Catalytic Reactions with N-Mesityl Substituted N-Heterocyclic Carbenes

Chapter 9

Catalytic Reactions with *N*-Mesityl Substituted N-Heterocyclic Carbenes

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1. Introduction

Reactions catalyzed by N-heterocyclic carbenes have been known longer than the N-heterocyclic carbenes themselves. The thiamin catalyzed benzoin reaction engendered great excitement over its unusual – and for a while incomprehensible – mechanism, but the connection between the thiazolium ylide identified as the key nucleophilic catalyst and its characterization as an N-heterocyclic carbene grew only slowly. Nowadays, the idea of nucleophilic carbenes acting as highly versatile catalysts is widely accepted, and new NHC-catalyzed transformations appear almost weekly in the primary literature. In addition to a renaissance in benzoin and Stetter chemistry, NHC-catalyzed reactions are now most closely associated with the remarkable collection of transformation of α,β-unsaturated and α-functionalized aldehydes. This field has exploded since 2004 and now constitutes one of the most dynamic areas of homogeneous catalysis.

Even a brief survey of the literature reveals one recurring catalyst motif of *N*-mesityl substituted N-heterocyclic carbenes, with the triazolium derivatives capturing the majority of the catalysts used. In this chapter we seek to give an overview of the development of these catalysts, a survey of the diverse and mechanistically intricate reactions they catalyzed, and an explanation for the origin of the superiority of these catalysts on new generation of NHC-catalyzed reactions.

1.1. Historical background

Liebig reported the first Benzoin dimerization of aldehyde catalyzed by cyanide ion in 1833[1], but it was not until 1903 that Lapworth elucidated the mechanism of this remarkable reaction.[2] These seminal papers were important not only for the nascent field, but they also constituted the first full mechanistic elucidation of an organic

reaction. In 1943, almost one hundred years after Liebig's report of the cyanide catalyzed benzoin reaction, Ugai[3] disclosed the use of thiamine (Vitamin B1) as the catalyst for the same transformation (Figure 9.1). This unexpected finding emerged from biological studies of thiamine-dependent enzymes involved in many biological pathways.[4] Breslow[5] extensively studied the mechanism of the thiamine-catalyzed benzoin reaction and proposed the structure of the key enaminol intermediate, now commonly referred to as "the Breslow intermediate." While these efforts were thorough, reexaminations of the mechanism has continued and revealed complicated nuances in the rate-determining step[6] and the nature of the reactive intermediates.[7]

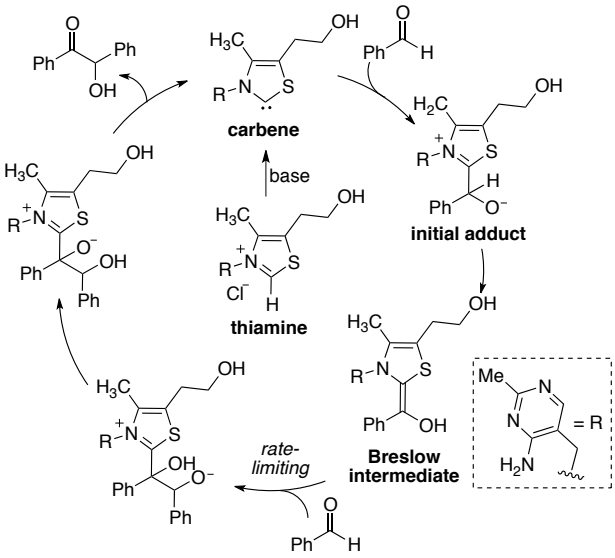


Figure 9.1. The mechanism of thiamine-catalyzed benzion reaction

1.2. State of the art prior to 2004

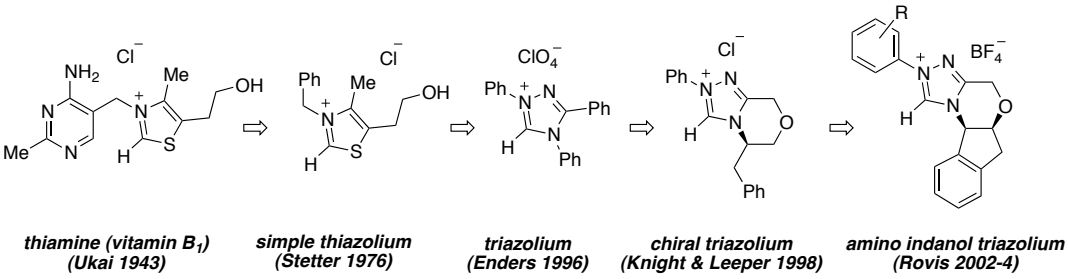
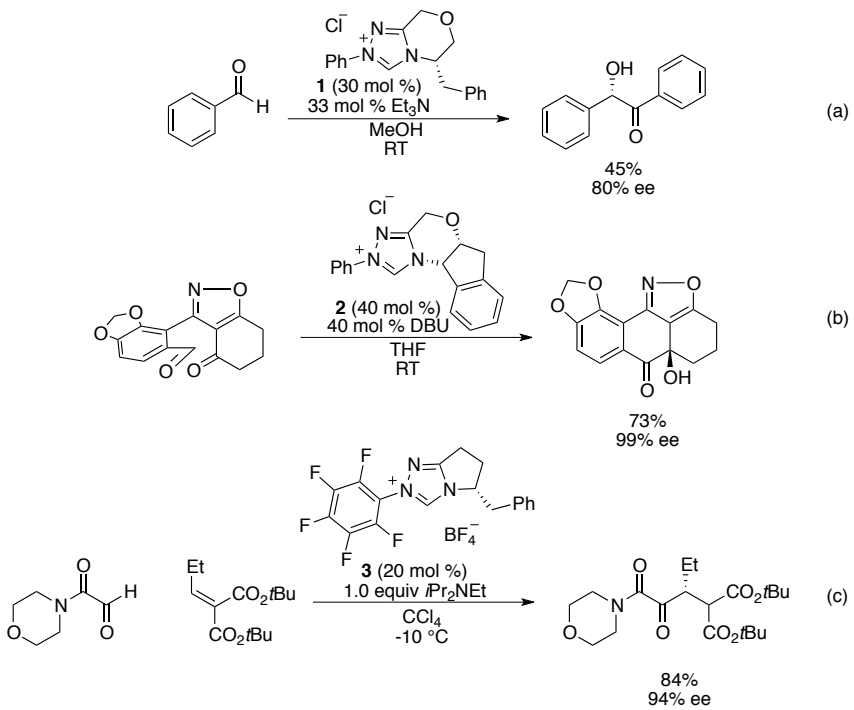


Figure 9.2. The progression of NHC precatalysts

Ugai's report encouraged improvements in the efficiency of the Benzoin reaction and attempts to control the stereochemistry. The first major innovation arrived when Stetter simplified thiamine by replacing the heterocycle with an aryl or alkyl groups in 1976.[8] Another twenty years progressed before Enders and Teles disclosed a new catalyst design and detailed studies of a triazolium salt (Figure 9.2).[9] Contemporaneously, Miyashita introduced imidazolium NHC catalyst in his studies.[10] The introduction of both the imidazole and triazole cores for N-heterocyclic carbene sparked the surge in finding more reactive and essentially led to the development of chiral NHC precatalysts for both the benzoin and the related Stetter reactions.[11] Enders and Teles were able to improve the enantioselectivity of both processes in comparison to the first attempt by Sheehan with a chiral thiazolium salt[12], but it was still many years before an effective catalyst was to be found. Another breakthrough in designing chiral triazolium salt for carbene catalysis arose from the use of chiral amino alcohol, reported by Knight and Leeper in 1998. Chiral triazolium salts such as **1** were found to be effective for dimerization of aldehyde, affording the products up to ca. 80% ee (Scheme 9.1a).[13] A significant improvement was reported by Rovis, who employed chiral aminoindanol for the preparation of a series of catalyst of type **2**,[14] which were competent for highly enantioselective intramolecular Stetter[15] and benzoin[16] reactions (Scheme 9.2b). Modifying the protocol from Knight and Leeper, Rovis was able to introduce the electron-withdrawing *N*-C_6F_5 moiety into the chiral triazolium salts (i.e. **3**) and used it to catalyze a highly enantioselective intermolecular Stetter reaction (Scheme 9.1c).[17] The modular nature of this new procedure[18] allowed the generation and identification of diverse, new NHC catalysts for challenging transformations.



Scheme 9.1

1.3. *N*-Mesityl catalysts as the key innovation

At the outset of our studies in 2003, we postulated that the combination of a N-heterocyclic carbene catalyst and α-functionalized aldehyde could unlock catalytically generated reactive species beyond that of the traditional "acyl anion equivalent" formed in the benzoin and Stetter reactions. One of our primary goals was to develop esterification and amidation reactions without the need for coupling reagents, which we believed could be achieved by the catalytic generation of "acyl azoliums," which would serve as equivalents to activated esters. One of our initial test reactions for this process was the conversion of cinnamaldehyde to dihydrocinnamic esters. Initially, we believed that the success of this reaction would require us to suppress competing benzoin and Stetter reactions. Our thinking was that bulky groups on the NHC precatalyst would lead to the formation of a Breslow intermediate too sterically hindered to undergo reactions via the acyl anion equivalent. We reasoned

that the bulky mesityl moiety would shepherd the reactions of the conjugated Breslow intermediate to the distal position. Indeed, NHC-precatalysts lacking *N*-mesityl groups gave poor results for the desired reaction (Figure 9.3). The bis *N*-mesityl imidazolium catalyst **8** was a good catalyst, but we found that this catalyst was poorly effective for the redox esterification of other α,β-unsaturated aldehydes. By combining the *N*-mesityl substituent and the triazolium core of **7**, we synthesized the novel catalyst **9**, which has emerged as the prototypical catalyst for a remarkable range of new NHC-catalyzed reactions.[19] As this chapter will show, nearly all of these reactions require the *N*-mesityl group or similar substituent[20] for effective reactions.

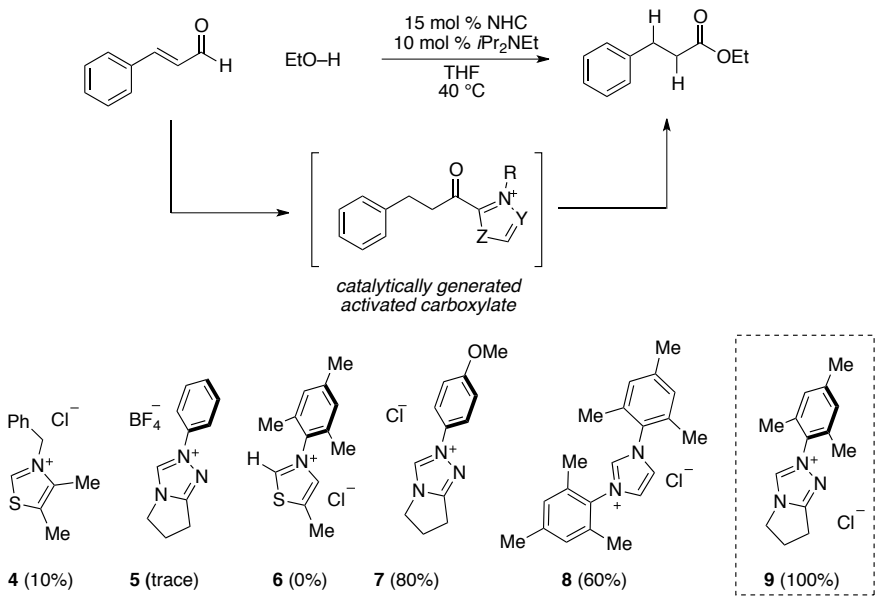


Figure 9.3. Our impetus for developing *N*-mesityl NHC catalysts

Further synthetic effort from our group along with mechanistic investigations have led to the development of the chiral *N*-mesityl triazolium salt **10**[21] and a chiral *N*-mesityl imidazolium salt **11** (Figure 9.4).[22] After our original report in 2005, other researches have extended the use of the mesityl moiety to furnish new catalyst type with interesting reactivity (i.e. **12**[23] or **13**[24]). Arguably the *N*-mesityl catalysts, especially triazolium salts **9** and **10**, are the field's key innovation and have emerged as the most

versatile and widely used NHC catalysts. Figure 9.4 depicts the syntheses of azolium salts bearing the *N*-mesityl moiety.

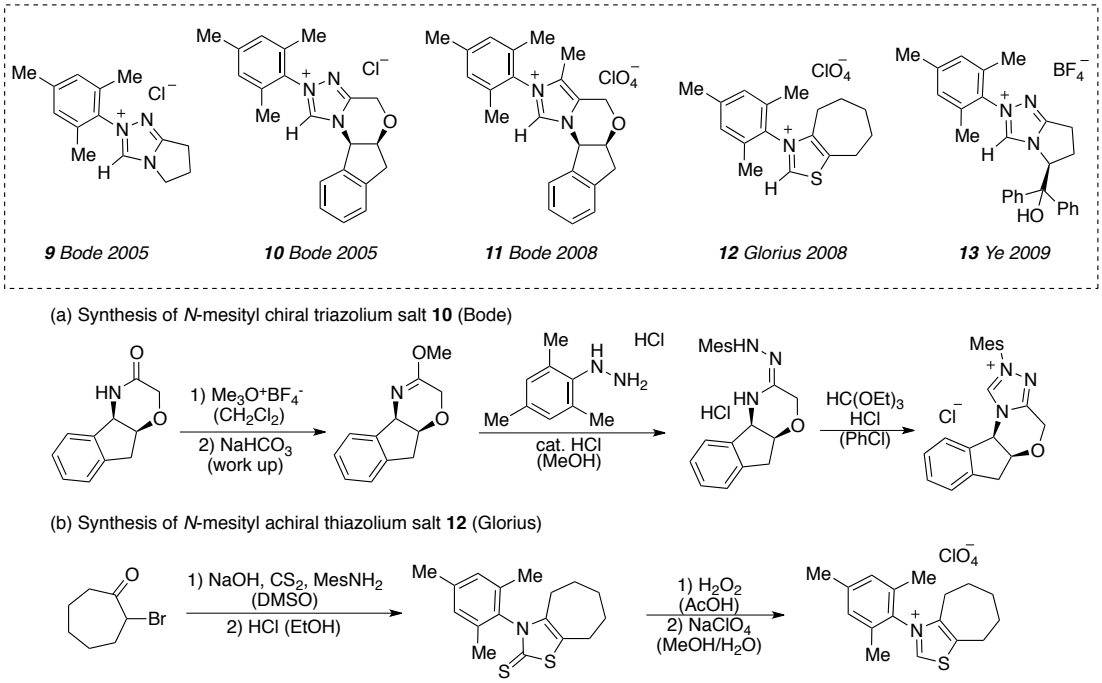


Figure 9.4. N-mesityl NHC catalysts and their syntheses

2. The *N*-Mesityl Group: A Mechanistic Aspect

2.1. Catalytic Generation of Reactive Species via *N*-Mesityl NHCs

The exceptional nature of N-heterocyclic carbene as small organic molecule catalyst lies in their ability to access multiple, catalytically generated reactive species from the simple combination of commercial substrate and catalyst. For example, five discrete reactive intermediates can be accessed from an *N*-mesityl catalyst precursor and an α,β-unsaturated aldehyde (Figure 9.5)! The acyl anion, homoenolate, and enolate equivalents serve as nucleophilic species, and the acyl azolium and unsaturated acyl azolium are excellent electrophiles with remarkable chemistry. Most importantly, all five intermediates can be accessed in catalytic, enantioselective reactions by employing a chiral NHC precursor. Previously, our group has reviewed the chemistry of these catalytically generated species,[25] but we were not able to explain the

mechanistic rationale for the exceptional catalytic activity of triazolium NHCs bearing the *N*-mesityl moiety. In the subsequent sections, we will elucidate this phenomenon and highlight recent, exciting chemistry that these catalysts offer.

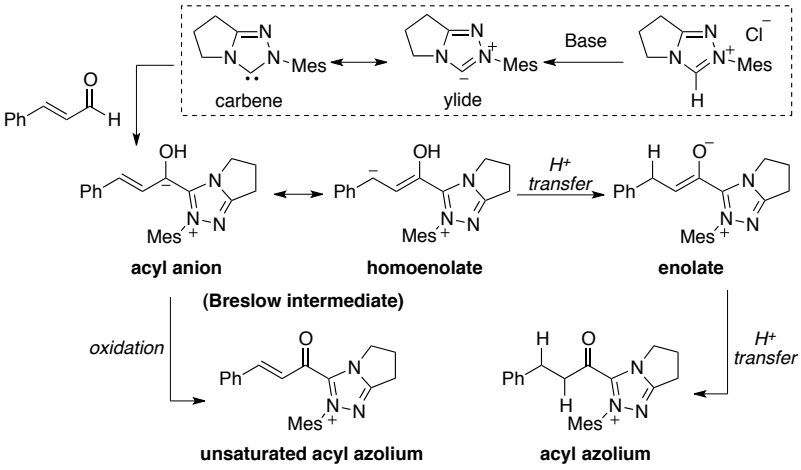


Figure 9.5. Catalytic generation of five discreet intermediates via NHC catalysis

2.2. The Kinetic Effect of the *N*-Mesityl Group

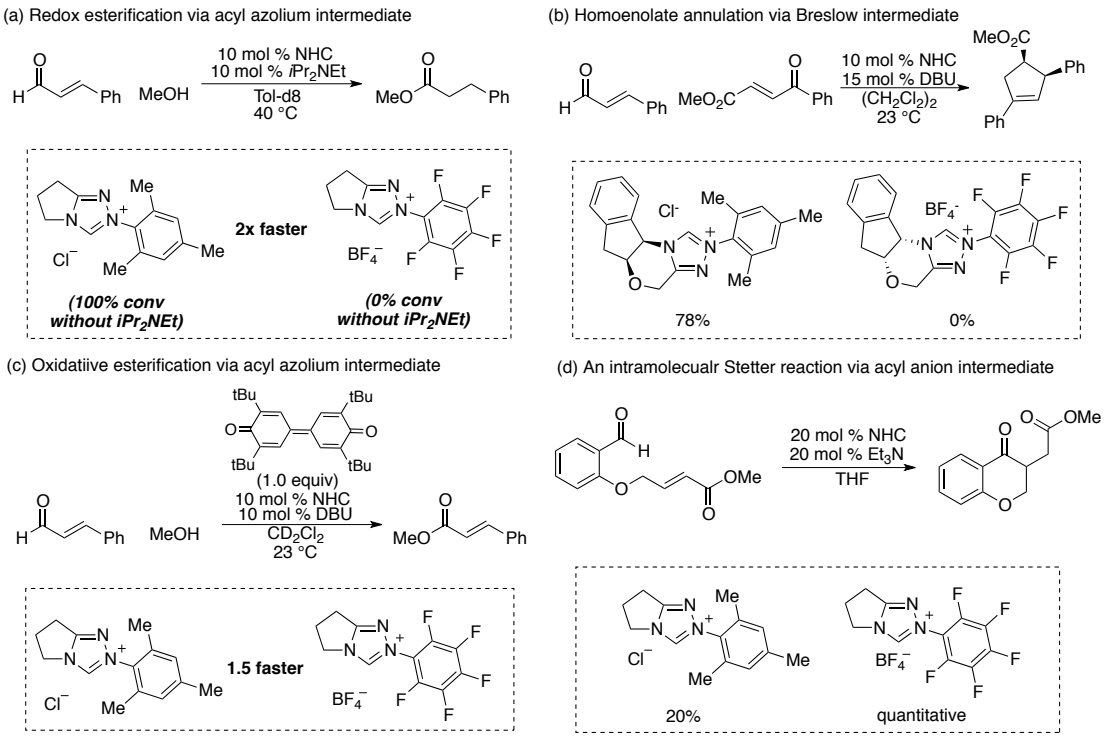


Figure 9.6. Representative reactions and activities of *N*-mesityl vs. *N*-C_6F_5 NHCs

A brief survey of the literature, along with accumulated experience, confirms that essentially all reactions with α,β-unsaturated aldehydes require the *N*-mesityl catalysts (Figure 9.6). While other NHC catalysts such as those bearing *N*-C_6F_5 groups have proven to be useful for many transformations (*vide supra*), they are less reactive or in certain cases displayed no reactivity for enals.

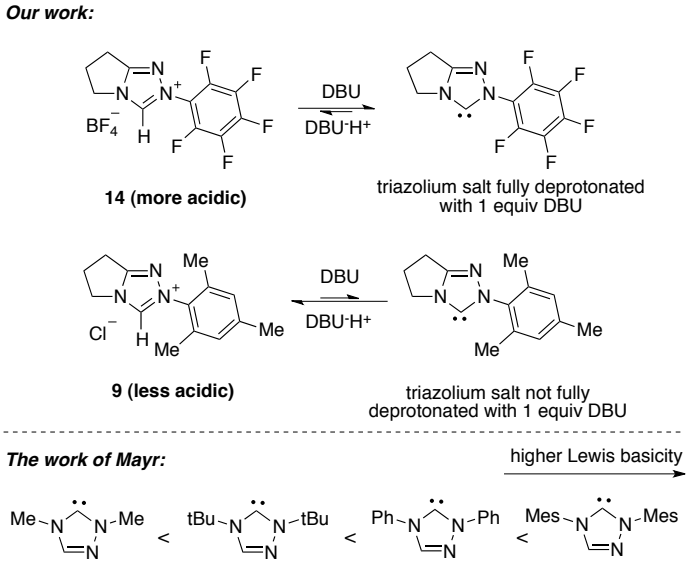


Figure 9.7. Relative basicity and acidity of various N-heterocyclic carbenes

In 2008 Rovis reviewed the effect of the various *N*-aryl substitution on triazolium derived NHCs in terms of reactivity, acidity, and enantioselectivity for various Stetter reactions.[26] Triazolium salts bearing highly electron-donating group such as the *N*-mesityl group are less acidic than the *N*-C_6F_5 variants. Indeed, titration experiments revealed complete deprotonation of **14** by DBU in CD_2Cl_2, while the extent of deprotonation for **9** was negligible (Figure 9.7).[27] We were therefore very surprised to find that the *N*-mesityl salts were able to catalyze many transformations even in the absence of an external base additive, while other classes of azoliums salts could not do![28] These findings raised the question of how a triazolium salt that is much less acidic generate enough active carbene for a given catalytic cycle? Taking together this

knowledge and the reactions in Figure 9.6 as mechanistic probes, we undertook careful comparison studies by catalyst analog synthesis, labeling experiments, and consideration of all the elementary steps. Contemporaneous with our investigation, Mayr reported that the *N*-mesityl carbenes are not very nucleophilic but are highly Lewis basic (Figure 9.7).[29]

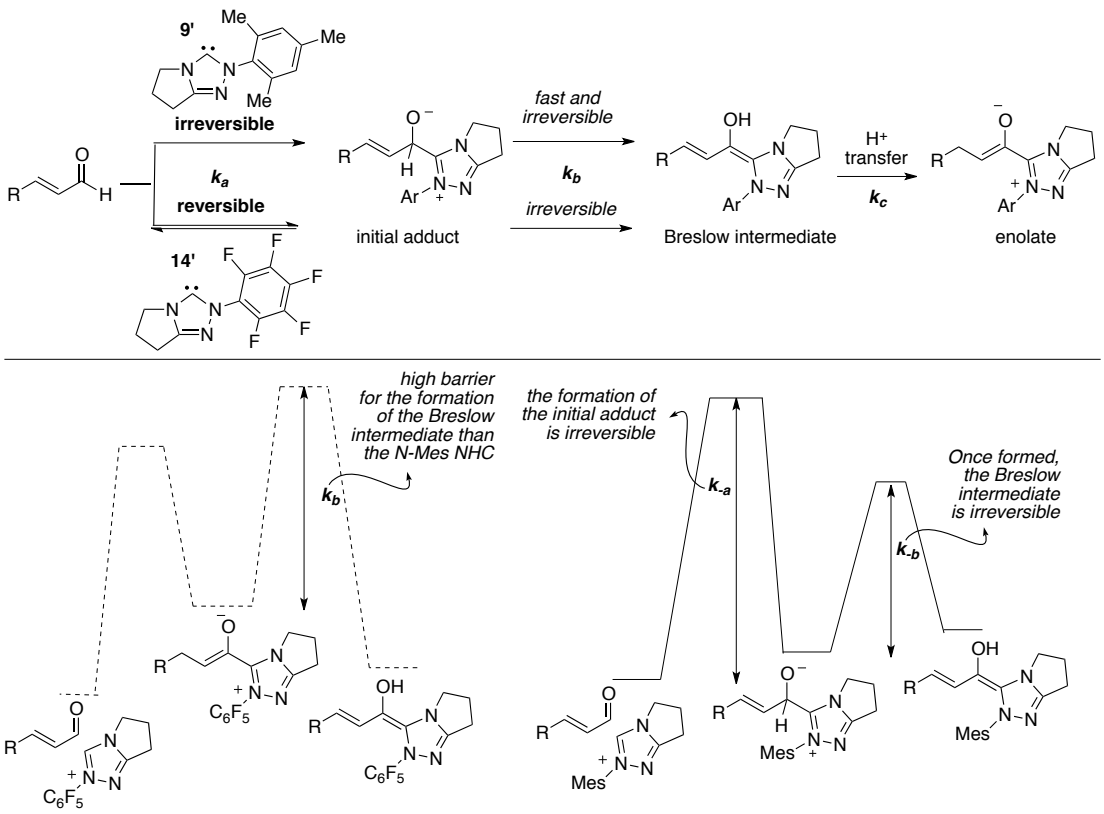
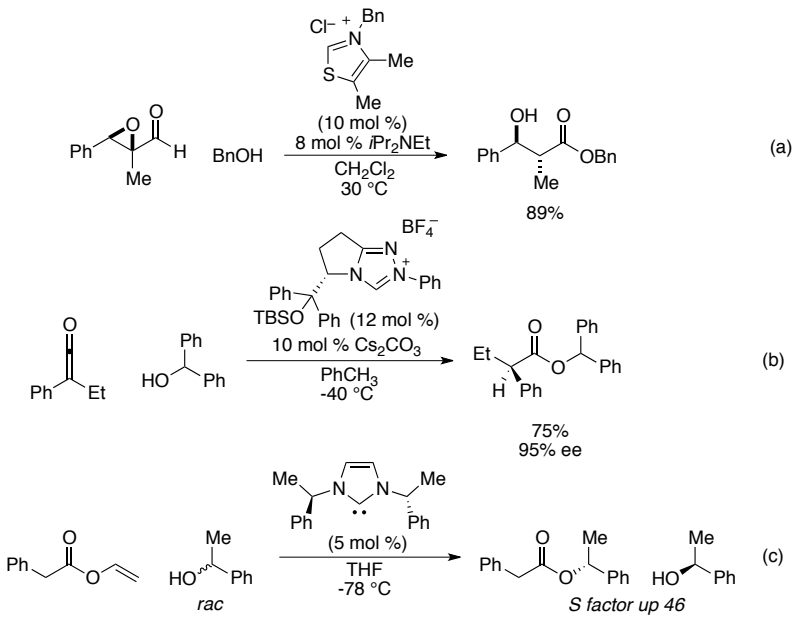


Figure 9.8. The kinetic effects of the *N*-mesityl group.

Our investigations revealed that the *N*-mesityl group alters the kinetic profile of the catalytically generated reactive intermediates, rather than dramatically influencing their thermodynamic stability. This effect has its origin in both the steric and the electronic nature of the catalyst (Figure 9.8). First, the formation of the initial aldehyde-NHC adduct is essentially irreversible with the *N*-mesityl catalyst, but is reversible for less sterically demanding catalysts (i.e. **14**). The steric bulk of the mesityl moiety appears to prolong the lifetime of the intermediate and make this NHC

a slower leaving group, which renders the barrier of the back reaction higher in energy (k_{-a}; Figure 9.8). Second, the formation (k_b) of the Breslow intermediate (i.e. homoenolate or acyl anion equivalents) is accelerated and appears to also be irreversible. The electron-rich nature of the mesityl moiety results in a highly reactive Breslow intermediate towards electrophile or oxidant. This step (k_c) for the *N*-mesityl catalyst is faster than the other NHCs. The two energy diagrams in Figure 9.8 summarize our finding and compare the reaction profile for the *N*-C_6F_5 and *N*-mesityl catalysts.



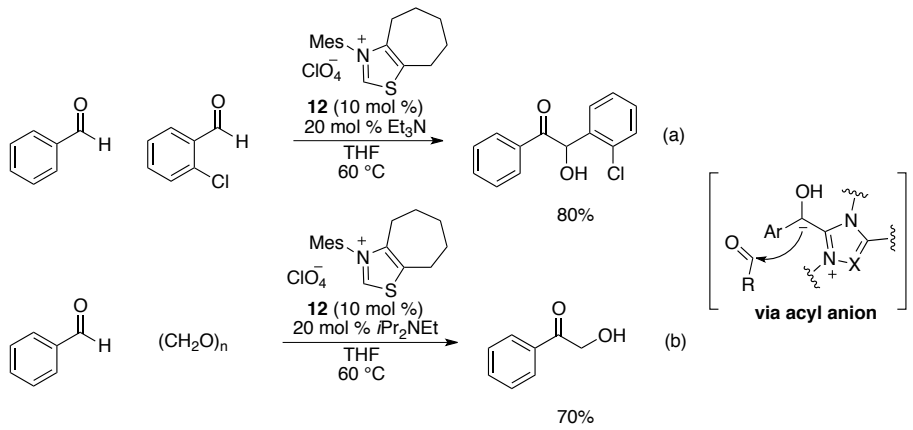
Scheme 9.2

It is worth noting here that other triazolium salts do show good catalytic reactivity for substrates other than enals. α-epoxyaldehyde[30], α-haloaldehyde[31], ketene[32], acyl silane[33], and ester[34] have been all shown to be competent reactions partners in various NHC catalyzed acylation and annulation[35] reaction with simpler NHC precatalysts (Scheme 9.2). We consider the fact these substrates do not necessarily require the kinetic enhancement by the mesityl moiety to be "the exceptions that prove the rule."

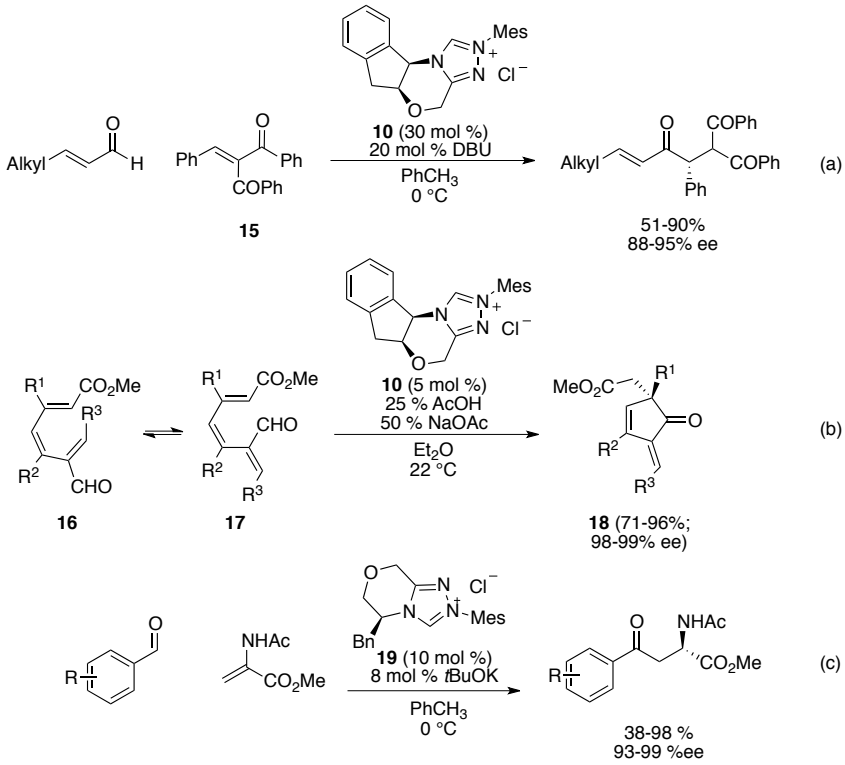
3. NHC Catalysis by Class of Reactive Intermediates

3.1 Acyl Anion Equivalent

The *N*-mesityl catalysts are not always required for simple benzoin and Stetter reactions, but are still often among the best catalysts for enantioselective or product-selective variants. In certain cases, we[27] and others[36] have noted a decrease in catalytic activity of the *N*-mesityl catalysts, such as during an intramolecular cyclization event where the steric bulk of the mesityl group impedes the reaction rate. Despite of this, recent literature has shown that exciting new reactivities can be garnered from the *N*-mesityl triazolium catalysts for challenging transformations. Glorius has reported two impressive examples of chemoselective crossed-benzoin reactions[37] between two aromatic aldehydes (Scheme 9.3a).[38] The sterically hindered catalyst **12** prefers to add at the least hindered aldehyde, resulting in a highly nucleophilic Breslow intermediate/acyl anion that adds quickly to the electron-deficient aldehyde. Glorius also reported another case of an addition of aromatic aldehyde to paraformaldehyde (Scheme 9.3b).[39] While the formation of the Breslow intermediate derived from simple aldehyde is reversible[27], lower effective concentration of the needed formaldehyde in equilibrium led to the NHC addition first to benzaldehyde and the resulting chemoselectivity.



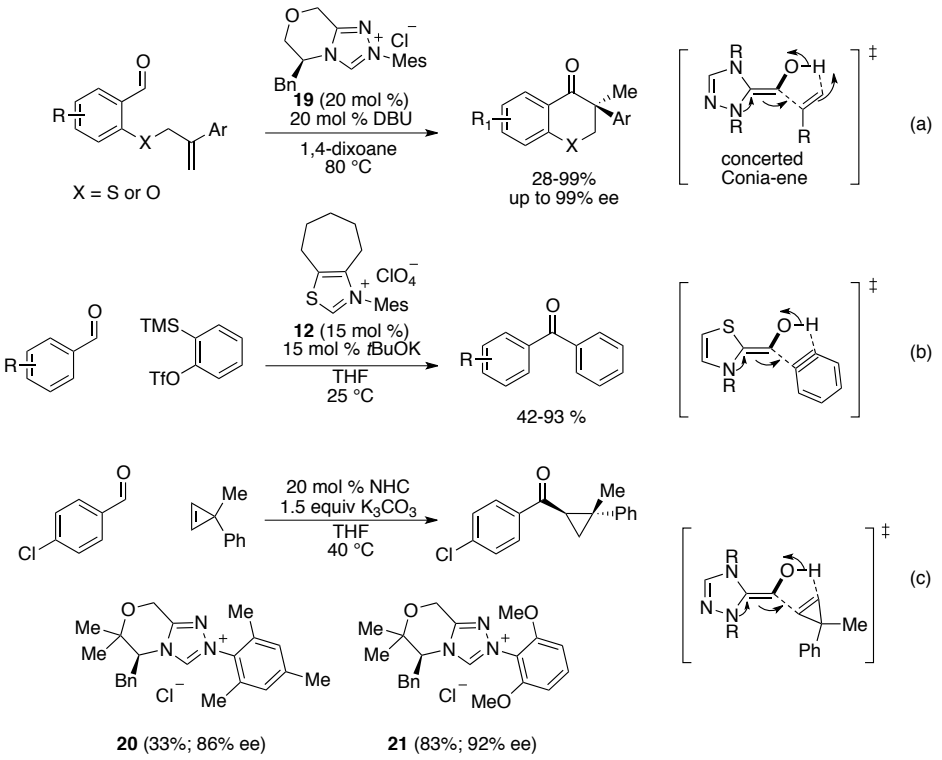
Scheme 9.3



Scheme 9.4

Apart for the benzoin reaction, the *N*-mesityl catalysts have recently gained attention for being able to catalyze challenging Stetter reactions – the conjugate addition reaction between acyl anion and α,β-unsaturated acceptor. While a large majority of reports on Stetter reactions shows the *N*-C_6F_5 catalysts developed by Rovis [14, 17-18, 26,40] as most reactive and selective, the use of enals in combination with the *N*-mesityl catalyst offers a new mode of reactivity for the Stetter reaction. To demonstrate this, Chi[41] disclosed an intermolecular enantioselective Stetter reaction of various aliphatic α,β-unsaturated aldehydes with chalcones (i.e. **15** in Scheme 9.4a). Equally impressive is the enantioselective intramolecular Stetter reaction of trienes such as 16 to afford 18 reported by Xu[42] (Scheme 9.4b). The use of acetic acid as the cocatalyst was found to be advantageous in preventing catalyst decomposition. From a synthetic utility point of view, Glorius[43] developed a highly enantioselective synthesis of α-

amino acid derivatives by means of NHC-catalyzed enantioselective intermolecular Stetter reaction (Scheme 9.4c). Mechanistic studies revealed a diastereoselective protonation as the key stereocontrol element.



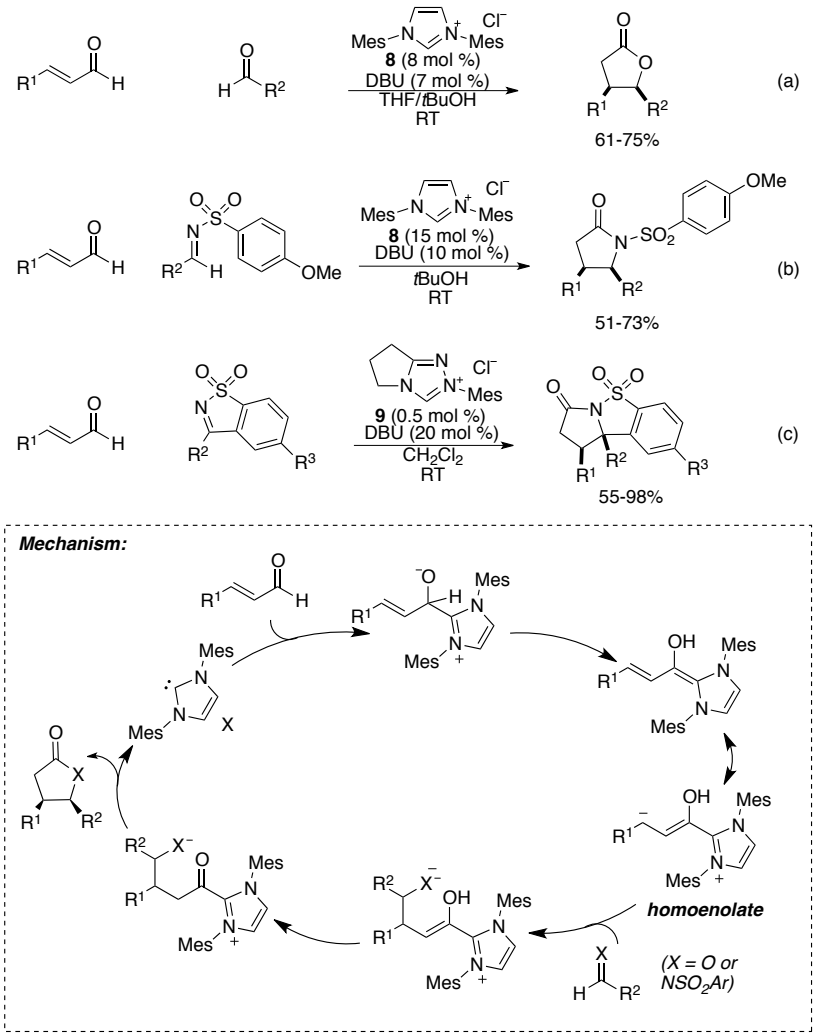
Scheme 9.5

By extending the concepts of the Stetter reaction, Glorius was able to develop various hydroacylation reactions[44] by addition of the acyl anion to unactivated alkene[45], benzyne[46], and cyclopropene[47] (Scheme 9.5). Computational studies showed that these reactions occur via a concerted conia-ene partway rather than a stepwise mechanism. Similarly, Rovis had previously suggested a reverse Cope-elimination as a possible mechanism.[48] While the two *N*-mesityl catalysts shown in Scheme 9.5 perform well for these reactions, a more electron rich catalyst such as **21** (Scheme 9.5c)[49] was necessary for more challenging olefin partners in hydroacylation reactions involving the Breslow intermediate. The irreversible nature of the formation of this intermediate species nicely rationalizes the need for electron-rich, sterically hindered

NHCs in these transformations by precluding the reverse reaction reactions that might otherwise occur prior to the favored pathways.

3.2 Homoenolate Equivalent

3.2.1 1,2-Addtion reactions of the homoenolate equivalent

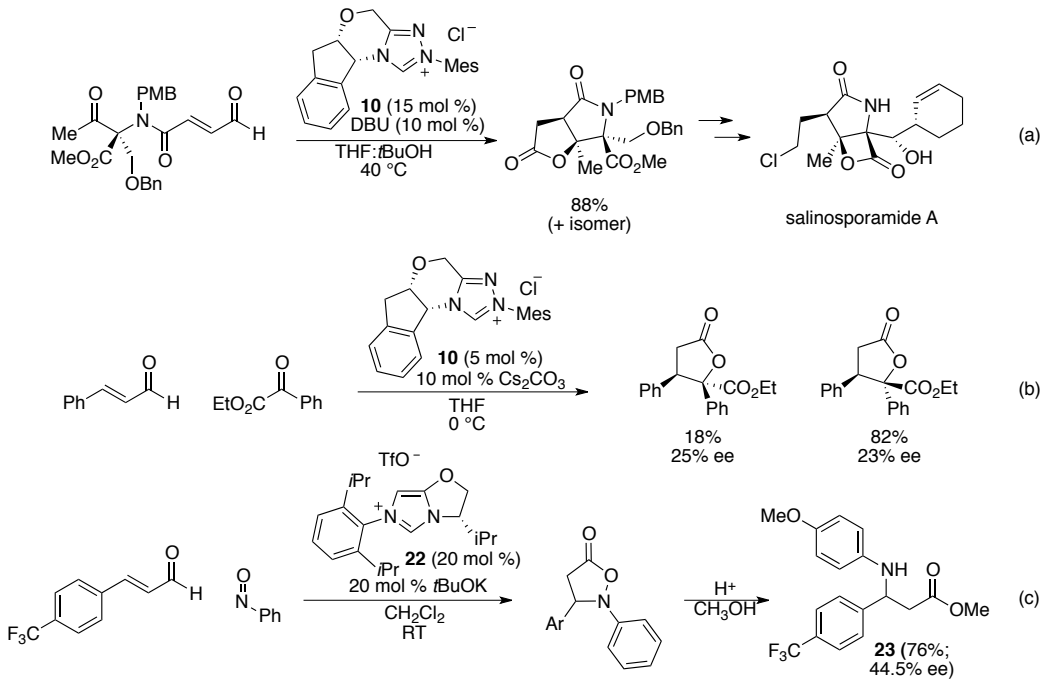


Scheme 9.6

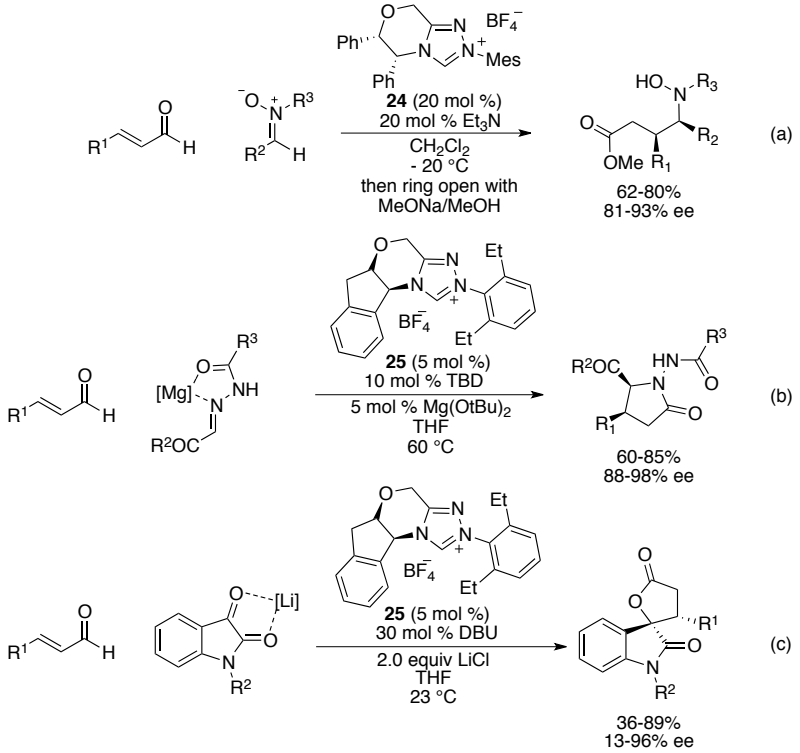
As part of our initial thinking about the generation of new reactive species by the combination of NHC and α,β-unsaturated aldehyde, we recognized the potential for the catalytic generation of "homoenolate equivalent." At the outset of this research in 2003, the chemical community was captivated by emerging results on the generation

of enolate equivalents from aldehydes and ketones using proline-derived catalysts. The synthetically valuable homoenolate equivalent, in contrast, could be effectively formed only under harsh or operationally difficult conditions. Furthermore, no enantioselective homoenolate additions were known. Our successful conversion of cinnamaldehyde to dihydrocinammic esters (Figure 9.3) implied the generation of a homoenolate equivalent and invited attempts to trap it with carbon electrophiles, rather than allowing it to undergo protonation. With this idea formulated, its execution proved to be surprisingly straightforward: simply combining cinnamaldehyde and an electrophilic aldehyde in the presence of IMesCl (**8**) and base led to formation of a γ-lactone product resulting from electrophilic trapping of a catalytically generated homoenolate equivalent in which both our group[50] and Glorius'[51] simultaneously reported (Scheme 9.6a). Our work also extended to the syntheses of γ-lactam via homoenolate addition to *N*-sulfonyl imines[52] (Scheme 9.6b) and saccharine derived imines (Scheme 9.6c).[53] A general catalytic cycle of these reactions is shown below.

Although these reactions are often diastereoselective, rendering these processes enantioselective using the existing chiral *N*-mesityl catalysts is still challenging.[54] For example, low enantioselectivity was observed during our formal synthesis of salinosporamide[55] (Scheme 9.7a). Similar level of enantioinduction was also documented by You[56] during their attempt to render γ-lactone synthesis enantioselective (Scheme 9.7b) or by Zhang and Ying[57] during their synthesis of protected β-amino ester **23** (Scheme 9.7c). While a solution by new catalyst design has not truly emerged, Scheidt focuses on the use of nitrone substrate[58] or preorganization by Lewis acids[59] with either uncommon protecting group[60] or more activated substrate[61] (Scheme 9.8).



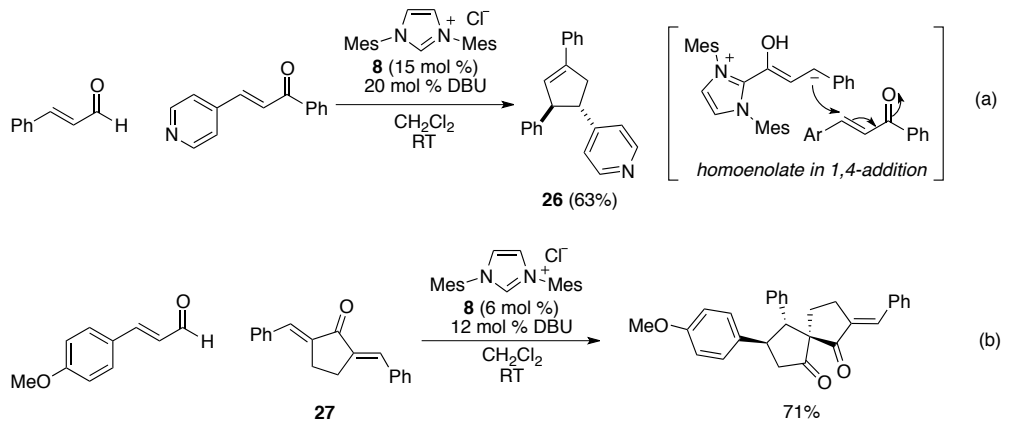
Scheme 9.7



Scheme 9.8

3.2.2 1,4-Addtion reactions of the homoenolate equivalent

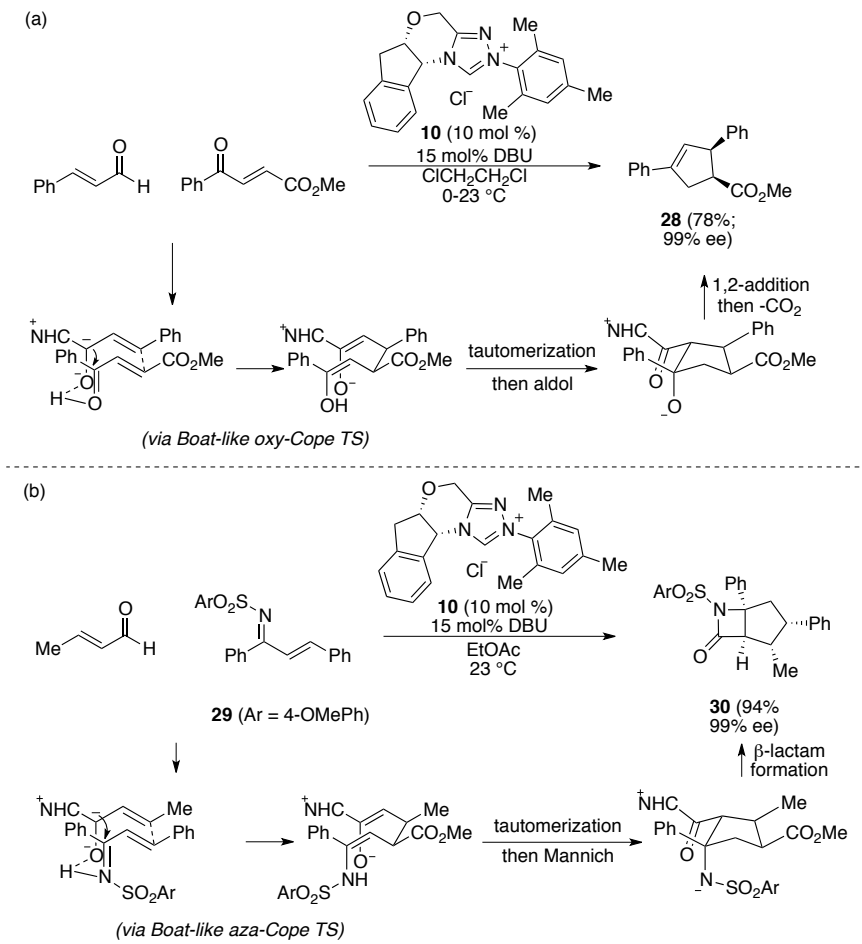
The conjugated Breslow intermediate can also act as nucleophile for conjugate addition with various unsaturated electrophiles.[62] One commonly used catalyst for this transformation is again the bismesityl imidazolium salt **8** (IMesCl). Nair reported the first example of what appeared to be the trapping of a catalytically generated homoenolate by a Michael-type addition. Surprisingly, the products observed were not the expected cyclopentanones but rather cyclopentenes, which are formed by an intramolecular aldol cyclization, lactonization, and decarboxylation.[63] Later they were able to further optimize the reaction to employ chalcones bearing heterocycles (Scheme 9.9a).[64] Using the same protocol, certain dienones such as **27** were found to be excellent coupling partners, this time forming the originally expected cyclopentenones (Scheme 9.9b).[65]



Scheme 9.9

Chiral *N*-mesityl substituted triazolium precatalysts have proven to be exceptional catalysts for highly enantioselective variants of the cyclopentene-forming annulation. Unexpectedly, *cis*-substituted cyclopentenes (rather than the trans-products observed in Nair's work above) were formed. We currently attribute this to a highly organized transition state in the addition of the homoenolate equivalent to the enone, one that can be thought of as involving a stepwise or possibly concerted crossed-benzoin/oxy-

Cope reaction (Scheme 9.10a).[66] The key decarboxylative formation of cyclopentenes **26** and **18** results in the loss of a stereocenter and a synthetic handle. This stereochemical information can be preserved in other variations of this annulation. For example, unsaturated imines (i.e. **29**) undergo a remarkable annulation leading to the formation of bicyclic β-lactams with outstanding yields and enantioselectivities (Scheme 9.10b).[67] Alternatively, enone **31** contains a pendant hydroxyl group, which can intercept the activated carboxylate formed during the cascade annulation reaction and prevent the cyclopentene-forming decarboxylation reaction (Figure 9.9).[68] Remarkably, changing the catalyst from *N*-mesityl substituted triazolium **10** to the nearly identical *N*-mesityl substituted imidazolium **11** resulted in different products.



Scheme 9.10

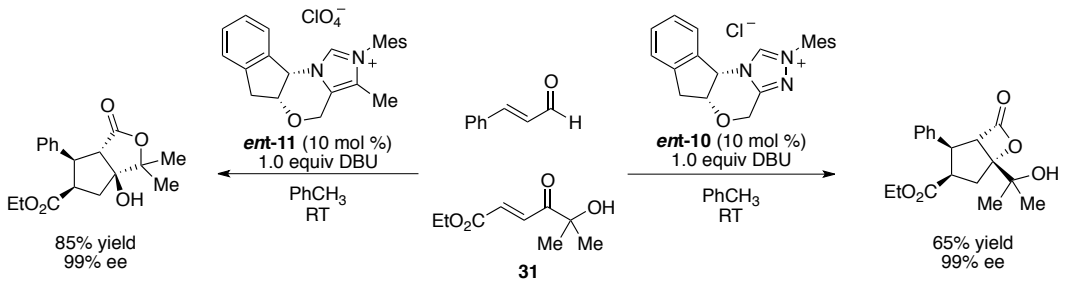
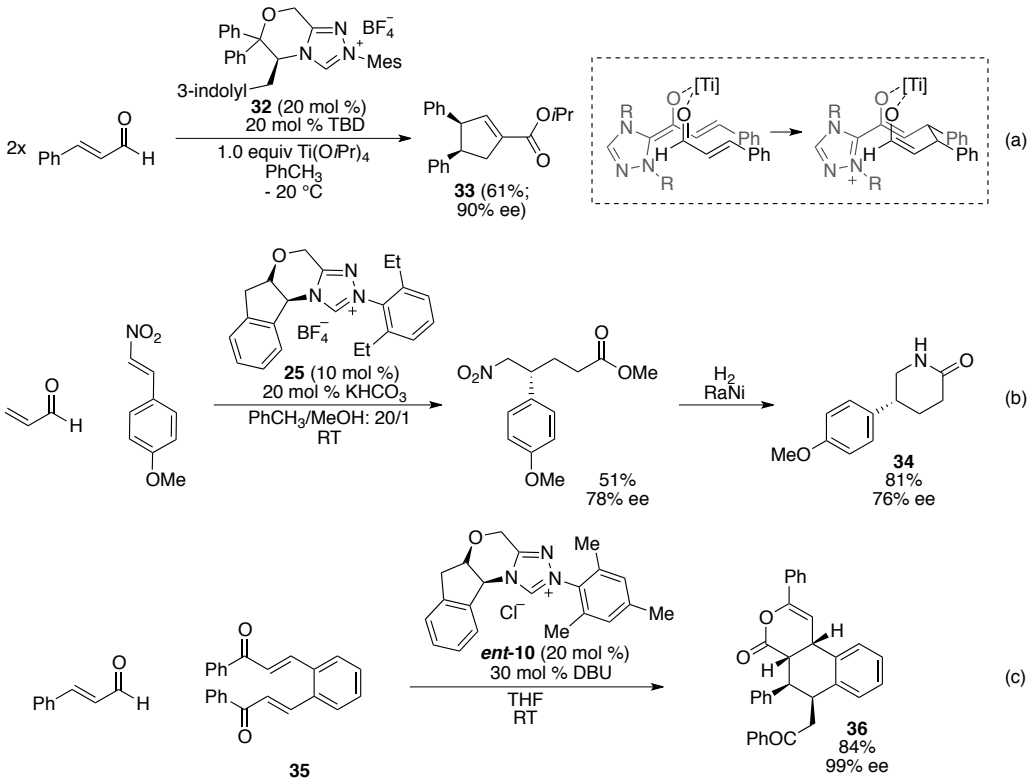


Figure 9.9. Stereodivergence from chiral *N*-mesityl triazolium vs. imidazolium catalysts

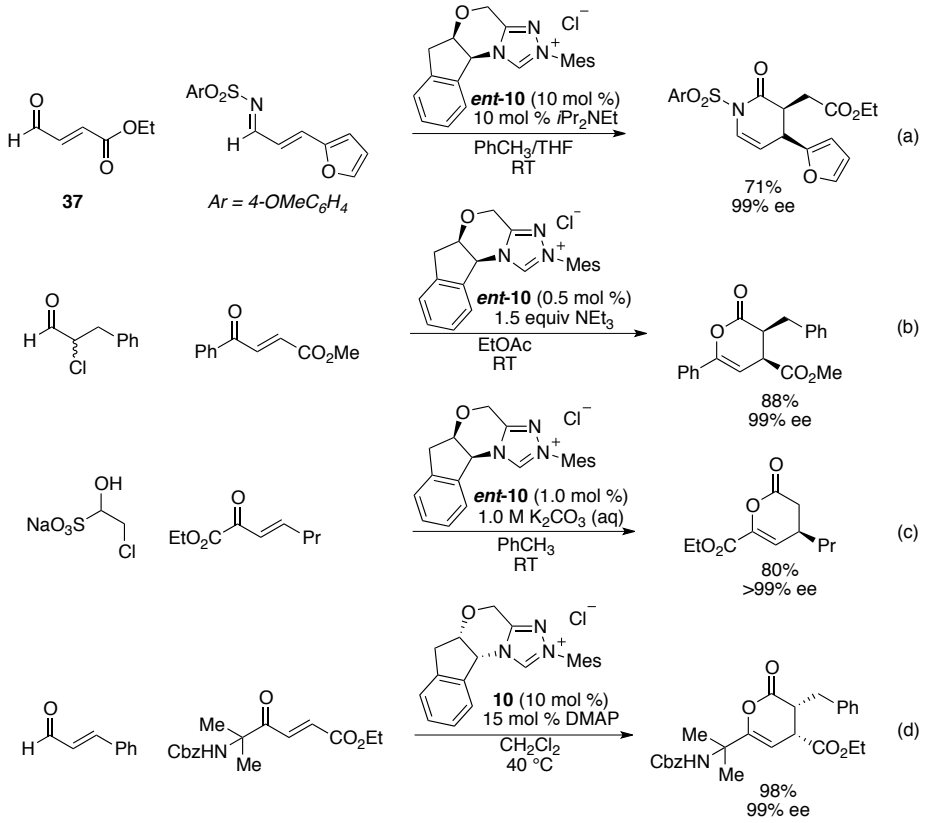


Scheme 9.11

As seen in the previous section with 1,2-addition of homoenolate generated via NHC catalysis, conjugate addition of the same species can also be rendered enantioselective using chiral *N*-mesityl precatalysts; in this case, usually with high selectivity. Scheidt was able to report a dimerization reaction of enals in the absence of other electrophiles via the homoenolate pathway (Scheme 911a), in which the additive Ti(O*i*Pr)$_4$ serves the role of Lewis acid for chelation and an external nucleophile for

catalyst turnover.[69] Besides enones or enals as conjugate acceptors, β-nitrostyrene derivatives[70] can also be used as demonstrated by Liu, who showcases the versatility of this method in the synthesis of δ-lactam **34** (Scheme 911b).[71] Chi shows that the use of dienones such as **35** can furnish exquisite homoenolate-enolate cyclization cascade, yielding enantiopure product with high level of molecular complexity (**36** in Scheme 9.11c).[72]

3.3 Enolate Equivalent



Scheme 9.12

Inspection of the reaction pathways shown in Figure 9.5 reveals the potential formation of yet another catalytically generated reactive enolate species by the protonation of the homoenolate/Breslow intermediate.[21a] The existence of this intermediate can also be inferred in the redox esterification of α,β-unsaturated and α-

halo-aldehydes. At the outset of our studies the enantioselective trapping of this catalytically generated ester enolate equivalent with carbon electrophiles seemed like a far-fetched idea. We were, however, pleasantly surprised to find that both the generation and utility of this species is one of the most facile and versatile enantioselective C–C bond forming processes to have been disclosed in NHC catalysis.

In 2006 we reported the first successful generation and enantioselective C–C bond formation featuring the catalytically generated ester enolate equivalents. This work, which also debuted *N*-mesityl substituted aminoindanol-derived triazolium salt **10**, revealed the azadiene -Diels Alder reaction of unsaturated imines and the catalytically generated enolates (Scheme 9.12a).[21a] Already then, we recognized that the generation of the NHC-bound, chiral ester enolate equivalents was not limited to α,β-unsaturated aldehydes as substrates. Our group pioneered highly enantioselective NHC-catalyzed oxo-diene Diels-Alder reactions from chloroaldehydes (Scheme 9.12b) [73] and their bisulfite salts adduct surrogates (Scheme 9.12c).[74] With improved underlying mechanistic understanding garnered over the years, our group demonstrated that protonation of homoenolate derived from simple aldehyde (i.e. cinnamaldehyde instead of **37**) requires a weak base – which generates a strong conjugate acid – and employed this knowledge for oxo-diene Diels-Alder reactions of simple enals[75] (Scheme 9.12d). Computational studies in collaboration with the group of Prof. Marisa Kozlowski at the University of Pennsylvania indicated that the reaction proceeds via the deprotonated enolate, in which the oxygen of the enolate preassociates with the carbonyl of the diene (so called "oxy-anion steering mechanism" in Figure 9.10).[76] The calculated transition state follows a concerted, yet

highly asynchronous [4+2] cycloaddition, rather than an alternative stepwise Michael addition-cyclization pathway.

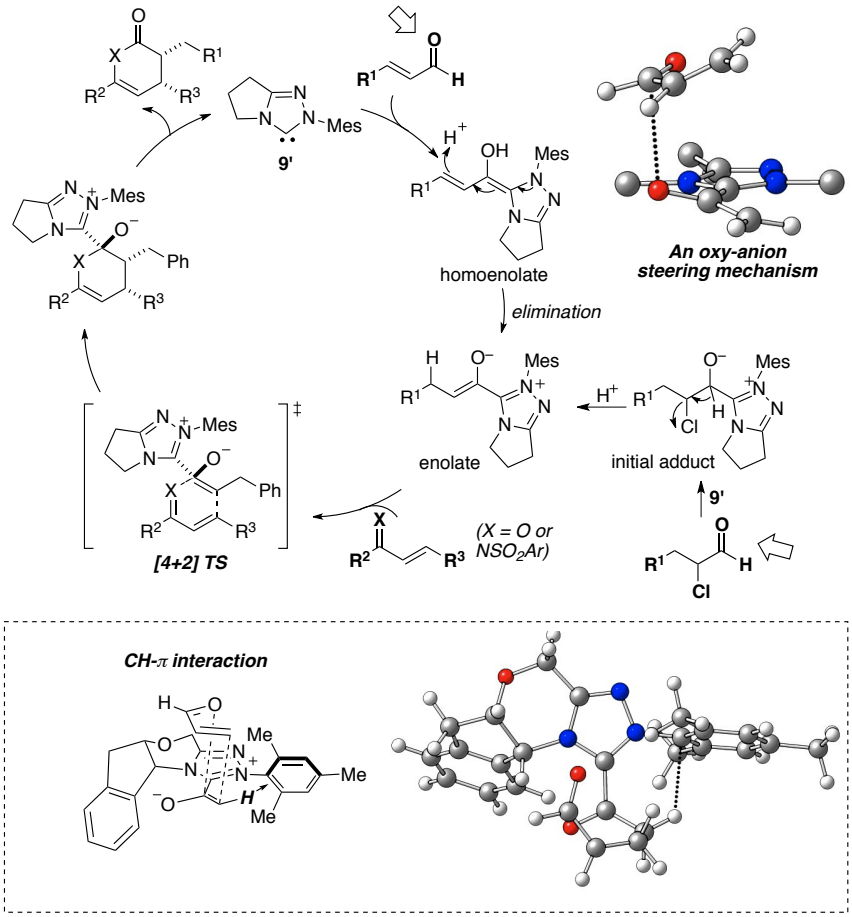
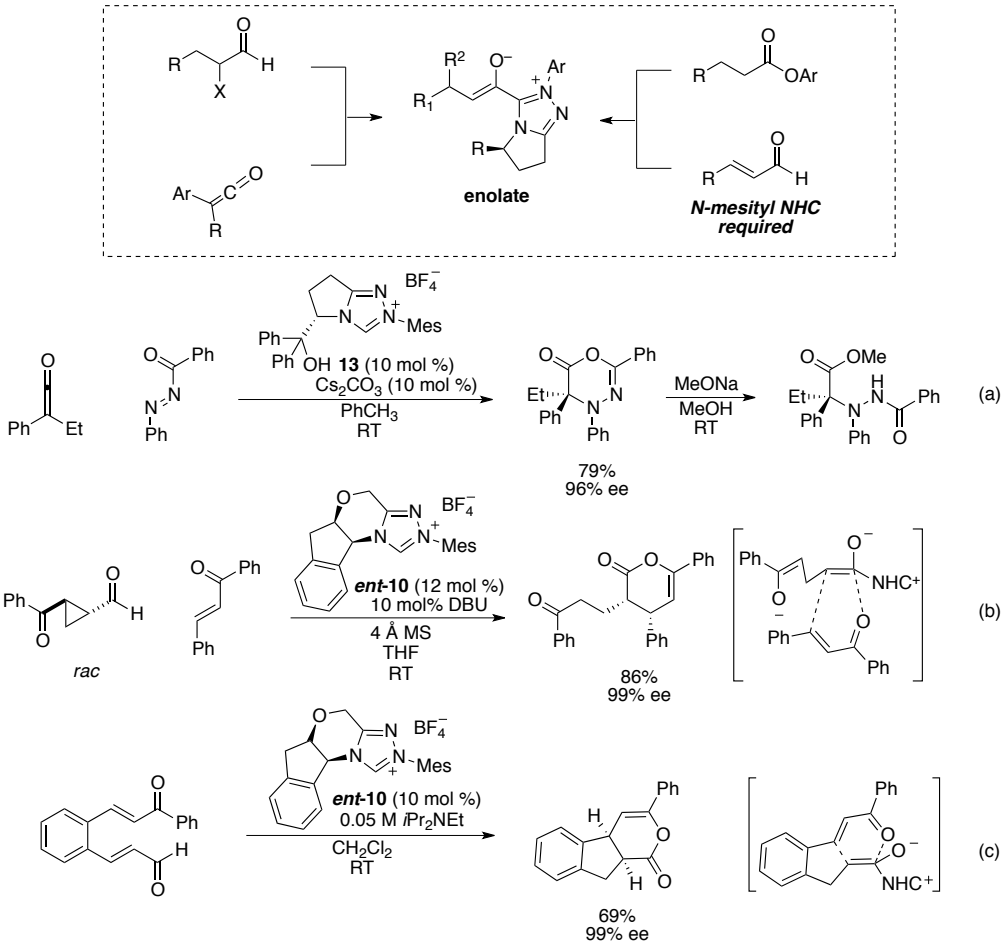


Figure 9.10. The mechansim of NHC-catalyzed Diels-Alder reactions

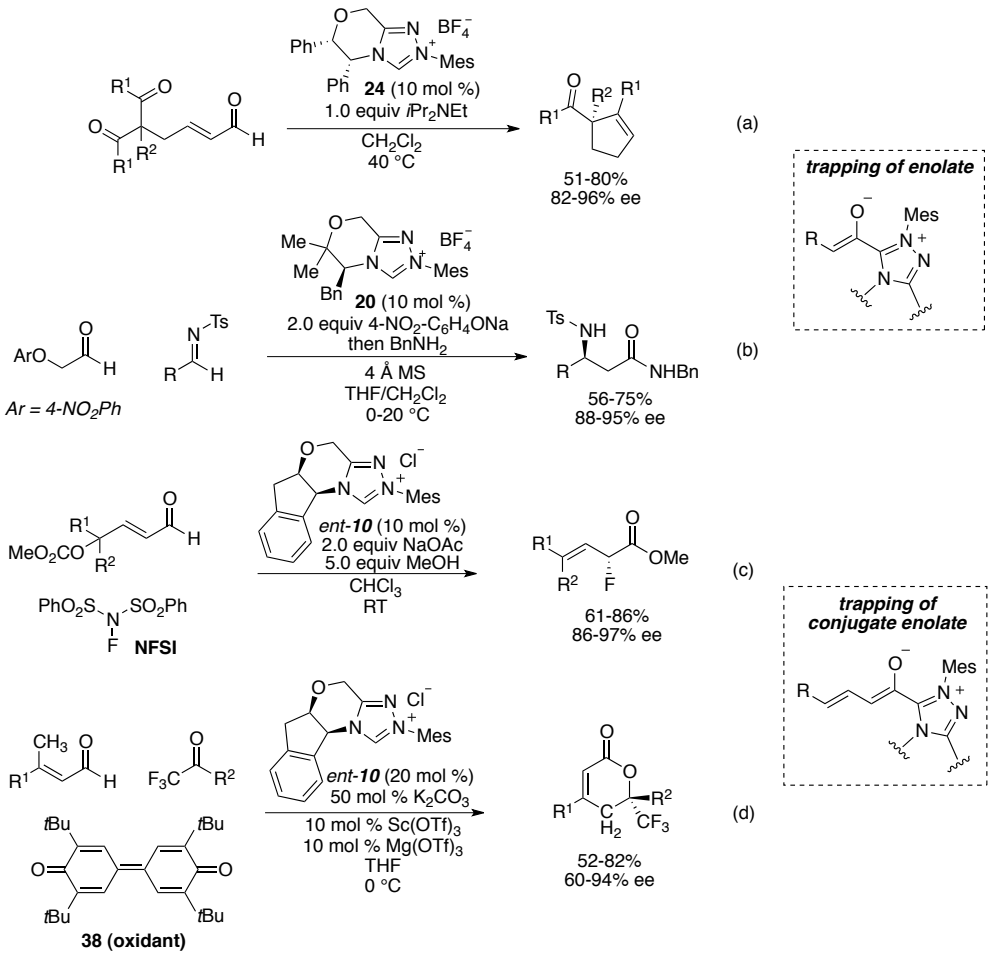
We have noted that many NHC-catalyzed reactions of substrates other than enals do not require the *N*-mesityl substituent catalysts; however these NHCs are required for high conversion and improved enantioselectivity in C–C bond-forming reactions involving the enolate species.[27] In order to better understand the role of the mesityl group in these reactions, our and Kozlowski's groups performed extensive computational and experimental studies on the NHC-catalyzed hetero-Diels Alder reaction, in which the *N*-substitution of the triazolium salts influences the stereochemical outcome. The use of other *N*-aryl NHCs was possible here due to the

fact that the redox reaction of α-chloroaldehyde proceeds via an elimination mechanism proposed by Nowak[77] and not through the Breslow intermediate (the rate acceleration effect from the mesityl moiety is not essential). The yields, however, were far lower than with the *N*-mesityl substituted catalysts. Computational model suggests a C-H π interaction between the substrate and the *N*-aryl moiety of the catalyst as the key enantiocontrol element (Figure 9.10). Electron-withdrawing group decreases this interaction and causes erosion in the enantioselectivity of the product (i.e. 78% ee for the C_6F_5 group) in comparison to the mesityl group (>99% ee), which maximizes this favorable interaction.



Scheme 9.13

Beyond the work from our group, important contributions from Ye (Scheme 9.13a)[24] and Chi (Scheme 9.13b)[78] have extended the suitable precursors to stable ketenes, other α-functionalized aldehydes, and even saturated esters.[79] Subsequent works have expanded the substrate scope[80] of NHC-catalyzed [4+2] cycloadditions to include, for example, those of enals with vinyl ketones[81] or modified chalcones,[82] and Scheidt[83] also demonstrated an intramolecular variant of these reactions (Scheme 9.13c).



Scheme 9.14

Besides the Diels-Alder manifold, other uses of NHC-bound chiral ester enolate equivalent as nucleophiles for aldol[84] or Mannich[85] reactions have been reported by the group of Scheidt (Scheme 9.14a-b); the latter comprises an enantioselective synthesis of protected β-amino acid derivatives. More interesting mechanistically is

the catalytic generation of a conjugated enolate as a novel nucleophilic species in NHC chemistry. The group of Lin and Sun has reported an enantioselective fluorination by mean of internal redox reaction of enals bearing a leaving group at the γ position, using NFSI as the electrophilic fluorinating agent (Scheme 9.14c).[86] Using trisubstituted enals together with an external oxidant **38**, Chi reported an enantioselective aldol-cyclization cascade from unsubstituted conjugated enolate to trifluoromethyl ketones (Scheme 9.14d).[87] We anticipate that this mode of reactivity via conjugated enolate will find new discovery and more application in the future.

3.4 Activated Carboxylate Equivalent

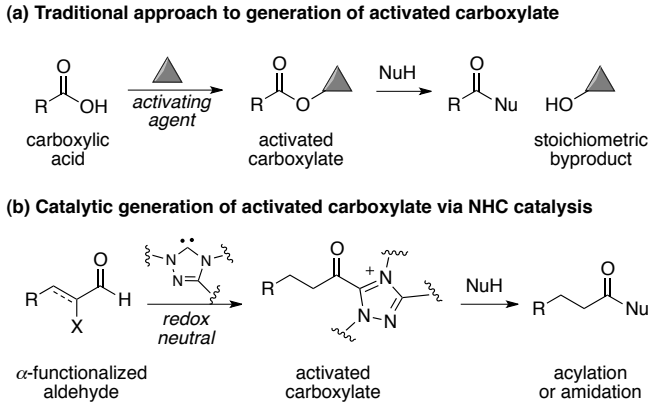


Figure 9.11. Generation of activated carboxylate for acyltion and amidation chemistry

Our original entry into NHC-catalysis was motivated by the desire to develop catalytic methods for amide and ester formation. The typical synthesis of carboxylic esters, amides, and thioesters utilizes super-stoichiometric amounts of expensive coupling reagents, bases, and additives to affect the union of a carboxylic acid and a nucleophile (Figure 9.11a). Such reactions routinely produce several equivalents or more of byproducts, necessitating complicated workups or other strategies, such as solid supports, for isolating the desired products. Furthermore, despite the ubiquity of

carboxylic acid derivatives containing neighboring stereocenters, i.e. amino acid residues, there are few catalytic methodologies for the direct synthesis of carboxylic acid derivatives from constituent fragments with concomitant introduction of stereochemical complexity.[88] The synthesis of carboxylic acid derivatives typically progresses through the intermediacy of "activated carboxylates" usually formed by the combination of a carboxylic acid and a coupling reagent. Given that these intermediates are rarely isolated, we believed that ester and amide forming processes featuring catalytically generated activated carboxylates should be feasible. This idea, coupled with a report from Townsend[89] on the thiamine mediated biosynthesis of clauvulanic acid, led us to postulate that NHCs could effect the catalytic generation of activated carboxylates from α-functionalized aldehydes. The advantage of using *N*-heterocyclic carbene is the ability to catalytically generate activated carboxylate in a redox neutral fashion and without any superstoichiometric byproducts (Figure 9.11b).

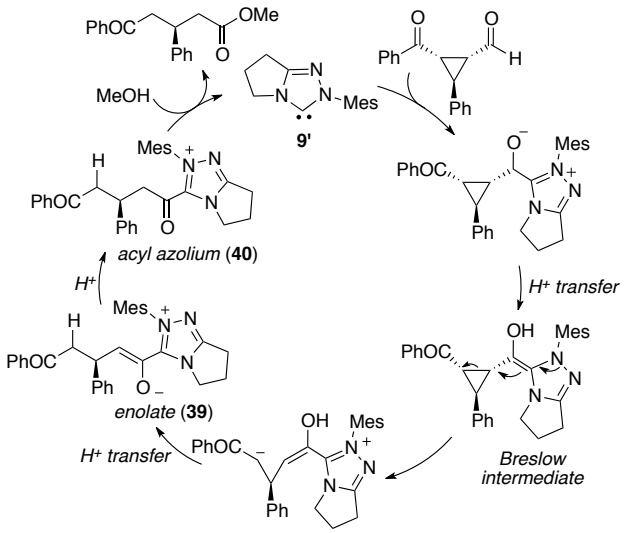
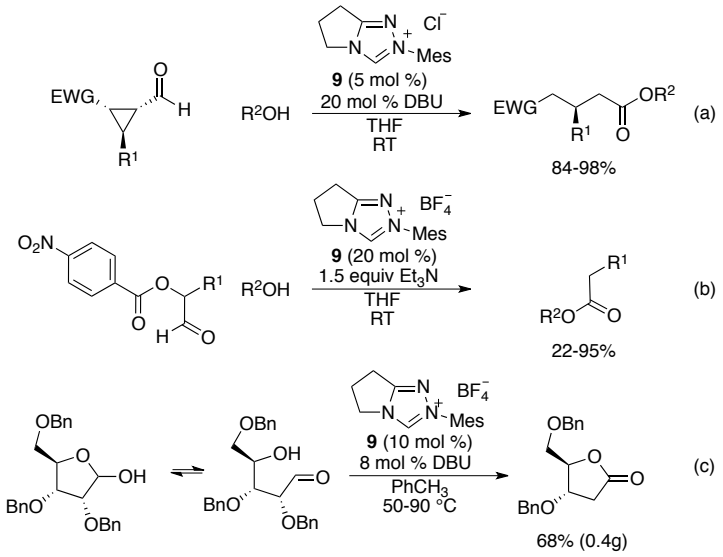


Figure 9.12. Catalytic cycle for a redox esterification reaction of formylcyclopropane.

Since the first reports of such reactions on α–epoxyaldehydes (Scheme 9.2a) [30] from our group and on α-haloaldehydes from the Rovis group[31], the substrate scope has been extended to just about any aldehyde with a reducible functionality. With many

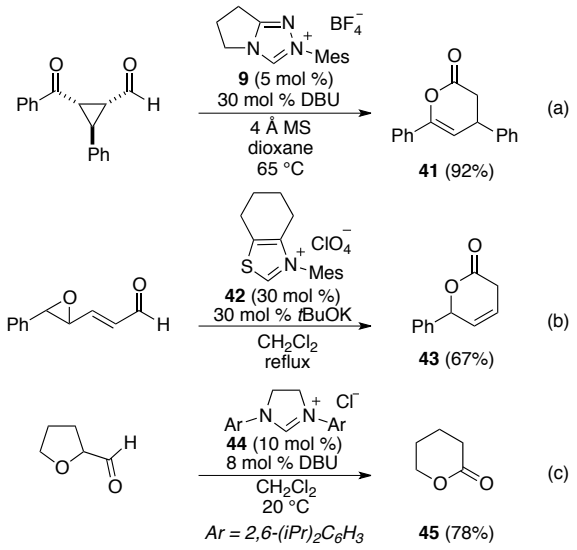
of these aldehydes, the *N*-mesityl substituted catalysts are not essential; the *N*-C_6F_5 ones are often superior. But in redox reaction of unsaturated aldehydes, in particular, the use of *N*-mesityl catalysts is preferred. Our group has also reported a redox esterification reaction with achiral *N*-mesityl salt **9** and formylcyclopropanes bearing an electron-withdrawing group (Scheme 9.11a).[90] The mechanism of this reaction follows the course of protonation of enolate **39** to form acyl azolium **40**, which serves the role of the activated carboxylate for the esterification step (Figure 9.12). Similar to this approach, Smith has reported another redox esterification of α-aroyloxyaldehydes using the same catalyst (Scheme 9.11b)[91] while the intramolecular variants of this particular reaction with ribose and protected carbohydrate derivatives were reported by the group of Wendeborn at Syngenta (Scheme 9.11c).[92] This example is synthetically useful for rapid diversification of sugar commodities.



Scheme 9.15

This redox neutral strategy using sterically hindered NHCs can be applied to ring expansion reactions of α-functionalized aldehydes with intramolecular acylation as the catalyst turnover strategy. Using the same mechanistic rational as in Figure 9.12,

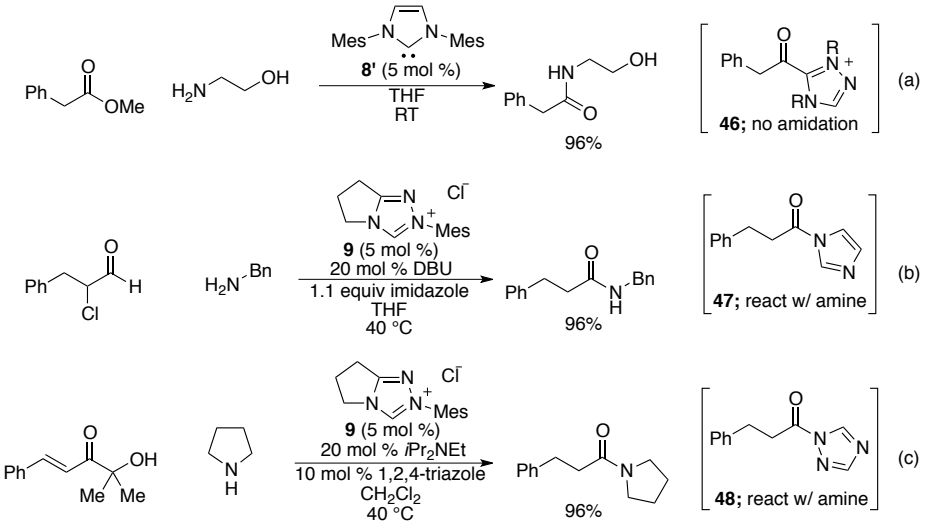
You has shown that dihydropyranone **41** can be synthesized from the same formylcyclopropane in the absence of an external nucleophile and a proton source (Scheme 9.16a).[93] Likewise, She combined the redox processes of enal and epoxyaldehyde in a relay redox/ring-expansion cascade leading to another dihydropyranone (**43** in Scheme 9.16b).[94] Lastly Gravel shows that tetrahydrofurfural can be opened and lactonized intramolecularly by NHC **44** (Scheme 9.16c).[95]



Scheme 9.16

The first reaction catalyzed by *N*-mesityl azolium salts was the IMesCl-catalyzed transesterification pioneered by Nolan, Waymouth, and Hedrick in 2002.[96] Based on this and biological studies of thiamine-phosphate dependent enzymes[97], Movassaghi observed that acyl azolium species does not react with amine – an intriguing property that could be used for catalytic esterification of amino alcohols (Scheme 9.17a).[98] While this is impressive, a direct catalytic amidation is still highly desirable and potentially synthetically powerful. In 2007, our group and Rovis' simultaneously reported the use of cocatalytic reagent such as imidazole[99] or HOAt[100] as a general solution to NHC-catalyzed amidation reactions of α-functionalized aldehydes

(Scheme 9.17b). To avoid the formation of imine from aldehyde and amine, our group has introduced α'-hydroxyenone[101] as aldehyde surrogate for amidation[102] and others[103] (Scheme 9.17c).



Scheme 9.17

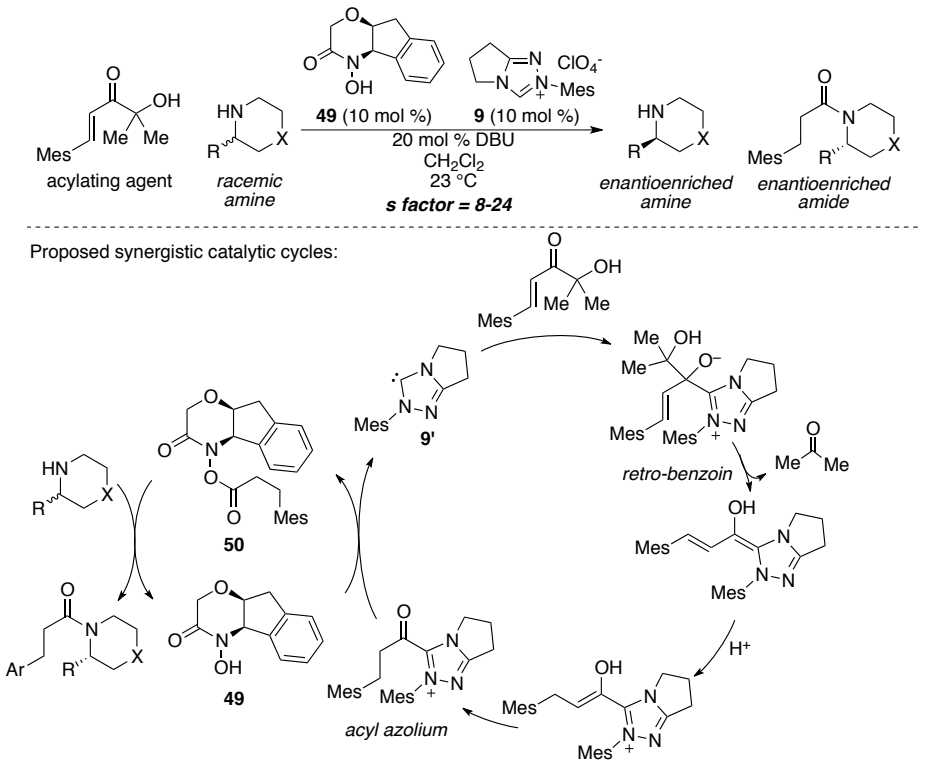


Figure 9.13. Synergistic catalytic kinetic resolution of cyclic secondary amines.

With this knowledge in hand, our group was also able to engineer a general solution to catalytic kinetic resolution of cyclic secondary amines[104] – compounds of contemporaneous interests for which other catalytic methods of resolution have not proven successful. With the help of the chiral hydroxamic acid cocatalyst **49,** this reaction has a broad substrate scope; substituted piperidines, morpholines, piperazines and azepane all reacted in high selectivity. Figure 9.13 summarizes the synergistic catalytic cycle of this kinetic resolution. It is worth noting here that all approaches to catalytic amidation rely on the same strategy of transferring the acyl azolium (**46;** unreactive towards amine) to acyl imidazole **47**, acyl triazole **47**, or acyl hydroxamate **50** (Scheme 9.17).

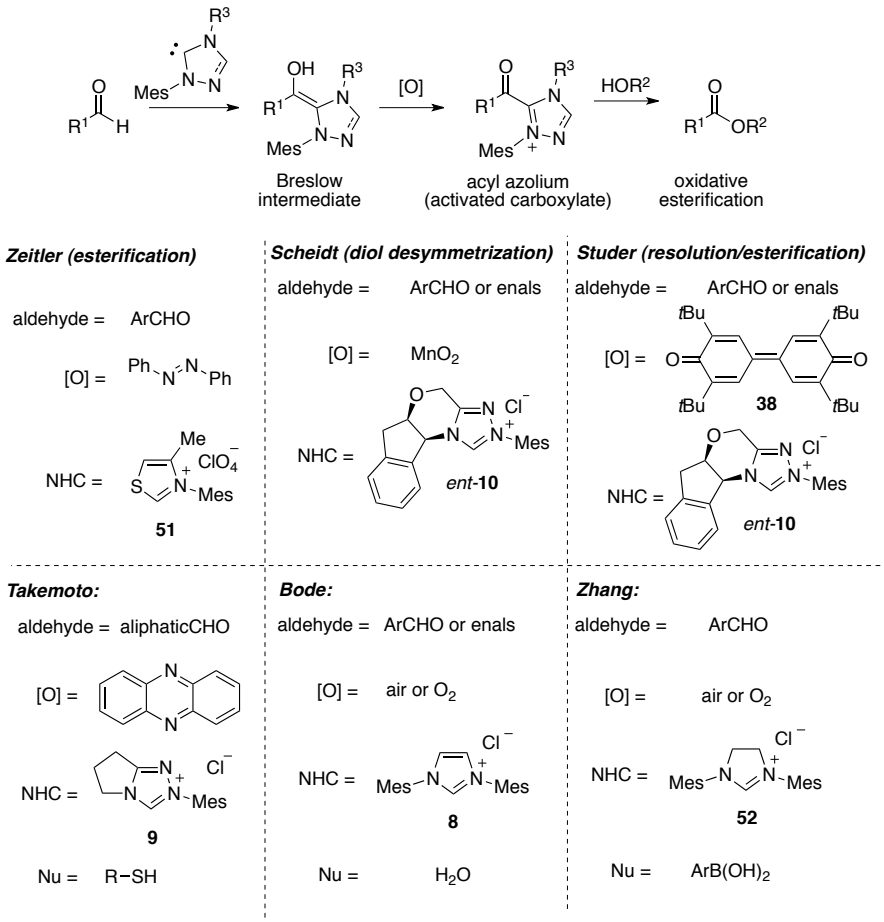


Figure 9.14. A brief summary of NHC-catalyzed oxidative acylation reactions

While the previous redox approach to esters and amides is desirable in terms of efficiency and sustainability, oxidative esterification, in which the aldehyde stating materials can be oxidized to generate the activated carboxylate in mild condition, is also synthetically useful. This reaction operates by oxidation of the Breslow intermediate directly to the acyl azolium[105] without the protonation sequence (Figure 9.14). This concept has gained much attention from researchers in the field. Many oxidants such as azobenzene,[106] MnO_2[107], or diquinone 38[108] have been used together with a number of *N*-mesityl NHCs for oxidative esterification of simple aromatic aldehydes and enals. Contemporaneously, the works from our group[109] and Zhang[110] have shown that air (O_2) can be used as the stoichiometric oxidant instead of small molecule organic oxidant. The last remaining challenge in this field is the NHC-catalyzed oxidation of aliphatic aldehyde, in which Takemoto has reported the only solution up to date.[111] Figure 9.14 summarizes these approaches.

3.5 α,β-Unsaturated Activated Carboxylate Equivalent

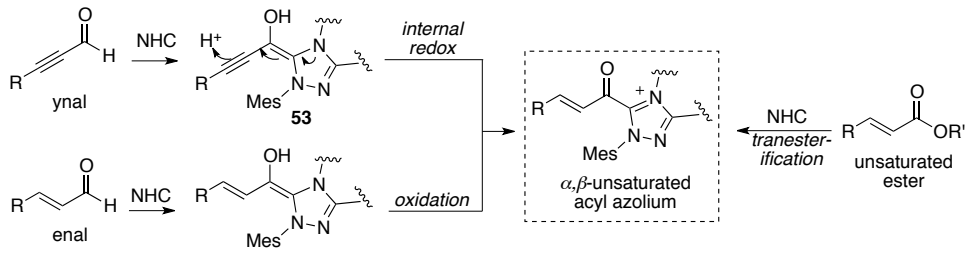
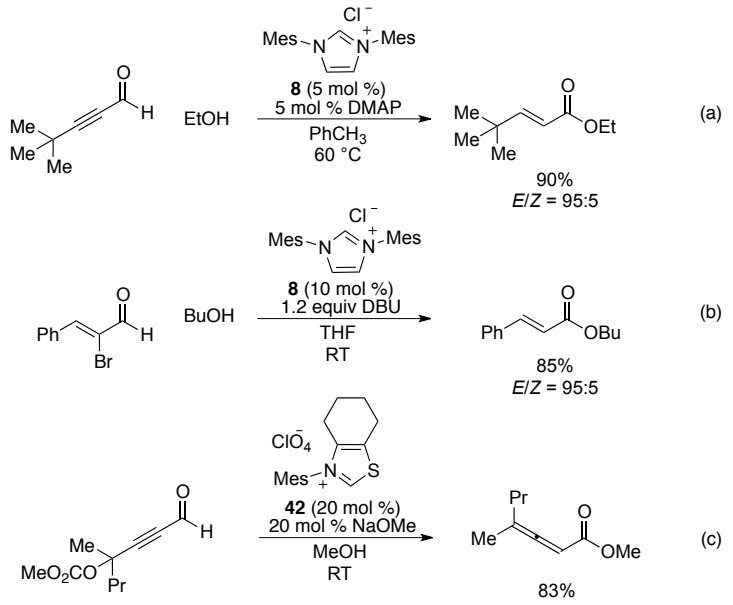


Figure 9.15. Catalytic generation of α,β-unsaturated acyl azolium for NHC catalysis

The catalytically generated acyl azolium species are the key intermediates in NHC-catalyzed esterification and amidation reactions. The same principles also make possible the catalytic generation of *α,β*-unsaturated acyl azolium (Figure 9.15), which undergoes a diverse range of enantioselective C–C bond formation. In 2006 Zeitler

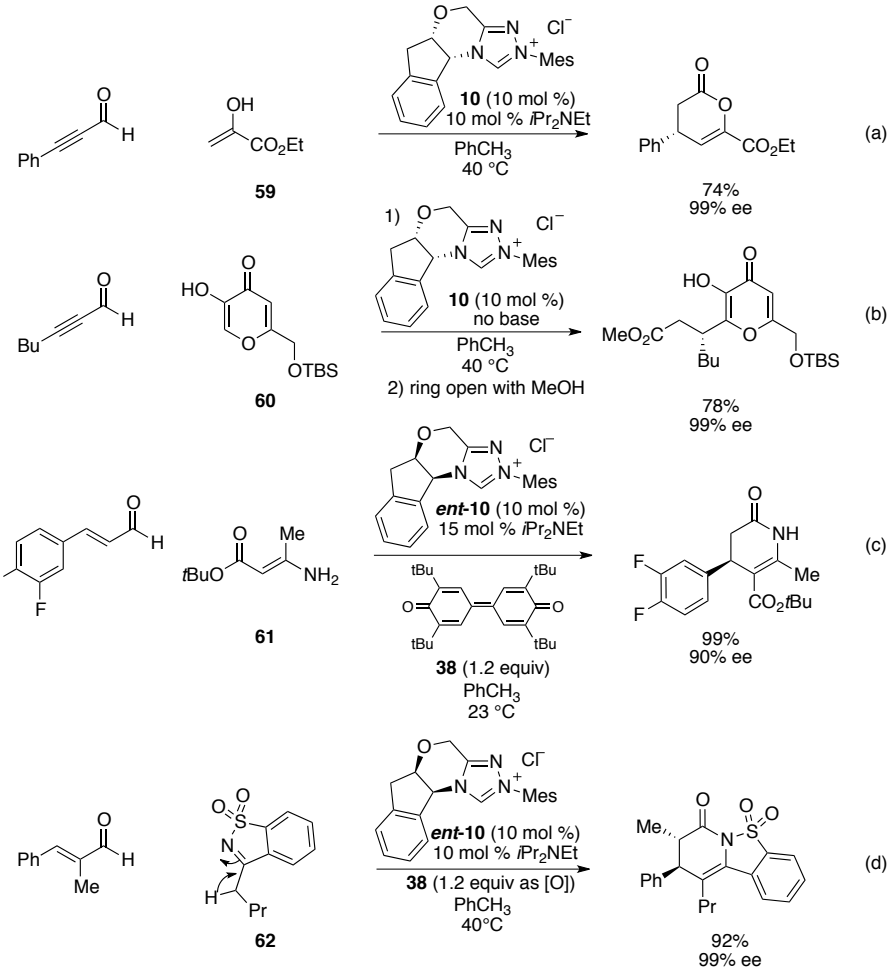
reported a protocol for the stereoselective generation of unsaturated acyl azolium with IMesCl (**8**) and ynals as acylating agents (Scheme 9.18a).[112] A conceptually related redox esterification from α-bromo-enals has been recently reported by Du (Scheme 9.18b).[113] Zeitler's mechanistic proposal involves the intermediacy of conjugated Breslow intermediate such as **53** above and its allenoate tautomer, which has been recently verified by trapping in another study by Sun (Scheme 9.18c).[114]



Scheme 9.18

The electrophilic nature of this intermediate suggested that it could be used for new reactions. Given the long-known fact that acyl azolium species have a metastable hydrate form in equilibrium[97], we began our investigations by trapping *α,β*-unsaturated acyl azolium (**54**) generated from ynal with stable enols. This combination leads to a hemiacetal (i.e. **55**), which is rendered long-lived enough by the *N*-mesityl catalyst (slow turnover) to undergo a Claisen rearrangement to give intermediate **56** (Figure 9.16, top). Upon tautomerization, lactone formation finishes the catalytic cycle and affords the resulting dihydropyranones in excellent yield and enantioselectivity. The synthetic utility of this methodology is demonstrated in the

functionalizations of ethyl pyruvate **59** and kojic acid derivative **60** (Scheme 9.19a-b).[28a] We were able to extend this methodology to the coupling of stable, unprotected enamines (i.e. **61**) with enals in the presence of oxidant **38** to afford enantioenriched dihydropyridinones, which are of pharmaceutical interest but no method for catalytic asymmetric synthesis previously existed (Scheme 9.19c).[115] More recently we showed that the enamine tautomer of various saccharine-derived *N*-sulfonylimines such as **62** may be intercepted in a highly stereoselective manner with trisubstituted enals[116] – a class of substrates whose reaction is a long-standing challenge in organocatalysis (Scheme 9.19d).



Scheme 9.19.

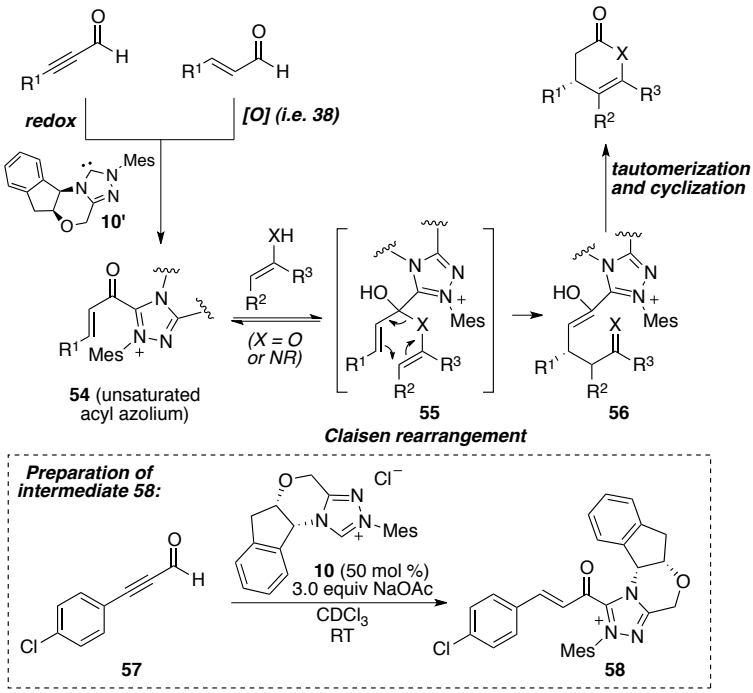
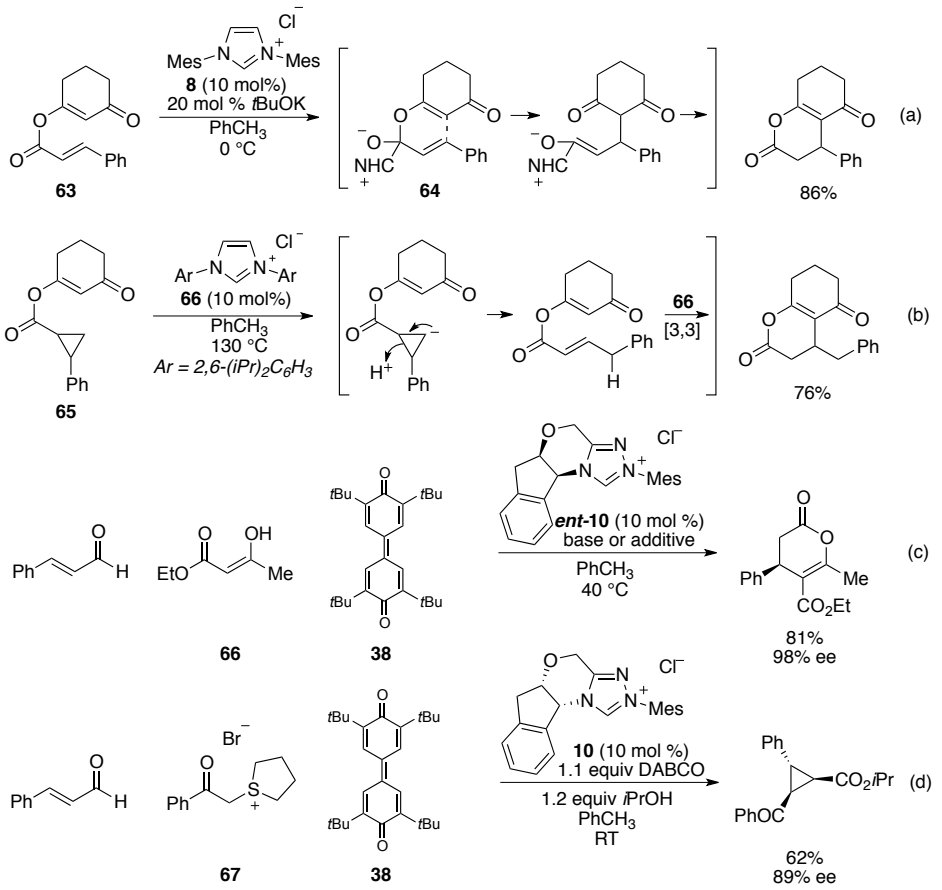


Figure 9.16. A general mechanism of NHC-catalyzed Claisen rearrangements

As a part of our mechanistic research program, we were able to prepare α,β-unsaturated acyl azolium **58** by a simple combination of ynal **57** and *N*-mesityl chiral triazolium salt **10** (Figure 9.16, below).[117] The mesityl moiety provided kinetic stability to this highly reactive intermediate and allowed for sufficient lifetime during characterization (UV-Vis, 2D NMR, and high-resolution mass spectrometry). Our detailed kinetic studies regarding the reactions of acyl azolium **58** revealed catalyst turnover as the rate-limiting step and that it had similar physical properties as a biosynthetic intermediate previously studied by Townsend[118] in 2007 and then later by Mück-Lichtenfeld, Mayr, and Studer in 2012.[119] Both of these studies argued for the possibility of thiazolium- and imidazolium-derived unsaturated acyl azolium as Michael acceptors – a situation we ruled unlikely for the Claisen reactions based on the related works of Coates and Curran[120], our extensive kinetic data, and the observation that good Michael donors we tested (thiol, hydroxamic acid, cumarin, etc.) all failed to react.[121] Computational studies by Schoenebeck rationalized the

origin of stereocontrol and confirmed once again the proposed [3,3]-sigmatropic rearrangement mechanism.[122]



Scheme 9.20

Just a few months prior to our first publication[28a], Lupton reported a similar reaction involving α,β-unsaturated acyl azoliums generated via transesterification of enol esters (i.e. **63**) and IMesCl (**8**) to afford dihydropyranone products (Scheme 9.20a).[123] The original proposed mechanism also postulated a direct conjugate addition from the breakdown of hemiacetal **64**, but was later revised to implicate the Claisen reaction as the key C–C bond forming step based on a cross-over experiment[124] and observation of byproduct, at least for some substrate classes.[125] Most impressively, Lupton has utilized this rearrangement strategy in the total synthesis of deoxyloganin[126] and the cyclization of cyclopropyl enol ester **65** (Scheme 9.20b).[127] Following our work and

that of Lupton, Xiao[128] and Studer[129] employed 1,3-dicarbonyl compounds such as **66** as the enol component in a related cascade reaction via the intermediacy of unsaturated acyl azolium in good yield and enantioselectivity (Scheme 9.20c). This mode of reactivity has received much attention between 2011 and 2012.[130] Recently, Studer has further increased the scope of activated ketones to include sulfur ylide **67** in his oxidative cyclopropanation reaction of enals with *i*PrOH as the terminal nucleophile (Scheme 9.20d).[131]

3.6 Conclusion and Outlook

Although NHC-catalysis is by no means limited to catalysts bearing *N*-mesityl or related groups, the role of *N*-mesityl substituted triazolium precatalysts in unlocking many of the new reaction manifolds cannot be underestimated. Few would have anticipated the diversity of the reactions and products or the outstanding stereocontrol offered by essentially one class of catalysts. As this field progresses, opportunities for new catalyst designs to open further pathways and expand the class of substrates amenable to NHC-catalysis abound. Most importantly, we anticipate that future innovations in catalyst design will make possible reactions from even simpler starting materials so that NHC-catalysis can move beyond its current niche of fine chemical products to impacting the industrial production of organic molecules – a field currently dominated by heterogeneous metal catalysis.

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