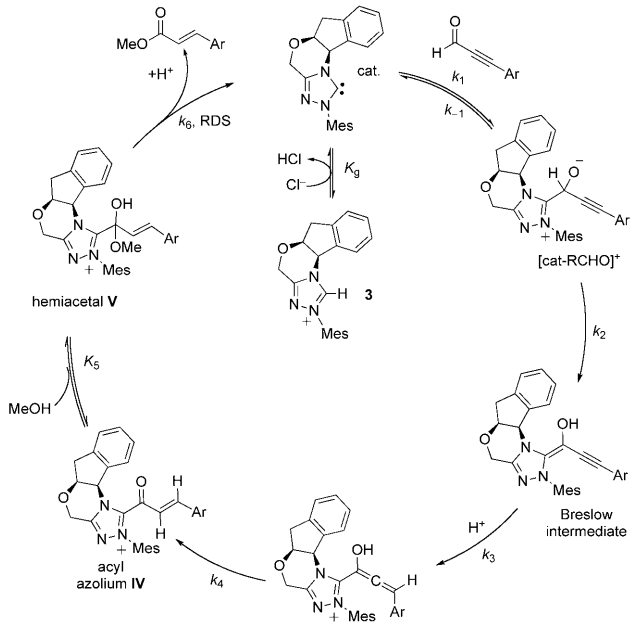


Figure 4. Linear free-energy relationship (Hammett study) for NHC-catalyzed redox reaction with *para*-substituted ynals: $\rho = -0.69$ ($Z = CF_3$, Cl, H, Me, or OMe as indicated in the plot). $y = -0.6901\,x + 0.0326$, $R^2 = 0.903$.



Scheme 5. Breakdown of hemiacetal **V** is the rate-limiting step in NHC-catalyzed redox esterifications of ynals.

intermediate, which we cannot detect, must be in rapid equilibrium with unsaturated acyl azolium **IV** (i.e. the keto form). Although the equilibrium favors the α,β-unsaturated acyl azolium, the reaction is governed by the kinetic profile of the pathways available to the hemiacetal. Electron-withdrawing groups on the acyl azolium stabilize the hemiacetal and decrease the rate of ester formation. This is consistent with the negative ρ value (albeit small) from the Hammett plot for redox esterification reactions (Figure 4), as well as the previous observation that electron-deficient ynals underwent faster Claisen reaction as these compounds have a higher proportion of the hemiacetal intermediate required for the Claisen rearrangement. This finding also corresponds with the studies of Breslow,[7] Daigo,[8] and Owen,[12] who have studied the reactions of simpler acyl azoliums generated under stoichiometric conditions and found the hemiacetal to be kinetically relevant. Our work demonstrates that the unusual reactivities and kinetics observed under catalytic conditions are governed by the unique properties of the catalytically generated α,β-unsaturated acyl azoliums rather than by any of the prior C–C bond formations or protonation steps[30] involved in its formation.

In summary, we have successfully generated and characterized the acyl azolium intermediates key to the reactions of N-heterocyclic carbenes and α-functionalized aldehydes. The confirmation that this intermediate is involved in both NHC-catalyzed acylation and annulation reactions has allowed us to demonstrate that a common intermediate, hemiacetal **V**, is the kinetically important species in both of these processes. These studies reveal the origin of the unique reactivities and selectivities observed in NHC-catalyzed reactions and confirm that NHC-catalyzed annulation reactions of α,β-unsaturated acyl azoliums proceed through a Coates–Claisen reaction rather than a direct Michael addition. Our kinetics investigations provide a rate law (see the Supporting Information) that rationalizes the observed kinetics of both the esterifications and annulation pathways and considers the catalyst generation and inhibition processes that are the origin of the unexpected rate orders in the nucleophiles. These observations will serve as a guideline for future mechanistic investigations and identification of new reactions proceeding through catalytically generated acyl azoliums.

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[1] a) J. L. Moore, T. Rovis in *Topics in Current Chemistry, Vol. 291* (Ed.: B. List), Springer, Berlin, **2009**, pp. 77–144; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655; c) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674–7678; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506–7510; d) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541; e) P.-C. Chiang, J. W. Bode in *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools* (Ed.: S. Díez-González), Royal Society of Chemistry: Cambridge, **2010**, pp. 399–435.

[2] a) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371; b) N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519; c) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127; d) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331–6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205–6208.

[3] a) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, *120*, 8855–8858; *Angew. Chem. Int. Ed.* **2008**, *47*, 8727–8730; b) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371–374; c) H. Inoue, K. Higashiura, *J. Chem. Soc. Chem. Commun.* **1980**, 549–550.

[4] a) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277–280; b) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108–1113; c) X.-N. Wang, H. Lv, X.-L. Huang, S. Ye, *Org. Biomol. Chem.* **2009**, *7*, 346–350.

[5] a) R. Kluger, K. Tittmann, *Chem. Rev.* **2008**, *108*, 1797 – 1833; b) R. Frank, F. Leeper, B. Luisi, *Cell. Mol. Life Sci.* **2007**, *64*, 892 – 905.

[6] a) M. Merski, C. A. Townsend, *J. Am. Chem. Soc.* **2007**, *129*, 15750 – 15751; b) N. Khaleeli, R. Li, C. A. Townsend, *J. Am. Chem. Soc.* **1999**, *121*, 9223 – 9224.

[7] R. Breslow, E. McNelis, *J. Am. Chem. Soc.* **1960**, *82*, 2394 – 2395.

[8] K. Daigo, L. J. Reed, *J. Am. Chem. Soc.* **1962**, *84*, 659 – 662.

[9] F. G. White, L. L. Ingraham, *J. Am. Chem. Soc.* **1962**, *84*, 3109 – 3111.

[10] T. C. Bruice, N. G. Kundu, *J. Am. Chem. Soc.* **1966**, *88*, 4097 – 4098.

[11] G. E. Lienhard, *J. Am. Chem. Soc.* **1966**, *88*, 5642 – 5649.

[12] a) T. C. Owen, A. Richards, *J. Am. Chem. Soc.* **1987**, *109*, 2520 – 2521; b) T. C. Owen, J. N. Harris, *J. Am. Chem. Soc.* **1990**, *112*, 6136 – 6137.

[13] a) M. Movassaghi, M. A. Schmidt, *Org. Lett.* **2005**, *7*, 2453 – 2456; b) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798 – 13799; c) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796 – 13797; d) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190 – 1191.

[14] a) G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2002**, *4*, 3583 – 3586; b) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873 – 3876; c) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131 – 3134; d) S. S. Sohn, J. W. Bode, *Angew. Chem.* **2006**, *118*, 6167 – 6170; *Angew. Chem. Int. Ed.* **2006**, *45*, 6021 – 6024; e) Y. Suzuki, K. Muramatsu, K. Yamauchi, Y. Morie, M. Sato, *Tetrahedron* **2006**, *62*, 302 – 310; f) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418 – 2439; g) P. C. Chiang, Y. Kim, J. W. Bode, *Chem. Commun.* **2009**, 4566 – 4568; h) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628 – 13630; i) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Tetrahedron* **2009**, *65*, 3102 – 3109; j) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992 – 1995.

[15] a) R. Breslow, R. Kim, *Tetrahedron Lett.* **1994**, *35*, 699 – 702; b) Y.-T. Chen, G. L. Barletta, K. Haghjoo, J. T. Cheng, F. Jordan, *J. Org. Chem.* **1994**, *59*, 7714 – 7722; c) M. J. White, F. J. Leeper, *J. Org. Chem.* **2001**, *66*, 5124 – 5131; d) L. Pignataro, T. Papalia, A. M. Z. Slawin, S. M. Goldup, *Org. Lett.* **2009**, *11*, 1643 – 1646; e) a recent NMR study of the Breslow intermediate revealed a structure other than that expected and commonly formulated: A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles, *Angew. Chem.* **2010**, *122*, 7063 – 7063; *Angew. Chem. Int. Ed.* **2010**, *49*, 7120 – 7124.

[16] W. Schrader, P. P. Handayani, C. Burstein, F. Glorius, *Chem. Commun.* **2007**, 716 – 718.

[17] Zeitler first invoked the intermediacy of α,β-unsaturated acyl azoliums in the NHC-catalyzed redox esterification of ynals to give (*E*)-α,β-unsaturated esters. K. Zeitler, *Org. Lett.* **2006**, *8*, 637 – 640.

[18] Our recently reported NHC-catalyzed Coates–Claisen reaction also features α,β-unsaturated acyl azoliums as important intermediate in the catalytic cyle. J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810 – 8812.

[19] a) T. K. Harris, M. W. Washabaugh, *Biochemistry* **1995**, *34*, 14001 – 14011; b) T. K. Harris, M. W. Washabaugh, *Biochemistry* **1995**, *34*, 13994 – 14000; c) M. W. Washabaugh, W. P. Jencks, *Biochemistry* **1988**, *27*, 5044 – 5053.

[20] Carboxylic acids appear to form adducts with triazolium salt **3** through an addition to C-2. This is similar to the behavior of other triazolium salts, see: a) 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; b) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 2860 – 2861. The formation of the carboxylic acid is suppressed by employing activated molecular sieves.

[21] a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176 – 14177; b) this processes was characterized as a rearrangement in a most recent report: L. Candish, D. W. Lupton, *Org. Lett.* **2010**, *12*, 4836 – 4839.

[22] Z. Q. Zhu, J. C. Xiao, *Adv. Synth. Catal.* **2010**, *352*, 2455 – 2458.

[23] S. De Sarkar, A. Studer, *Angew. Chem.* **2010**, *122*, 9452 – 9455; *Angew. Chem. Int. Ed.* **2010**, *49*, 9266-9269.

[24] The discussion regarding NHC-catalyzed reaction without added base has been reported in Ref. [18]. Our current understanding is that the counter anion serves the role of base in generating a trace amount of the active NHC species, which initiates the catalytic cycle.

[25] For various discussions regarding the interaction of NHCs and protic nucleophiles, see: a) N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5813 – 5840; b) M. A. Schmidt, P. Müller, M. Movassaghi, *Tetrahedron Lett.* **2008**, *49*, 4316 – 4318; c) N. Kuhn, E. Mallah, C. Maichle-Mößmer, M. Steimann, *Z. Naturforsch. B* **2009**, *64*, 835 – 839; d) L. Myles, R. Gore, M. Spulak, N. Gathergood, S. J. Connon, *Green Chem.* **2010**, *12*, 1157 – 1162.

[26] The observed non-integral rate orders may be attributed to an inhibition event. The rationalization of the observed rate law is discussed in the rate law derivation (see the Supporting Information). From the derivation, the rate law may be reformulated as: rate $= k_{obs}$[ynal]^1[precatalyst **3**]^1[MeOH]^0. This reformulation changes the activation entropy for the redox esterification reaction to $+3.95\,cal\,K^{-1}\,mol^{-1}$ while the activation enthalpy remains unchanged. In any case, the change in $\Delta S^{\neq}$ does not affect the interpretation of the proposed mechanism.

[27] R. M. Coates, B. D. Rogers, S. J. Hobbs, D. P. Curran, D. R. Peck, *J. Am. Chem. Soc.* **1987**, *109*, 1160 – 1170.

[28] For a similar approach to the measurements of the difference in the activation parameters between two competing pathways, see: M. Nigam, M. S. Platz, B. M. Showalter, J. P. Toscano, R. Johnson, S. C. Abbot, M. M. Kirchhoff, *J. Am. Chem. Soc.* **1998**, *120*, 8055 – 8059.

[29] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195.

[30] The redox reaction–protonation step is excluded from being rate limiting based on isotopic labeling experiments, which show no kinetic isotope effect for protonation (see the Supporting Information).

