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On the Mechanism of N-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums

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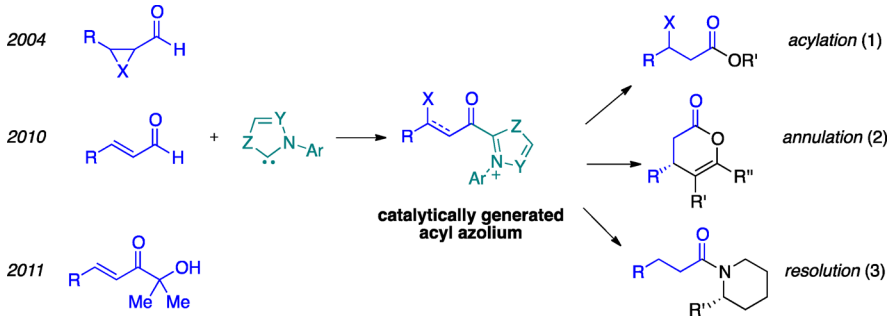

Catalytic reactions promoted by N-heterocyclic carbenes (NHCs) have exploded in popularity since 2004 when several reports described new fundamental reactions that extended beyond the long-studied generation of acyl anion equivalents. These new NHC-catalyzed reactions allow chemists to generate unique reactive species from otherwise inert starting materials, all under simple, mild reaction conditions and with exceptional selectivities. In analogy to transition metal catalysis, the use of NHCs has introduced a new set of elementary steps that operate via discrete reactive species, including acyl anion, homoenolate, and enolate equivalents, usually generated by oxidation state reorganization ("redox neutral" reactions). Nearly all NHC-catalyzed reactions offer operationally simple reactions, proceed at room temperature without the need for stringent exclusion of air, and do not generate reaction byproducts. Variation of the catalyst or reaction conditions can profoundly influence reaction outcomes, and researchers can tune the desired selectivities through careful choice of NHC precursor and base.

The catalytically generated homoenolate and enolate equivalents are nucleophilic species. In contrast, the catalytically generated acyl azolium and α,β-unsaturated acyl azoliums are electrophilic cationic species with unique and unprecedented chemistry. For example, when generated catalytically, these species transformed an α-functionalized aldehyde to an ester under redox neutral conditions without coupling reagents or waste. In addition to providing new approaches to catalytic esterifications, acyl azoliums offer unique reactivities that chemists can exploit for selective reactions.

This Account focuses on the discovery and mechanistic investigation of the catalytic generation of acyl azoliums and α,β-unsaturated acyl azoliums. These chemical species are fascinating, and their catalytic generation is an important development. Studies of their unusual chemistry, however, date back to the intense investigation of thiamine-dependent enzymatic processes in the 1960s. Acyl azoliums are remarkably reactive in acylation chemistry and are unusually chemoselective. These two properties have led to a new wave of reactions such as redox esterification reaction (1) and the catalytic kinetic resolution of challenging substrates (i.e., 3). Our group and others have also developed methods to generate and exploit α,β-unsaturated acyl azoliums, which have facilitated new C–C bond-forming annulations, including a catalytic, enantioselective variant of the Claisen rearrangement (2). From essentially one class of catalysts, the *N*-mesityl derived triazolium salts, researchers can easily prepare highly enantioenriched dihydropyranones and dihydropyridinones.

Although this field is now one of the most explored areas of enantioselective C–C bond forming reactions, many mechanistic details remained unsolved and in dispute. In this Account, we address the mechanistic inquiries about the characterization of the unsaturated acyl triazolium species and its kinetic profile under catalytically relevant conditions. We also provide explanations for the requirement and effect of the *N*-mesityl group in NHC catalysis based on detailed experimental data within given specific reactions or conditions. We hope that our studies provide a roadmap for catalyst design/selection and new reaction discovery based on a fundamental understanding of the mechanistic course of NHC reactions.

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1. Introduction

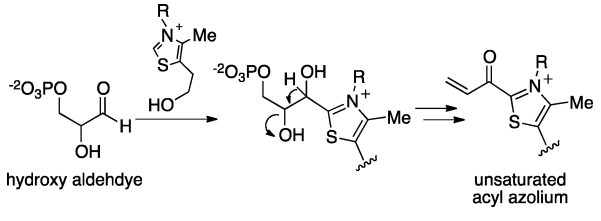
Catalysis in organic chemistry makes possible not only an enhancement of reaction rate or selectivity but also the generation of intermediates distinct from the inherent chemistry of the substrates. In the field of transition metal catalysis, chemists are now accustomed to complex reaction mechanisms that proceed via unexpected intermediates, often mediated by changes in the metal's oxidation state. Within the last ten years, the field of N-heterocyclic carbene (NHC) catalysis has introduced a new set of elementary mechanistic steps operating via the intermediacy of discrete reactive species generated by internal reorganization of oxidation states. The rich and unprecedented chemistry enabled by NHC catalysis engenders some of the most intriguing and complicated mechanistic pathways. There are many reviews of NHC-catalyzed reactions,[1] but none deals explicitly with mechanistic aspects. This Account documents our discovery and mechanistic investigation of two NHC-catalyzed reaction modes, the catalytic generation of acyl azoliums and the chemistry of α,β-unsaturated acyl azoliums.

2. Catalytic Generation of Acyl Azoliums

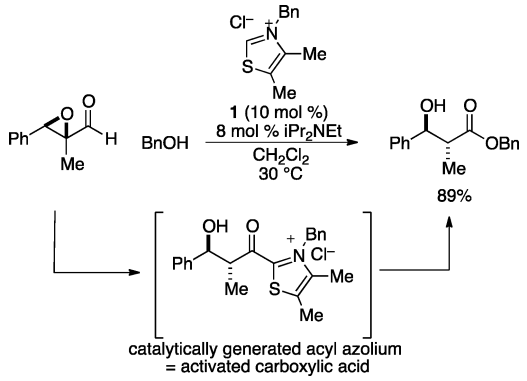
At the founding of our research group in 2003, catalytically generating activated carboxylic acids was part of a program aimed at discovering new ester and amide-bond forming reactions. Although there was contemporary work on generating enolates and other carbon nucleophiles for C−C bond forming reactions,[1] there was little precedent for generating an electrophilic species from easily handled precursors without the need for coupling reagents. As with so many innovations in organic chemistry, our inspiration came from Nature, in particular a report from Townsend on clavulanic acid biosynthesis via thiamine-catalyzed generation of α,β-unsaturated acyl azolium (Scheme 1).[2]

Townsend's mechanistic proposal led directly to our first report of catalytic generation of acyl azoliums and their use in esterifications. As substrates, we chose α,β-epoxy aldehydes due to the high interest in the β-hydroxyesters products (Scheme 2).[3] We were pleased to find that treatment of these

SCHEME 1. Townsend's Proposal for the Thiamine-Mediated Biosynthesis of Clavulanic Acid



SCHEME 2. Catalytic Generation of Acyl Azoliums as Activated Carboxylate in NHC Catalysis



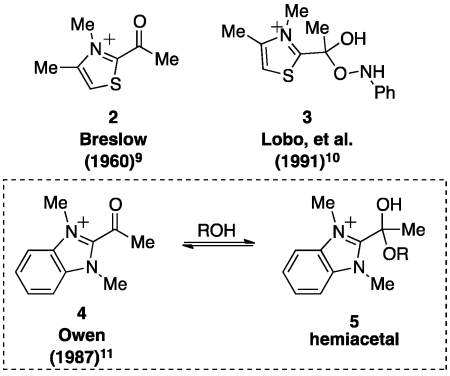
aldehydes with alcohol in the presence of simple thiazolium catalyst led to *anti*-β-hydroxyesters in good yield, without stoichiometric reagents or byproducts. Contemporaneously, Rovis et al. reported a similar generation of activated carboxylates using α-halo aldehydes.[4] These reactions actually had a chemical precedent in the conversion of chloral to dichloroacetic acid with cyanide reported by Otto Wallach[5] in 1873! These reactions are mechanistically simple, involving an addition of the NHC to an aldehyde followed by an E2-elimination to form an enol and an acyl azolium.[6] This paradigm, redox esterification of aldehydes bearing an α-heteroatom, has emerged as a general platform, viable for many substrates classes.[1b,c] The surprise was that while alcohols and thiols made outstanding nucleophiles, amines did not, a telltale sign of the acyl azolium's unusual nature.

Ten years later, the remarkable chemistry of acyl azoliums has been exploited for numerous valuable transformations including chemoselective acylation[7] and the catalytic, kinetic resolution of amines.[8] Many important contributions included preparations, characterizations, and studies of acyl imidazolium and thiazolium, beginning with Breslow in 1960 (i.e., **2**).[9] These revealed three important features of this species: (1) its reluctance to acylate amines,[10] (2) its facile acylation reaction in water and alcohol,[11] and (3) the equilibrium between acyl azolium and its hemiacetal (Scheme 3).[12] Driven by the role of acyl azolium in various biosynthesis with thiamine-dependent enzymes,[2,13] this insight is critical to properly understanding the contemporary chemistry of NHC-catalyzed reactions.

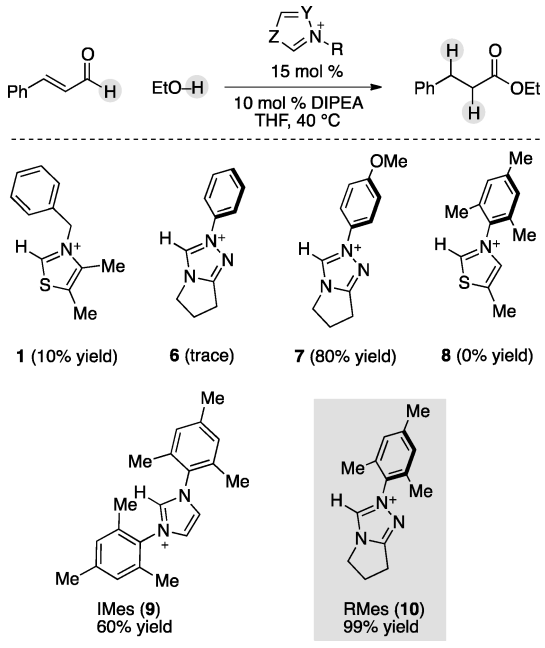
3. NHC-Catalyzed Reactions of α,β-Unsaturated Aldehydes

In late 2003, a target of our research was the catalytic generation of acyl azoliums from α,β-unsaturated aldehydes (Scheme 4). Although this process is conceptually similar to

SCHEME 3. Acyl Azoliums and Their Hemiacetals



SCHEME 4. Catalyst Development for Redox Esterifications of α,β-Unsaturated Aldehydes



the redox esterification of α,β-epoxyaldehydes, it is mechanistically quite different. The internal redox reaction of unsaturated aldehydes requires formation of the conjugated Breslow intermediate followed by protonation at the distal position.[14] In a well-chosen intramolecular model reaction, thiazolium catalysts were effective, but only under forcing conditions. For simpler substrates such as cinnamaldehyde, thiazolium precatalysts became ineffective, but the *N*-mesityl substituted imidazolium-derived carbene **9** (IMes) and methoxytriazolium salt **7** gave some conversion. By combining the features of both the triazolium core and the sterically hindered *N*-mesityl substitution, we succeeded in developing an extremely effective NHC for the generation of saturated activated carboxylate and many other reactions from enals.[15] This catalyst (**10**), which we call "RMes" (triazolium mesityl), was prepared[16] according to modified protocols from Knight and Leeper and Rovis et al.[17] It has proven to be the key to unlocking the rich chemistry of NHC-catalyzed reactions.

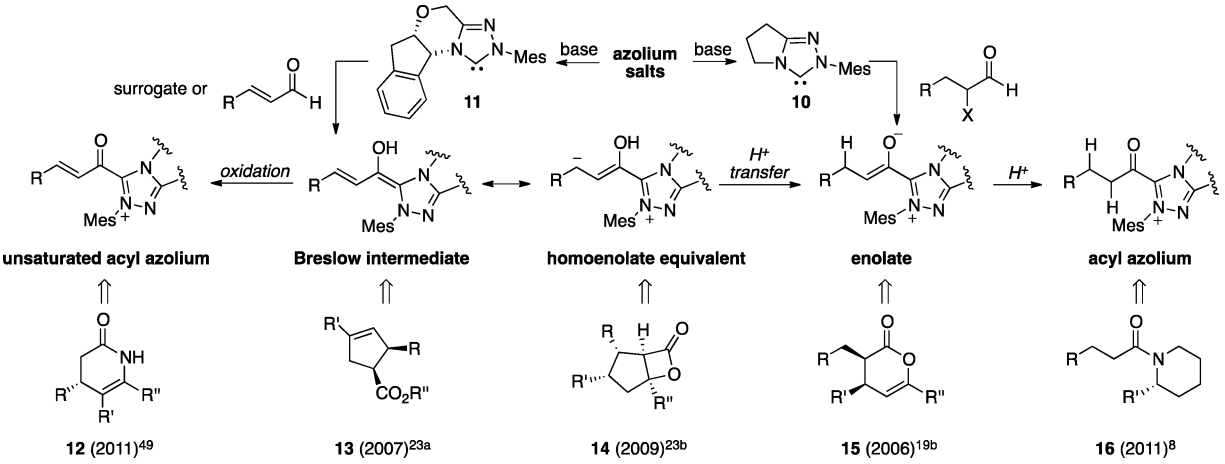
As a referee correctly pointed out, the redox esterification of enals is not a particularly useful transformation; we were taking a high-value starting material and converting it to a rather mundane product. But this simple transformation contained within it an entirely new field of catalytically generated reaction modes (Scheme 5). Seemingly small changes in the catalyst structure can play an enormous role in the reaction pathway, product, and stereoselectivity (Scheme 6). Early on, we found that imidazolium-derived NHCs, such as IMes, favored the homoenolate pathway, making possible the synthesis of γ-lactones and γ-lactams by the catalytic generation of a homoenolate equivalent.[18] In contrast, RMes favored the protonation of the homoenolate[15] to generate the enolate equivalent, as first disclosed for inverse electron demand Diels–Alder reactions.[19] In this case, a chiral *N*-mesityl substituted triazolium salt derived from aminoindanol proved to be highly effective for enantioselective catalysis. We were not alone in these discoveries, and many of our reports occurred contemporaneously with those of Rovis,[4] Glorius,[20] and Nair.[21]

4. Why the *N*-Mesityl Triazolium Catalyst?

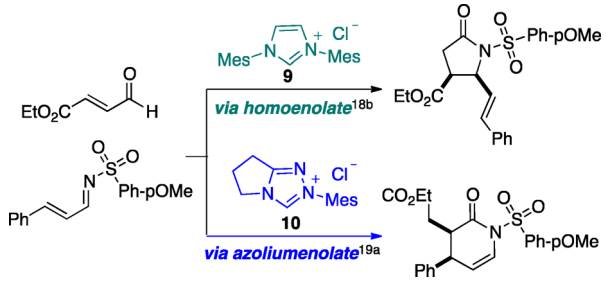
The *N*-mesityl substituted triazolium NHCs have proven to be the preferred catalyst for nearly all NHC-catalyzed reactions other than benzoin and Stetter processes. Precatalysts lacking the *N*-mesityl group very often fail to give the desired product. For many years, we did not understand the underlying mechanistic basis for this requirement. To better design new catalysts and reactions, we needed to understand the role of the *N*-mesityl group. Careful examination of the literature and competition experiments revealed the pattern in Scheme 7.[22] Without the *N*-mesityl group, poor yields or much slower reaction rates were obtained with α,β-unsaturated aldehydes[23] (Scheme 7a,b). In contrast, simple aldehydes could usually be used with other NHCs (Scheme 7d,e). In addition, other substrates for NHC catalysis such as chloroaldehydes,[4,19] ketenes,[24] and esters[25,26] did not require the mesityl group. But even in these cases, the *N*-mesityl catalyst **11** often proved to be better in terms of selectivity (i.e., Scheme 7c).[27]

We recognized that the "*N*-mesityl effect" was essential when the conjugate Breslow intermediate was involved in the reaction course. Reactions that did not involve the

SCHEME 5. Reactive Intermediates and Products Accessible from NHC Catalysis



SCHEME 6. Selective Catalysis in NHC Reactions



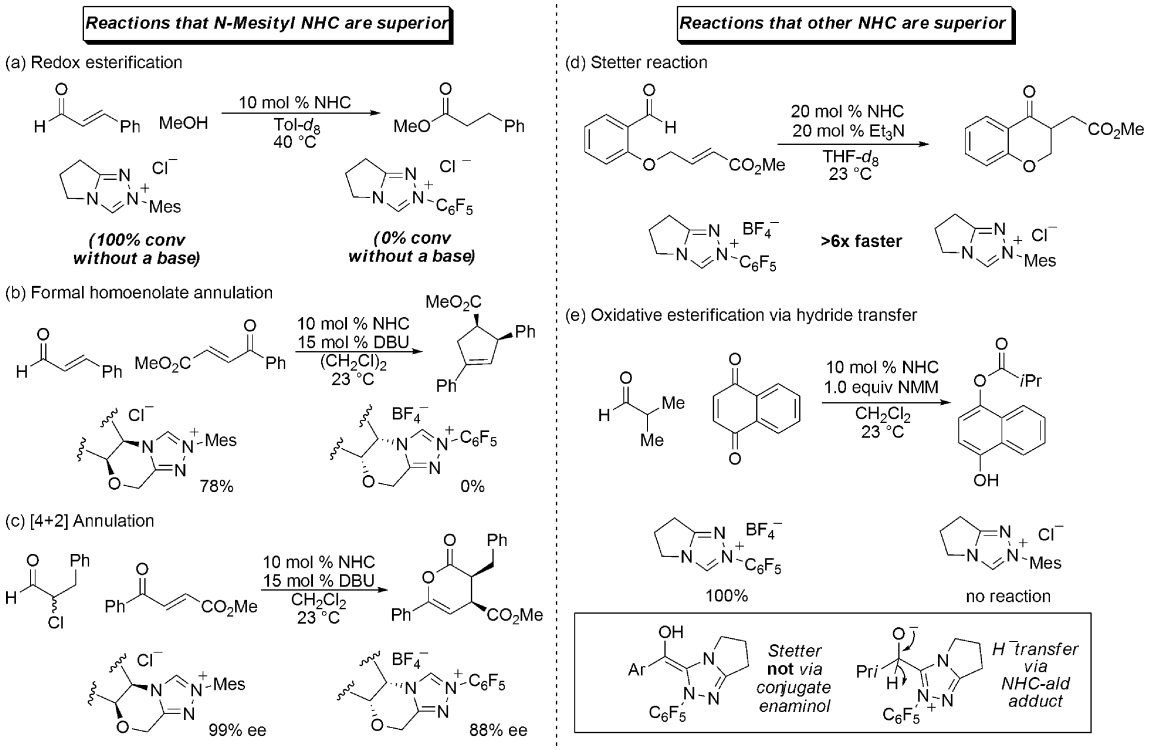
conjugated Breslow intermediate, those involving elimination[6] or hydride transfer[28] from the initial NHC-aldehyde adduct, could occur in the absence of this effect. What was particularly puzzling for us was the fact that *N*-mesityl triazolium **10** remained mostly protonated[29] in the presence of base such as DBU (equilibrium lies to the left), while the *N*-C_6F_5 triazolium **17** was almost completely deprotonated (Scheme 8a).

How could a catalyst that existed in such a small extent be a superior catalyst for any substrate? We first tested the hypothesis that *N*-mesityl NHC was unique due to the irreversible formation of the Breslow intermediate by subjecting deuterated cinnamaldehyde (**18**) to a standard esterification reaction in the presence of MeOH (Scheme 8b). If the formation of the Breslow intermediate was reversible for enal, H/D exchange should occur from the protonation of the Breslow intermediate (**19**), and protioaldehyde (−CHO) should be spectroscopically observed (as in the case of the Breslow intermediate generated from simple aldehyde such as benzaldehyde). But this was not the case for our reaction conditions. An additional clue came from α-hydroxyenones, as easily prepared surrogates to enals, which also required *N*-mesityl NHCs.[30] The success of this reaction necessitated that the NHC did not dissociate from the substrate before the retro-benzoin reaction (Scheme 8c). Rovis[31] and Sunoj[32] also concurred that the formation of the Breslow intermediate could be irreversible.

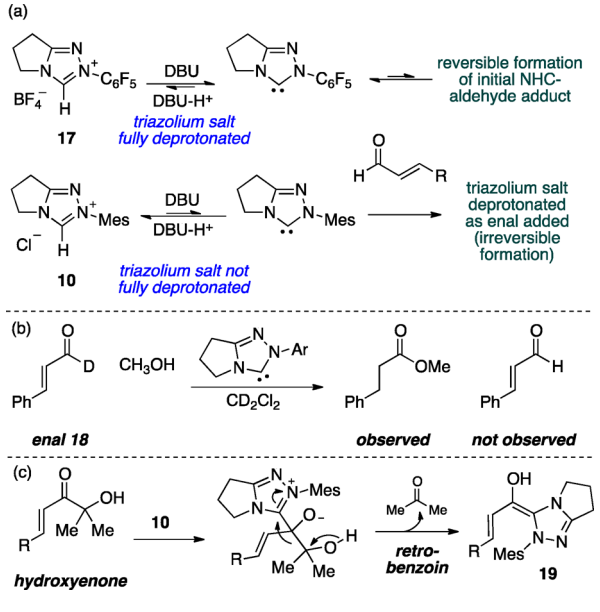
We could also eliminate the possibility that the difference in the NHC catalytic activity came from the acyl azolium downstream in the cycle from the acylation reactions of enal vs α-halo aldehyde (Scheme 9). If the acyl azolium were the culprit, the outcome would have been identical. This led us to examine the possibility that the formation of the Breslow intermediate was irreversible with the *N*-mesityl catalysts. Titration experiments with 2.2 equiv of cinnamaldehyde revealed that the formation of the *N*-C_6F_5 NHC−aldehyde adduct is reversible. In contrast, the *N*-mesityl triazolium salt was not deprotonated unless in the presence of an enal and formed an irreversible adduct with cinnamaldehyde.

The effect of the *N*-mesityl group in NHC catalysis is therefore kinetic, resulting from both steric and electronic factors. Catalyst **10** alters the reaction profile in two ways. First, the addition of this nucleophilic carbene to enals is essentially irreversible due to the steric impact of the mesityl group. The carbene in the NHC−enal adduct is a slower leaving group when it bears an *N*-mesityl group. Second, the resulting conjugated Breslow intermediate is more electron-rich and therefore a more reactive nucleophile. Our findings are consistent with those of Mayr[33] and of Smith and O'Donoghue.[34] The utility of *N*-mesityl NHCs has led to impressive advances from other research groups including the use of saturated aldehydes,[35] applications in natural product syntheses,[36] and new triazolium salts for challenging transformations.[37] Scheme 10 offers a rough guideline for catalyst selection.

SCHEME 7. Observation for Catalyst Preference in NHC-Catalyzed Reactions



SCHEME 8. Mechanistic Probes



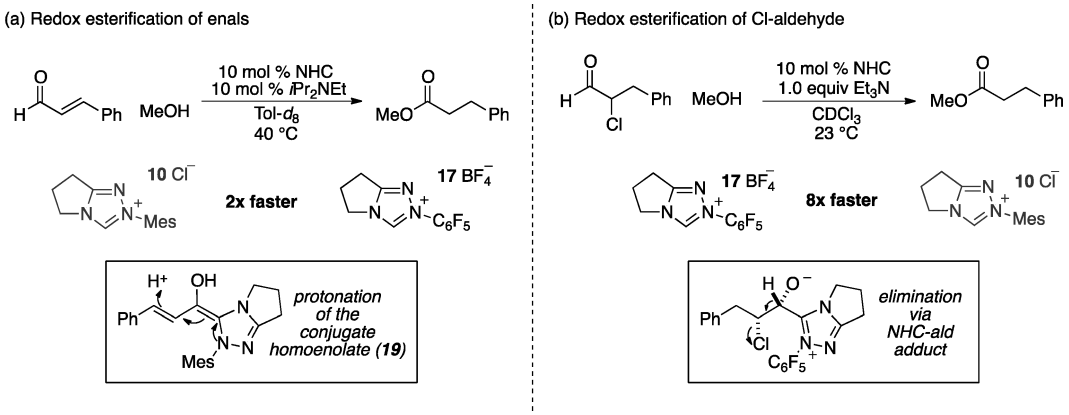
5. The Chemistry of α,β-Unsaturated Acyl Azoliums

The biosynthetic proposal of Townsend[2] tantalizingly hinted at the synthetic utility of α,β-unsaturated acyl azoliums (Scheme 1). This intermediate had been invoked in the redox reaction of ynals[38] reported by Zeitler in 2006,[39] but no successful attempts at trapping this electrophilic species at the β-carbon had appeared. We explored this idea by examining 2-naphthol as a nucleophile (Scheme 11). Two pathways were possible: (1) the O-acylation of 2-naphthol and (2) an annulation process involving sequential C−C and C−O bond formations.[40] Triazolium salts bearing an *N*-aryl group with one ortho substituent (**11** and **22**) delivered the annulation product **21** in high yield and enantioselectivity. Thiazolium salt and imidazolium salt were ineffective. Interestingly, electron-deficient aminoindanol-derived triazolium salt **25** was found to be effective for the other pathway, yielding ester **20** as the sole product.

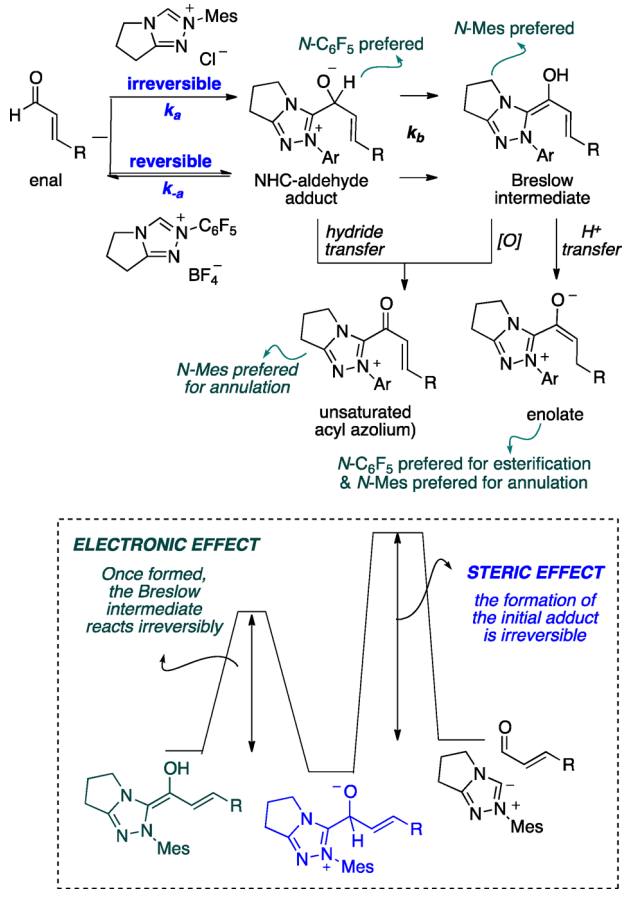
Encouraged by this, we investigated the scope of the nucleophile. We initially assumed this reaction occurred via 1,4-addition for the C−C bond formation, followed by lactonization. We were therefore surprised to find that good nucleophiles such as **30**−**33** failed to deliver any product (Scheme 12). The only exception was *N*-methylindole **26**, which underwent conjugate addition (**27**) when a stoichiometric amount of NHC and a terminal nucleophile were used. These observations were the starting point for us to reassess the reactivity of α,β-unsaturated acyl triazolium.

We recognized that enolic nucleophiles such as pyruvate ester and kojic acid were excellent partners (Scheme 13). The omission of the cocatalytic base had a beneficial effect for

SCHEME 9. Relative Rate Profiles of Two Conceptually Related Redox Esterification Reactions



SCHEME 10. A Roadmap for Catalyst Selection and a Conclusion Based on Our Study

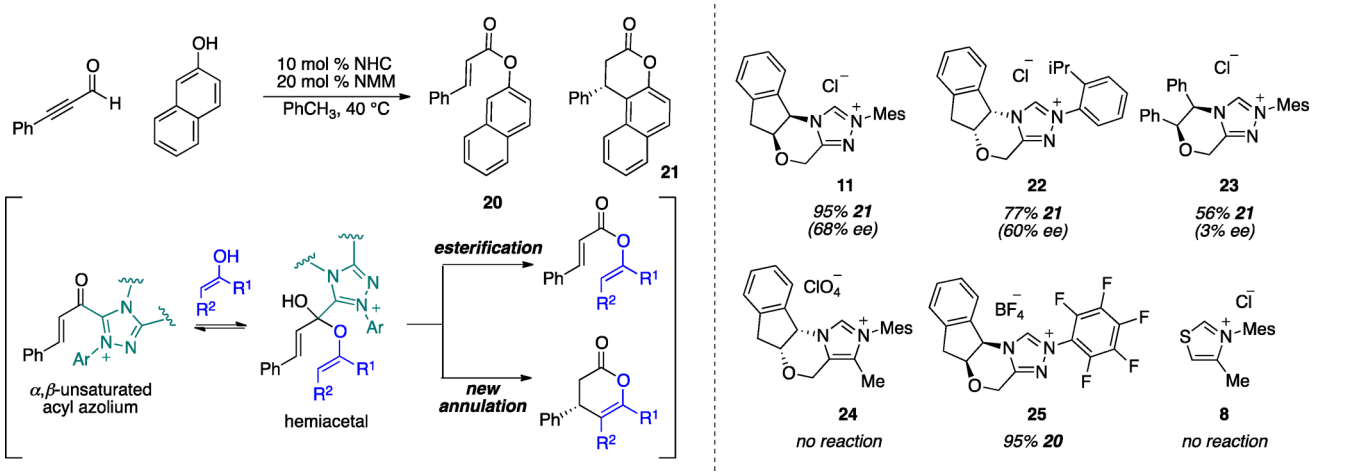


some reactions whose products (i.e., **35**) were prone to racemization; Cl^- was sufficient due to the irreversible addition to ynal. In all cases, the desired dihydropyranones were obtained in good yield and enantioselectivity. Just prior to our first communication,[41] Lupton's group[25] demonstrated a similar annulation concept using α,β-unsaturated ester and IMesCl (**9**) as the catalyst. They have since impressively expanded the chemistry of α,β-unsaturated acyl azoliums to the synthesis of deoxyloganin,[42] formal [4 + 2] cycloadditions,[43] and other related rearrangement cascades.[44]

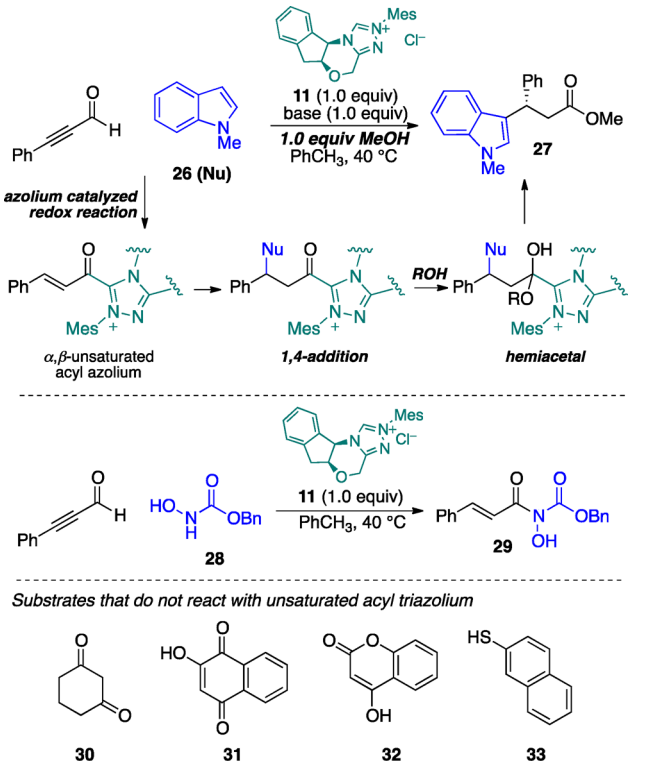
While these redox-neutral reactions were attractive, they required preparation of the ynal substrates. We wished to generate the same acyl azolium from the simpler α,β-unsaturated aldehyde. We identified oxidant **38**, reported by Kharasch[45] and popularized by Studer, as the best oxidant[46] for the oxidative Claisen reaction. Shortly thereafter, Studer[47] and Xiao[48] also reported reactions of α,β-unsaturated acyl azolium with 1,3-dicarbonyl compounds. We pursued the conceptually related annulation between enals and enamines (Scheme 14).[49] The Breslow intermediate was oxidized to the corresponding α,β-unsaturated acyl azolium, which engaged in an aza-Claisen rearrangement with the enamine to form unprotected dihydropyridinone[50] (**39**–**40**), in good yield and enantioselectivity. We also discovered that *N*-sulfonyl protected imine could be used as an enamine precursor[51] for the aza-Claisen annulation with trisubstituted enals,[52] a challenging class of substrate in NHC catalysis.[15] This reaction afforded highly substituted N-protected dihydropyridinones (**41**, **42**) in high yield and stereoselectivity. The concept of intercepting α,β-unsaturated acyl azolium for C–C bond forming reaction has exploded into a vibrant area of research.[35b,53]

In parallel with our studies of the NHC-catalyzed Claisen reaction, we aimed to decipher its mechanism. Examination of the literature revealed that Coates had earlier encountered the same mechanistic conundrum[54] for the related reaction of enolic compounds and acrolein diethyl acetal. He first suggested that the reaction occurred via a Michael-type addition, but later proposed, via careful kinetic studies together with Curran, a Claisen-type rearrangement from

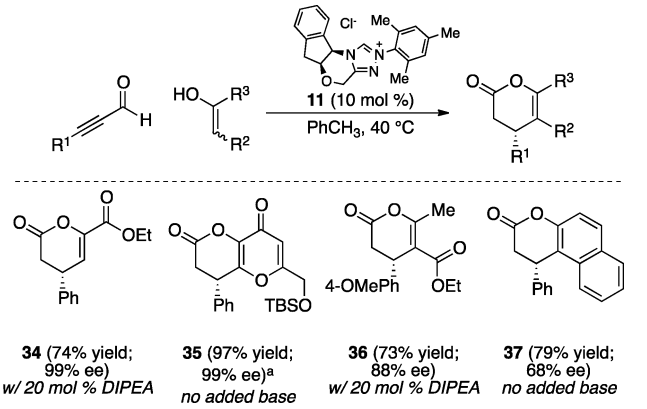
SCHEME 11. The Use of Enol Nucleophile and the Initial Catalyst Screening for Selective Catalysis



SCHEME 12. Attemps at 1,4-Addition



SCHEME 13. NHC-Catalyzed Enantioselective Claisen Annulations of Ynals and Enols

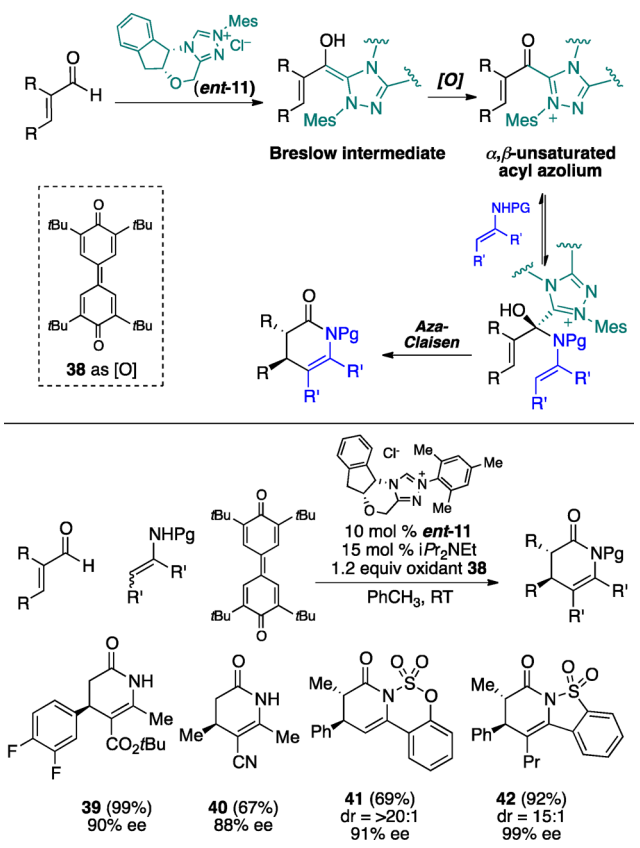


[a]The yield and ee were determined after ring-opening with MeOH due to the product's stability.

an acetal intermediate as the operative mechanism.[55] Stille[56] faced a similar situation when he studied the annulation processes between enamine and α,β-unsaturated acid derivatives, based on much earlier works of Stork[57] and Hickmott.[58] In the aza-variant, the final conclusion was less clear, and Stille coined the term "aza-annulation" to signify the difficulty in differentiating between the two mechanisms. What was clear, nonetheless, according to Hickmott's papers was that N-acylation occurred preferentially to C-alkylation.

Following in their footsteps, we proposed that the NHC-catalyzed annulations of α,β-unsaturated acyl azolium **43** proceeded by an initial reversible 1,2-addition of the enol or enamine to the acyl azolium (**44**), followed by a C−C bond formation (path B, Scheme 15). In contrast, 1,4-addition of the nucleophile to the acyl azolium would be irreversible (path A, Scheme 15). Either pathway would arrive at the same intermediate **45**, which tautomerized to **46** and cyclized to turnover the catalyst and liberate the product. Our proposal was based on kinetic evidence showing the reaction to be essentially zero order in the enol[59] and having activation enthalpy and entropy consistent with those of Coates and Curran (**49** to **50**).[55] The experimental and derived rate laws allowed us to conclude that [3,3]-rearrangement from the hemiacetal (or the collapse of a tight ion-pair) was the rate-determining step. Moreover, we observed and characterized the key α,β-unsaturated acyl triazoliums and studied

SCHEME 14. NHC-Catalyzed Enantioselective Annulations of Enals and Enamines

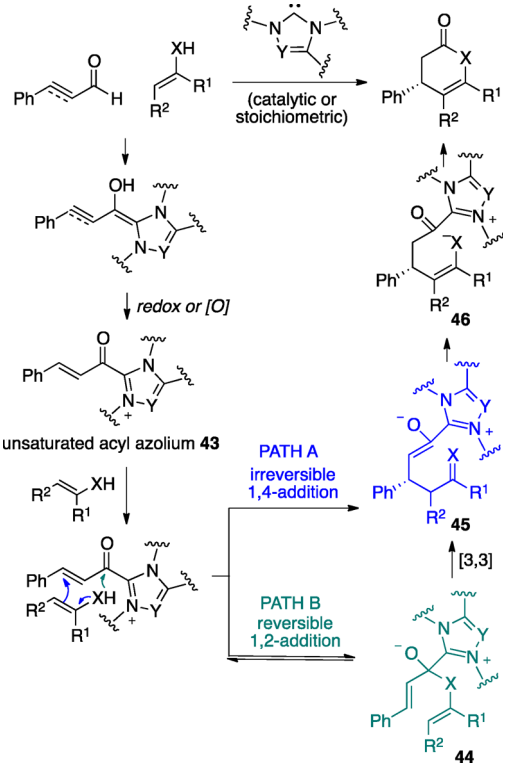


the kinetic profile of the related redox esterification reaction as a point of comparison.[60]

Most convincingly, sesamol as a substrate partitioned between C–C bond forming annulation product **47** and C–O bond formation of ester **48**. The differential activation parameters revealed that the activation barrier to the rearrangement reaction had a high entropic penalty ($\Delta\Delta S^{\ddagger}$), typical for a highly organized transition state. The outcome of the reaction could be adjusted by varying the electronic structure of the catalysts (Scheme 16). Based on an experiment in which α,β-unsaturated vinyl ester underwent cyclization without a crossover,[42] the Lupton group also revised their proposal to support sigmatropic arrangement as the key C–C bond forming step over a direct conjugate addition. Both our and Lupton's experiments illustrated that esterification and annulation products originated from a common hemiacetal intermediate (i.e., **44**); the alternative interpretation would require two distinct competing pathways: one unimolecular and the other bimolecular.

Extensive computational investigations in collaboration with the Schoenebeck group[61] provided a model for the stereoinduction and details on intermediates, transitions

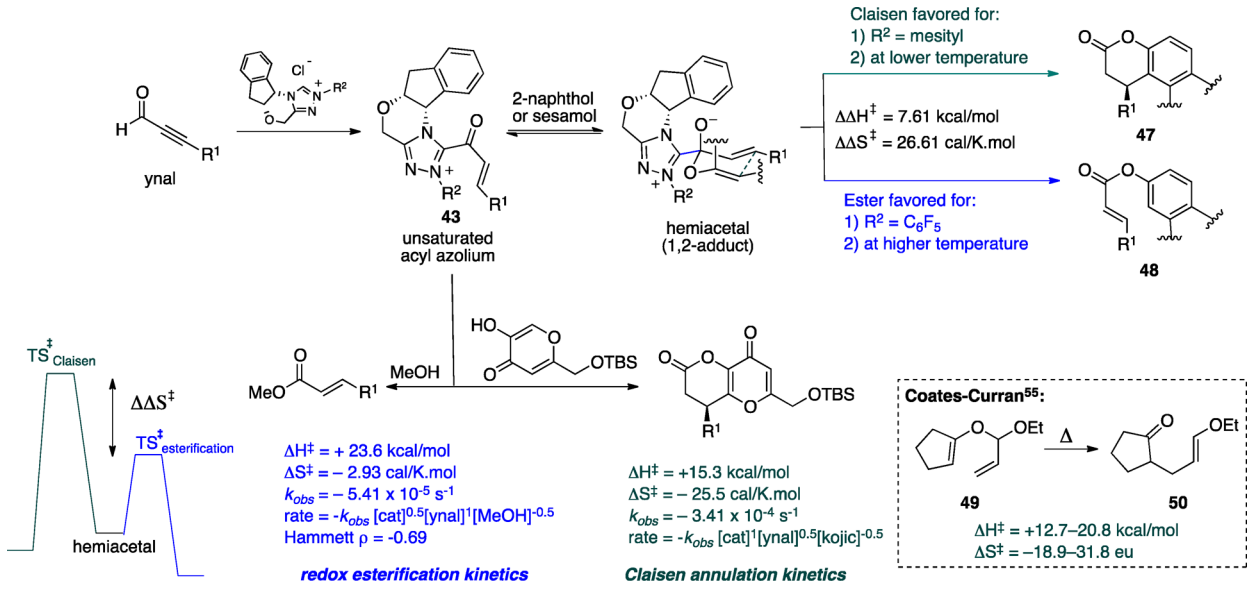
SCHEME 15. Possible Mechanistic Pathways



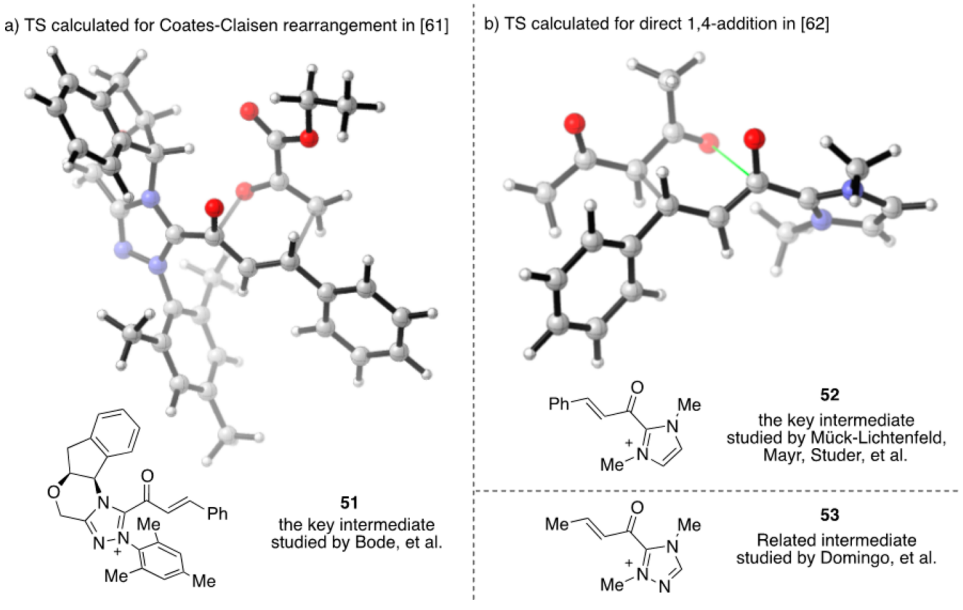
states, and favored protonation states. These findings demonstrated that, for the investigated substrates, both the Coates–Claisen and conjugate addition mechanisms had identical highly ordered transition state (TS) geometries, arising from the favorable O···C=O interaction. Later, Studer, Mayr, and Mück-Lichtenfeld[62] prepared and obtained the X-ray structure of α,β-unsaturated acyl imidazolium **52**. Using it as a stoichiometric substrate, they performed 1,4-additions with various nucleophiles and determined the electrophilicity of **52**. Furthermore, they and Domingo[63] separately attempted computational studies of the 1,2-addition intermediates but could not locate a transition state. Schoenebeck[61] and others[64] found a similar 1,2-addition intermediate for a triazolium-derived system, which was observed following the intrinsic reaction coordinate of the transition state. Scheme 17 compares the Coates–Claisen transition state (TS) with the reported 1,4-conjugate addition TS.

We never doubted that α,β-unsaturated acyl azoliums could undergo conjugate addition.[2b,13,40,43] As stated earlier, our original entry into the catalytic C–C bond forming chemistry of α,β-unsaturated acyl azolium (**51**) was attempted 1,4-additions; only when these reactions failed with nucleophiles that could not form enolic or enamine

SCHEME 16. The Kinetic Profile of NHC-Catalyzed Reactions with Unsaturated Acyl Azolium



SCHEME 17. Three Intermediates[61−63] Studied and Two TSs Showing Similar Features



tautomers did we consider the alternative Coates−Claisen mechanism.[65] The mechanistic difference probably arises from the nature of different azolium salts, an issue we have repeatedly observed.[19a,22,23b,23c] For example, we have noted the lower reactivity of acyl imidazoliums in esterification (also 1,2-addition) reactions; this was our original impetus to develop the *N*-mesityl triazolium salts.[15] As with many aspects of catalysis, seemingly small changes in the ligand or catalyst structure had a dramatic influence on the mechanistic course, which could be deployed for catalyst-controlled regio-, chemo-, or product-selective synthesis.

6. Conclusion

What started as a relatively simple, perhaps even naïve, redox esterification of enals opened a portal to a new world of efficient, enantioselective, and mechanistically complex catalytic reactions. The *N*-mesityl triazolium-derived NHCs proved to be the key for unlocking this protocol, leading to a flood of new discoveries that spewed forth faster than we

could properly study them. It is therefore encouraging to witness a recent surge of interest in understanding the key intermediates involved in the complex catalytic cycles of NHC catalysis, leading to the structural characterization of the azolium enolate,[66] aldehyde–NHC adduct,[34,67] and Breslow intermediate[68] or analogues.[69]

We hope the brief glimpse of the mechanistic insight from our research, along with pioneering studies of Lapworth,[70] Breslow,[9] Teles,[59,67,69b] and others,[66,69] have provided some small help toward larger goals. With many secrets unlocked and dozens of new reactions reported, the way forward to new reactions becomes clearer. If NHC catalysis can utilize simpler feedstock materials, it may begin to fulfill the promise of using small organic molecules to not only replace the use of transition metals in certain cases but also open new pathways not available by any method.

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FOOTNOTES

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The authors declare no competing financial interest.

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