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Chiral N-Heterocyclic Carbene-Catalyzed Annulations of Enals and Ynals with Stable Enols: A Highly Enantioselective Coates–Claisen Rearrangement

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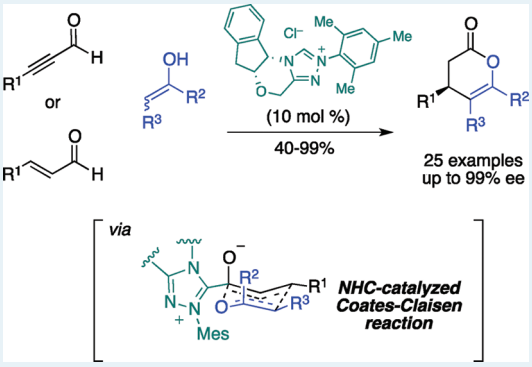
Supporting Information

ABSTRACT: A combination of a chiral N-heterocyclic carbene catalyst and α,β-unsaturated aldehyde leads to a catalytically generated α,β-unsaturated acyl azolium, which participates in a highly enantioselective annulation to give dihydropyranone products. This full account of our investigations into the scope and mechanism of this reaction reveals the critical role of both the type and substitution pattern of the chiral triazolium precatalyst in inducing and controlling the stereochemistry. In an effort to explain why stable enols such as naphthol, kojic acid, and dicarbonyl are uniquely efficient, we have postulated that this annulation occurs via a Coates–Claisen rearrangement that invokes the formation of a hemiacetal prior to a sigmatropic rearrangement. Detailed kinetic investigations of the catalytic annulation are consistent with this mechanistic postulate.

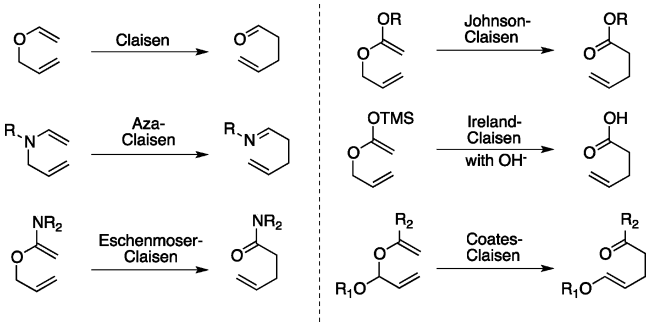


KEYWORDS: *N-heterocyclic carbene, Claisen rearrangement, redox reaction, acyl azolium, organocatalysis*

INTRODUCTION

Since its discovery in 1912[1] the Claisen rearrangement has been celebrated as one of the most powerful methodologies in organic chemistry. The sheer number of the existing variants of the Claisen rearrangement[2] emphasizes the captivation and utility of this carbon–carbon bond-forming reaction (Scheme 1). While many other highly valued C–C bond

Scheme 1. Selected Variant of Claisen Rearrangement



forming reactions, including aldol reactions, cycloadditions, conjugate additions, and benzoin/Stetter-type reactions, have progressed from racemic and diastereoselective variants to catalytic, enantioselective processes, progress in the development of catalytic asymmetric variants of the Claisen rearrangement has been slower. The use of chiral Lewis acid complexes to evoke reagent-controlled asymmetric Claisen reactions is well established,[3−5] but product inhibition typically requires the use of superstoichiometric quantities of the chiral reagents. Efforts to overcome these limitations by substrate design and the development of new catalysts have led to some enantioselective variants and the identification of formal Claisen rearrangements using metal catalysts such as Cu,[6,7] Mg,[8] Pd,[9−11] Au,[12] Ir,[13,14] and Ru.[15] The well-studied biological rearrangement of chorismate to prephenate promoted by the enzyme chorismate mutase[16] has long inspired organocatalytic approaches[17,18] to the Claisen rearrangement. Pioneering work by Curran[19] on urea-promoted Claisen rearrangement of allyl vinyl ethers has been recently developed by Hiersemann[20] and Kozlowski[21] and further elaborated into a highly enantioselective processes by Jacobsen.[22−24] These impressive achievements still leave room for new approaches to catalytic, enantioselective Claisen-type reactions that improve reaction times, substrate scope, and selectivity.

In the course of developing enantioselective, NHC-catalyzed reactions of catalytically generated reactive species,[25−27] we identified an intriguing annulation reaction of ynals and stable enols. Key to this approach is the catalytic generation of the α,β-unsaturated acyl azolium (**I**, Scheme 2) by an internal redox reaction of ynals. This new NHC-promoted transformation proved amenable to enantioselective catalysis with chiral

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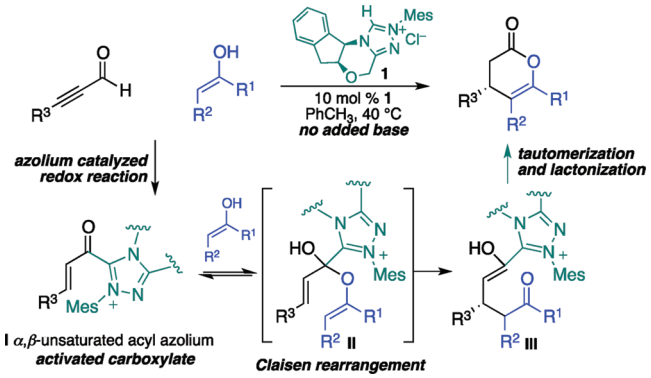
Scheme 2. An NHC-Catalyzed Claisen Rearrangement



triazolium salts to afford enantioenriched dihydropyranone products in excellent yield. Contemporaneously, Lupton has reported the related NHC-catalyzed annulation of α,β-unsaturated acyl fluorides and enol silanes[28] or unsaturated enol ester[29] using achiral imidazolium-derived NHCs, a process also thought to occur via a related unsaturated acyl azolium. Xiao,[30,31] Studer,[32,33] You,[34] and Ye[35] also reported similar annulation cascades. Lupton[36] has recently reported an elegant NHC-catalyzed formal [4 + 2] cycloaddition that proceeds via the catalytic generation of α,β-unsaturated acyl azolium. This unique C−C bond-forming activation mode represents the fifth discrete reactive species that can be generated from the combination of α,β-unsaturated aldehyde and an N-heterocyclic carbene. The other four (acyl anion equivalent,[37,38] homoenolate equivalent,[39,40] ester enolate equivalent,[41,42] and acyl azolium[43,44]) already have a rich chemistry of highly enantioselective C−C, C−O, and C−N bond-forming processes. An improved understanding of the mechanism and scope of reactions proceeding by the α,β-unsaturated acyl azoliums is critical to the further development of this field. In addition to their synthetic utility, α,β-unsaturated acyl azolium has also been invoked as an intermediate in the biosynthesis of secondary metabolites.[45]

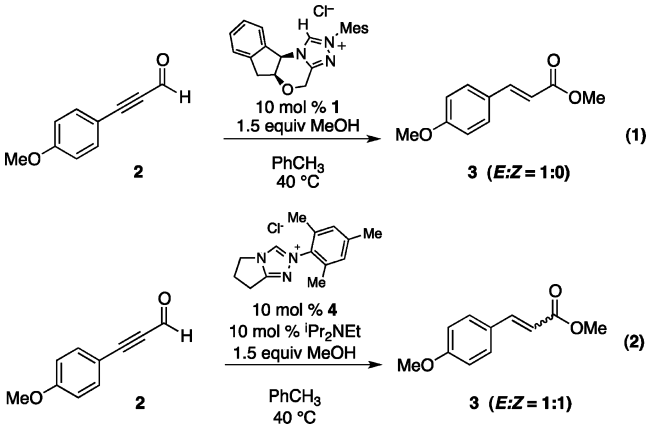
In our initial studies, we applied this finding to a catalytic, enantioselective Coates−Claisen reaction[46,47] of kojic acid derivatives to give enantioenriched products that have been proved to be both synthetically useful[48] and difficult to prepare otherwise.[49,50] We have also conducted extensive investigations into the reaction mechanism and confirmed that the reaction occurs via a Claisen-type rearrangement in our cases[51,52] rather than a 1,4-addition of the enol to the catalytically generated α,β-unsaturated acyl azolium.[53,54] Furthermore, our elucidated mechanism suggested that the Claisen rearrangement on the hemiacetal intermediate (**II**) should be the stereochemically determining step. These efforts, however, did not address the question of whether the NHC-catalyst was lowering the activation barrier for rearrangement or simply acting to preorganize the substrates. In this report, we document our investigation of various catalyst types and the substrate scope expansion of this reaction as well as our full investigations into the nature of this new class of NHC-promoted carbon−carbon bond formation.

RESULTS AND DISCUSSION

The possibility of affecting an NHC-catalyzed Claisen-type rearrangement emerged from our interest in NHC-catalyzed acylation reactions of alcohols[55] and amines.[56−58] Our own efforts, as well as prior works from Breslow,[59] Daigo,[60] White and Ingraham,[61] Bruice,[62] Lienhard,[63] and Owen,[64,65] have found that acyl azolium species are excellent acylating reagents for alcohol[66] and water but react only slowly with amine.[67] Daigo and Owen attributed this unusual behavior to the rapid formation of kinetically important hemiacetals in the acylation reaction, suggesting that intermediate **II** would have a significant lifetime during the acylation of enol.[68] Furthermore, our prior work on NHC-catalyzed annulations have evoked an NHC-mediated oxy-Cope rearrangement[69] as a possible pathway for C−C bond-forming reactions.

To generate the key α,β-unsaturated acyl azolium species, we adopted the clean and rapid redox esterification of ynals originally reported by Zeitler.[70] This reaction was thought to proceed via the catalytic generation of α,β-unsaturated acyl azoliums, a postulate that we have recently confirmed by characterization of this key intermediate.[71] Consistent with Zeitler, sterically hindered azolium catalysts such as IMesCl or **1** stereoselectively generated *E* ester **3** as the exclusive isomer deriving from an (*E*)-α,β-unsaturated acyl azolium species. Less sterically demanding catalyst, such as **4**, gave a mixture of *E* and *Z* isomers (Scheme 3). This stereoselective generation of the

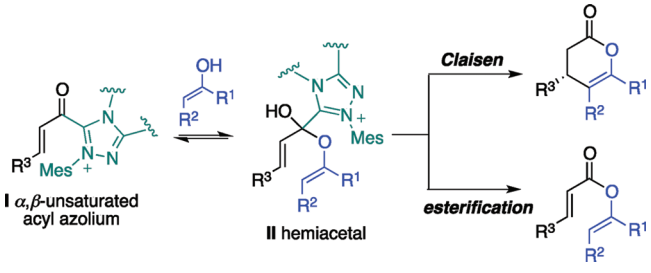
Scheme 3. Stereoselective Generation of α,β-Unsaturated Acyl Azoliums



key α,β-unsaturated acyl azolium intermediate should simplify the possible transition structures available during the Claisen rearrangement, conceivably leading to a high level of enantioinduction.

We anticipated that the correct combination of substrates and catalysts could lead to an annulation reaction via the Coates−Claisen pathway (Scheme 4). The competing reaction

Scheme 4. Competing Pathways of Hemiacetal Intermediate



would be the simple esterification; it was also conceivable that the resulting vinyl esters of α,β-unsaturated aldehydes could

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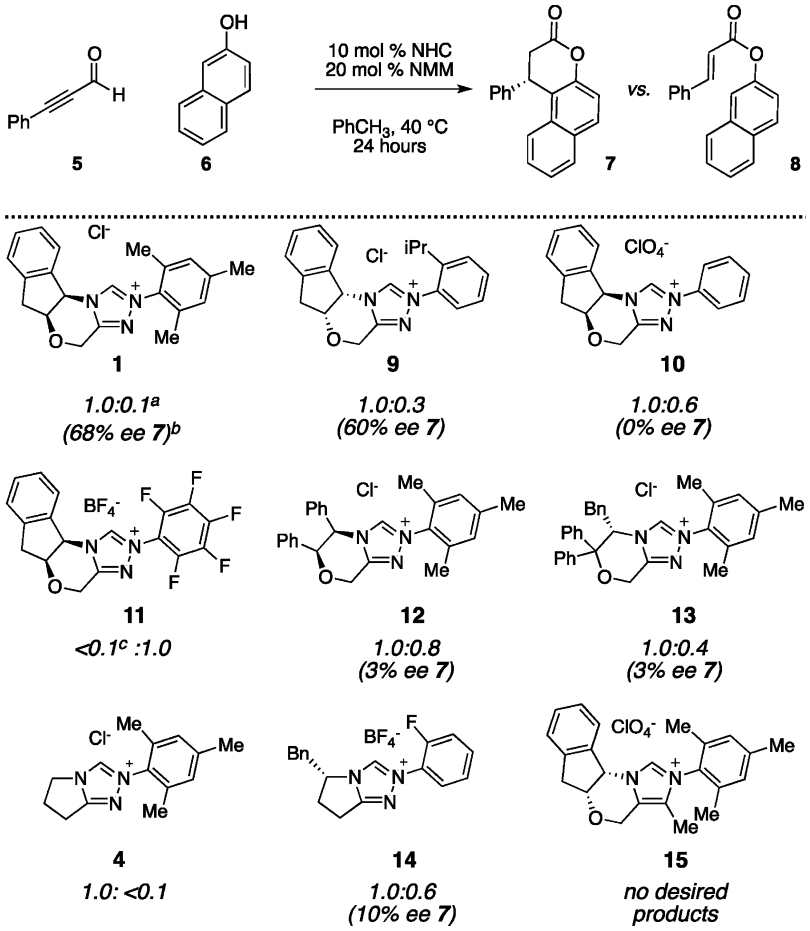
Table 1. Initial Investigation with 2-Naphthol



[a]The ratio of **7** to **8** was determined from ^{1}H NMR spectra of the crude mixture after 24 h. [b]Percent enantiomeric excess (% ee) was determined from SFC analyses. [c]% ee not determinable.

serve as substrates because these are known to be attacked by NHCs under the appropriate conditions.

We commenced our investigations by examining the acylation of 2-naphthol **6** and ynal **5** with various NHC precatalysts and *N*-methyl morpholine (NMM) as a catalytic base. Two products were observed: annulation product **7** and ester product **8** (Table 1). Control experiments established that the ester product was not converted to the annulation product under these conditions. Instead, the catalyst structure played a critical role in determining the product outcome. Electron-deficient aryl groups on the triazolium core (**11**) favored esterification, whereas *N*-mesityl substituent gave exclusively the annulation product. Other catalyst types gave a mixture of both. The choice of amine base played only a small role in determining the product distribution or enantioselectivity.

Although impressed with the ability of triazolium-derived carbenes to affect the desired annulation reaction, the suboptimal enantioselectivies forced us to reconsider our approach. In particular, we wished to perform catalyst development or screening on a more synthetically relevant substrate. An examination of the vast literature on Claisen rearrangements identified enantioselective rearrangements of kojic acid derivatives as an unmet synthetic need. For example, Wender has established Claisen rearrangements of kojic acid as a useful synthetic platform for synthesis of complex molecules but also noted the failure of traditional chiral Lewis acid approaches to the Claisen rearrangement of this particular substrate (Figure 1).[49]

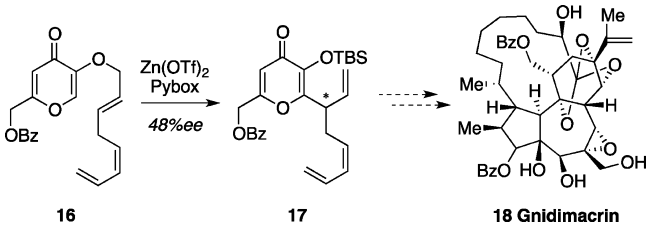


Figure 1. Wender's elaboration of Kojic acid.

We were pleased to find that the combination of kojic acid **20**, ynal **19**, and an NHC precatalyst led to the formation of the desired dihydropyranone (Table 2). This product proved to be somewhat unstable toward isolation by column chromatography, a problem that was overcome by adding MeOH at the completion of the reaction and stirring for 6 h, leading to the ring-opened products. In the course of our catalyst screening, we initially noted irreproducible outcomes with respect to the enantioselectivity. Control reactions showed that this issue arose from the propensity of this particular dihydropyranone adduct to undergo racemization, even in the presence of a weak base or acid. This issue was alleviated by conducting the reactions without added base, a surprising but effective solution.

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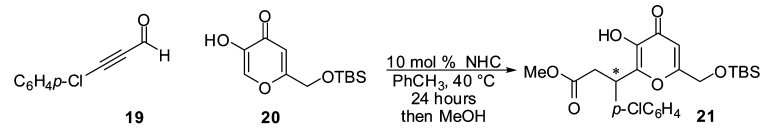
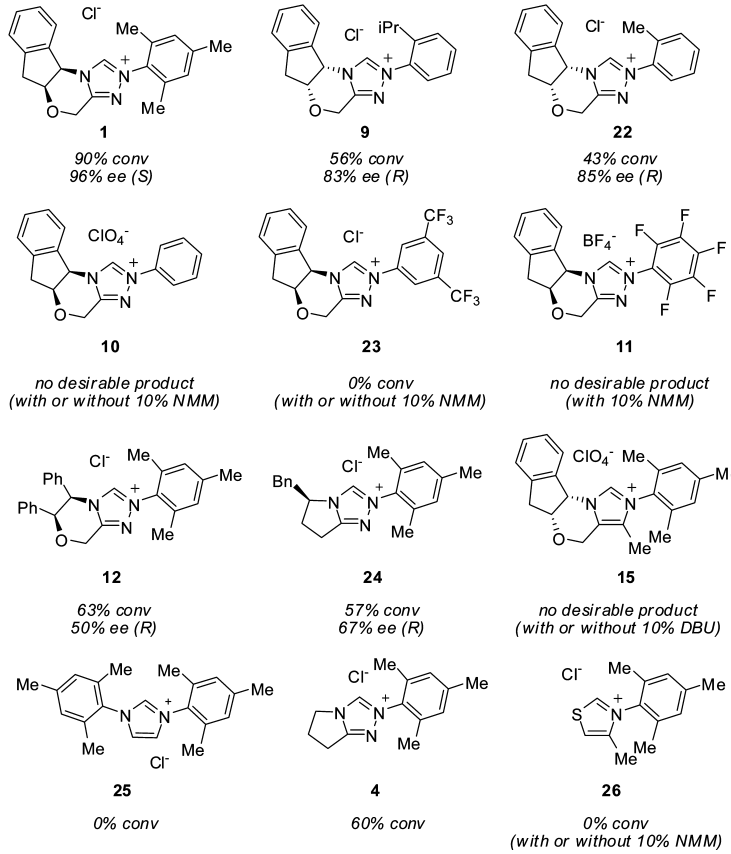
Table 2. Initial Catalyst Screening[a,b]





[a]Percentage conversion was determined from the ^{1}H NMR of the crude mixture after 24 h. [b]Percent enantiomeric excess was determined from SFC analyses.

This led to the optimized conditions: 1.0 equiv of kojic acid, 1.5 equiv of ynal, and 10 mol % triazolium **1** at 40 °C in toluene for 24 h. This base-free condition proved applicable to a full range of ynals with aliphatic, alkenyl, and aromatic substituents (Table 3). In nearly all cases examined, the desired product was obtained in excellent yield and enantiomeric excess.

We sought to further expand the substrate scope with regard to the enolic components and found that other stable enols undergo NHC-catalyzed couplings with ynals to give the expected dihydropyranone products. Pyruvic ester **38** and ethyl 3-oxobutanoate **41** were excellent substrates, provided that a weak amine base is added to promote enol formation. 2-Naphthol gave the corresponding dihydropyranone product, albeit with a diminished level of selectivity (Scheme 5). As expected from the work of others,[28−35] cyclic 1,3-diketone **43** should give the desired product in respectable enantiomeric excess when **1** is used as a precatalyst. To date, however, **43**, 2-hydrodroxynaphthoquinone **44**, hydroxycoumarin **45**, and thionaphthol **46** have not been suitable substrates in this variant of the Coates−Claisen reaction.

Two general features of this N-heterocyclic carbene catalyzed annulation deserve comment. First, in reactions with stable enols, including naphthol and kojic acid, no additional base was needed. This was attributed to the ability of the chloride counterion to serve as a base for generation of the active carbene; precatalysts with less basic counterions were not effective.[51] Second, regardless of whether a base was used, only triazolium catalysts that bear at least one ortho substitutent (**1**, **9**, or **22**; Table 2) were effective catalysts. Other azolium salts, such as imidazolium (**15** or **25**) or thiazolium (**26**) salts, did not give the desired product. Triazolium salt such as the pentafluorophenyl substituted derivative **11**, gave exclusively the ester product (vide infra). Among the chiral triazolium scaffolds examined, the aminoindanol core pioneered by Rovis[38] was uniquely effective in controlling the enantioselectivity. This was surprising, because other chiral scaffolds were often suitable for other classes of NHC-catalyzed annulations. It was also surprising that the aminoindanol core was again the superior choice, because this reaction involved a catalytically generated electrophilic species and all other NHC-catalyzed chemistry involved catalytically generated nucleophiles.

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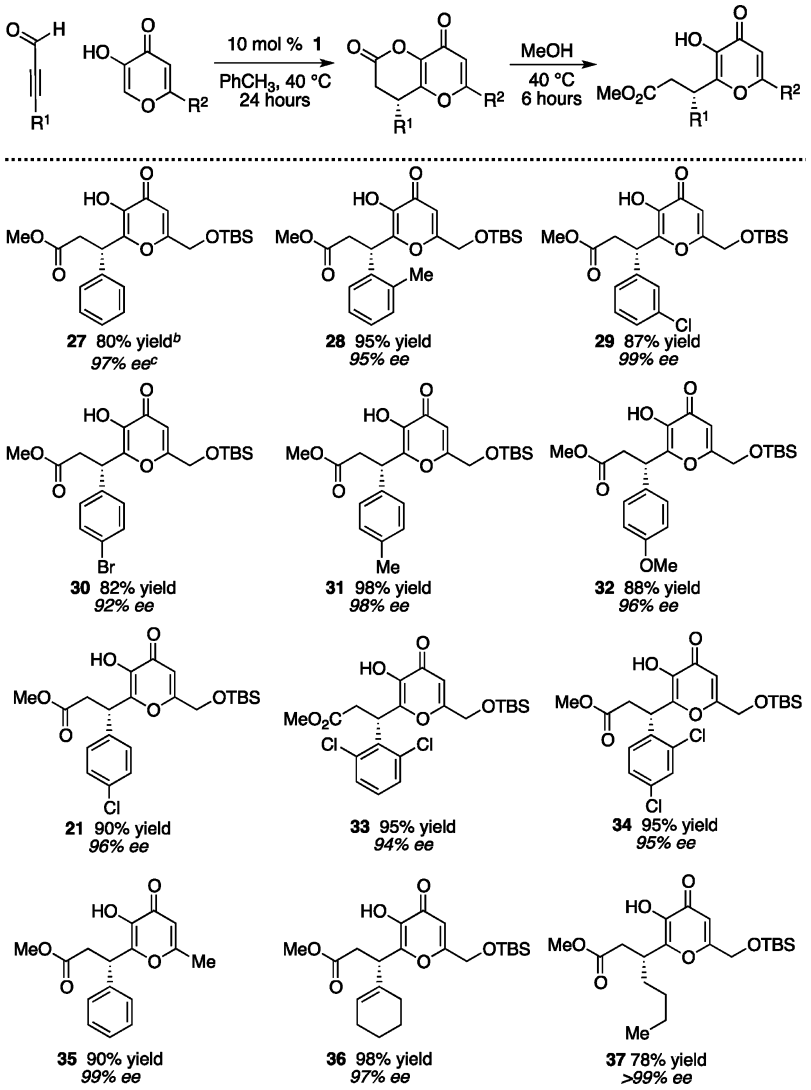
Table 3. Catalytic, Enantioselective Couplings with Kojic Acids[a]



[a]Reaction conditions: 0.1 M $PhCH_3$, 24 h. [b]Yield refers to isolated yield after chromatography. [c]Absolute configuration determined by conversion to (*S*)-phenylsuccinic acid.

Although ynals proved to be the ideal substrates for our optimization studies and mechanistic investigations, the relative difficulty of synthesizing and storing these compounds render them less attractive starting materials than other substrates typically used in NHC-catalyzed reactions. In his related studies on NHC-catalyzed annulations, Lupton employed α,β-unsaturated acyl fluorides or enol esters, which generate the α,β-unsaturated acyl azolium without redox chemistry.[28,29] In the context of oxidative esterifications of cinnamaldehyde, Studer[72] reported several examples of reactions that should proceed via the identical α,β-unsaturated acyl azolium species critical to the success of the Coates−Claisen reactions (Scheme 6). Indeed, we briefly explored the combination of enal and a stoichiometric oxidant as a route to these intermediates in our Communication.[51] Studer has nicely demonstrated this approach as a general entry to racemic dihydropyranone synthesis.[32]

After a standard course of screening for suitable oxidant, we found that the oxidant **47** reported by Kharasch[73] and utilized by Studer was superior to phenazine,[74] azobenzene,[75] MnO_2,[76] TEMPO,[77] or air.[78] Kojic acid derivative **20** proved again to be a good substrate for the coupling with both aliphatic and aromatic enals (regardless of the substitution) in this oxidative method; however, we noted the decrease in percent conversion in the absence of base. This was likely due to the decreased reactivity of enals, in comparison with the ynals, and the acidic phenolic proton of the reduced form of the oxidant, which caused catalyst inhibition. When a base such as $^{i}Pr_2NEt$ was employed, the catalyst reactivity was restored, but racemization during the formation of the desired products **51**−**53** was observed; however, the use of base in conjunction with enal substrates bearing aliphatic side chain did not present a problem. This approach is the preferred route to aliphatic-substituted products, in terms of both ease and availability of the starting enals (Table 4). In our hands, more-substituted enals, such as **54**−**56**, did not currently work with kojic acid as a reaction partner. In addition, we have demonstrated the generality of our methodology with various naphthols. Both 2- and substituted-naphthols proved to be viable substrates when coupling with either cinnamaldehyde or crotonaldehyde, although with decrease in stereoselectivity. The enantiomeric

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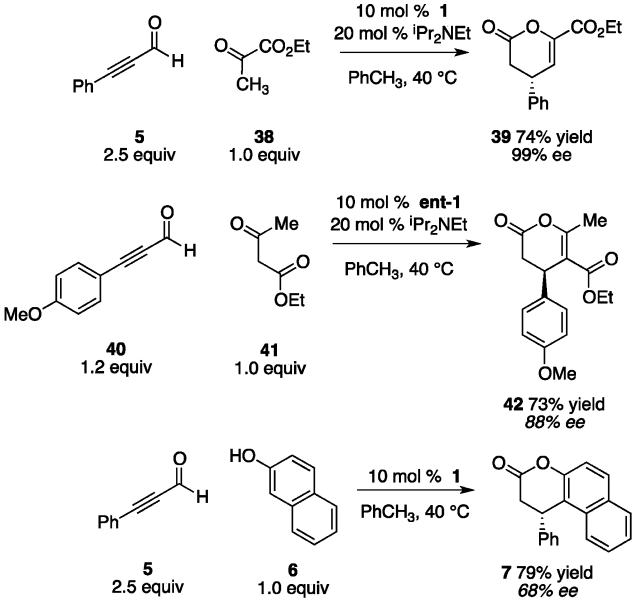
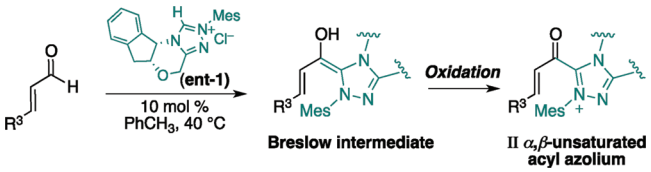
Scheme 5. Catalytic, Enantioselective Couplings with Other Enol Partners



Scheme 6. Catalytic Generation of α,β-Unsaturated Acyl Azolium from Enal via the Oxidation of the Breslow Intermediate



excess was improved with 1-naphthol; however, byproducts were observed and led to diminished chemical yield (Table 5).

MECHANISTIC CONSIDERATION

At the outset of our investigation into the reactivity of α,β-unsaturated acyl azolium, we anticipated that this transiently generated intermediate would serve as an excellent electrophile for conjugate addition reaction. This hypothesis was further supported by its postulated role in the biosynthesis of clavulinic acid, in which an α,β-unsaturated acyl azolium served as the electrophile for the conjugate addition with amine.[79] Our initial attempts at effecting conjugate additions with nucleophiles, including thiols, azide, hydroxamic acids, and electron-rich aromatic compounds, were unsuccessful. Upon further investigation of conjugate addition with 1-methylindole and α,β-unsaturated acyl azolium generated using stoichiometric amount of the NHC catalyst and in the absence of a competing nucleophile, we have since found that conjugate addition could be achieved (Scheme 7). Although the conversion was low, the formation of the expected product in respectable enantioselectivity demonstrated that the α,β-unsaturated acyl azolium is not precluded from the possibility of undergoing 1,4 addition with a suitable nucleophile.[80] The related annulations of α,β-unsaturated acyl azoliums and enols or enolates[28−35] have all invoked this mechanistic paradigm.

The much slower rate of 1-methylindole in comparison with stable enols (i.e., **20**, **38**, or **6**) and the failure of almost all other good Michael donors (**43**-**46**) to give the expected conjugate addition products prompted us to consider the Coates−Claisen mechanism. Extensive investigations reported in our prior Communication[51] established the catalytic cycle shown in Figure 2. The triazolium salt precatalyst (**III**) is deprotonated by a general base (i.e., the counterion) to generate active NHC **IV**. This species adds irreversibly to aldehyde to form an adduct that readily undergoes a proton transfer and an internal redox reaction to form α,β-unsaturated acyl azolium **I**. Following the well-known chemistry of acyl azolium,[59−65] this species and the enol are expected to be in equilibrium with hemiacetal **II**. According to a Coates−Claisen mechanism, this kinetically important hemiacetal undergoes a [3, 3]-sigmatropic rearrangement to afford adduct **VIII**, which undergoes tautomerization and lactonization to effect catalyst turnover and deliver dihydropyranone product (**X**).

Depicted in Figure 2, the key hemiacetal **II** is in an overall neutral form (with an oxy anion). It is also conceivable that hemiacetal **II** is protonated and exists as an ion pair with the counterion (Cl^-). An ongoing computational investigation to resolve this issue and its implication on enantioinduction will be disclosed in due course. As noted by both ourselves[51] and Coates and Curran[81] in their seminal investigation, it is not possible to completely distinguish between a "true" sigmatropic rearrangement and the breakdown of the acetal to a tight ion pair that undergoes a stepwise carbon−carbon bond-forming process via a highly organized transition state. This mechanistic conundrum has been well-described for some Claisen reactions.[2] The most accurate description of our reaction is perhaps an "ion-pair Claisen-type" rearrangement.

The derived and observed rate laws for the reaction of kojic acid **20** with 2,4-dichlorophenyl-substituted ynal **65** are shown in Table 6. This experimental rate law is consistent with a derived one, which takes into consideration the generation of the NHC from the azolium, a steady-state approximation of the initial aldehyde−NHC adduct, and the rapid equilibrium between **I** and its hemiacetal **II**.[82] The derived rate law also rationalizes partial rate orders of the reaction both in the aldehyde and the kojic acid (expressed as a general acid HX), which inhibits the generation of the N-heterocyclic carbene.[83−85]

We proceeded to determine the activation parameters via an Eyring analysis using the empirical rate law above. The NHC-catalyzed variant of the Coates−Claisen reaction has an activation enthalpy of 15.3 kcal/mol and activation entropy of −25.5 cal/K·mol (Figure 3). Both the activation enthalpy and entropy are consistent with those observed by Coates and Curran[81] ($\Delta H^{\ddagger}$ from 12.7 to 20.8 kcal/mol and $\Delta S^{\ddagger}$ from −18.9 to −31.8 eu). A large negative activation entropy is usually associated with an organized transition state, which also supported the proposed [3, 3]-sigmatropic mechanism.

A rate study comparing the relative reactivity of various para-substituted ynals for the Claisen rearrangement revealed no Hammett trend, whereas a linear free-energy relationship was observed for the redox esterification reaction of ynals[71] (Scheme 8). The lack of Hammett trend for the Claisen rearrangement was somewhat unexpected, and we attributed

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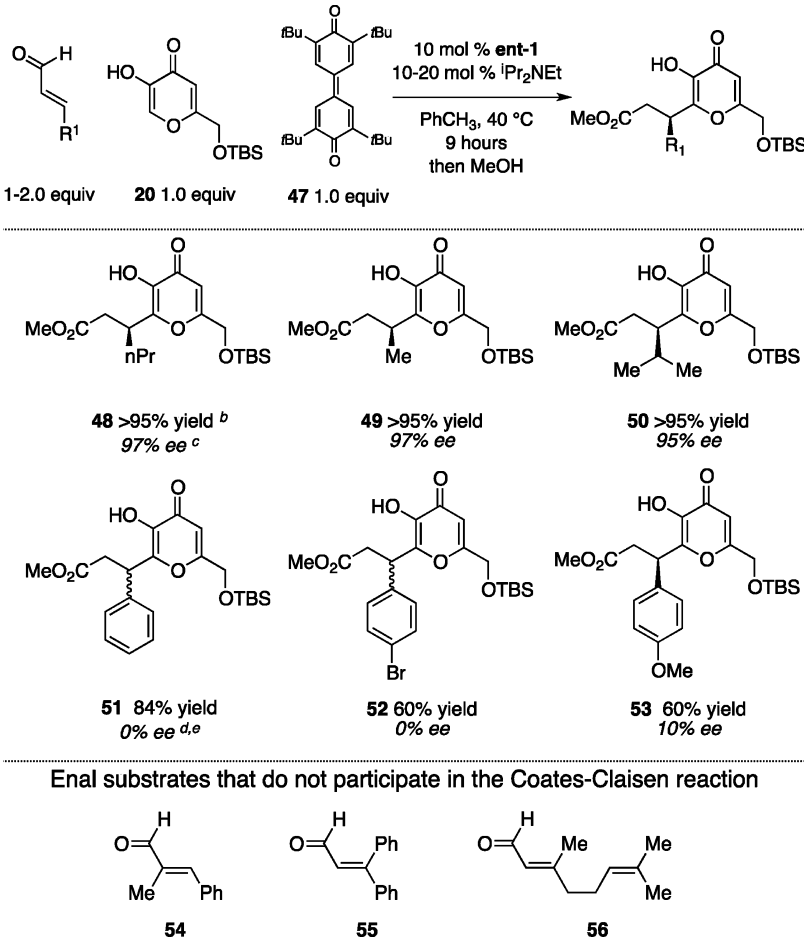
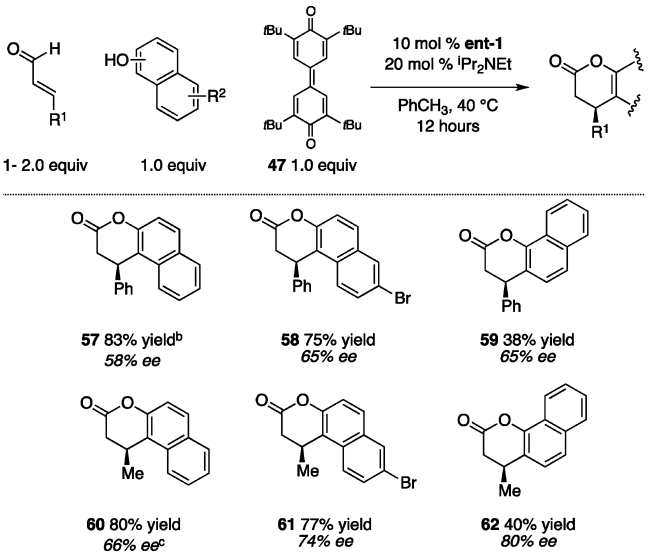
Table 4. Catalytic, Enantioselective Couplings with Enals[a]



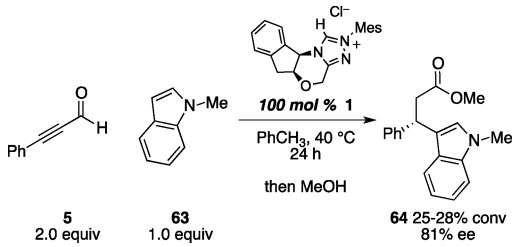
[a]Reaction conditions: 0.1 M $PhCH_3$, 9 h. [b]Yield refers to isolated yield after chromatography. [c]Absolute configuration was assigned by analogy from Table 3. [d]With 0.5 equiv of the **47** (without $^iPr_2NEt$), we obtained 50% conversion of the product (97% ee). [e]When 1.0 equiv of oxidant **47** was used (without $^iPr_2NEt$), we also obtained 50% conv of the product (88% ee).

Table 5. Catalytic, Enantioselective Couplings with Naphthols[a]



[a]Reaction conditions: 0.1 M $PhCH_3$, 12 h. [b]Yield refers to isolated yield after chromatography. [c]Absolute configuration was assigned by comparison of the $[\alpha]_D$ value with the literature value.

Scheme 7. A Conjugate Addition of 1-Methylindole to α,β-Unsaturated Acyl Azolium



this observation to ground state stabilization of α,β-unsaturated acyl azolium rather than a change in the mechanism.[86] Despite this, the difference in the reactivity of ynals between these two reactions proceeding via common hemiacetal intermediates allowed us to rule out catalyst turnover (which is the rate-determining step of the redox esterification[71]) as the rate-limiting step for this annulation reaction.

As pointed out by a referee in our Communication,[51] the negative order of kojic acid **20** in the observed rate law could arise by a mechanism in which the N-heterocyclic carbene played an active role in activating the nucleophile. For example, in the acylation reaction of acyl azoliums with alcohols, a

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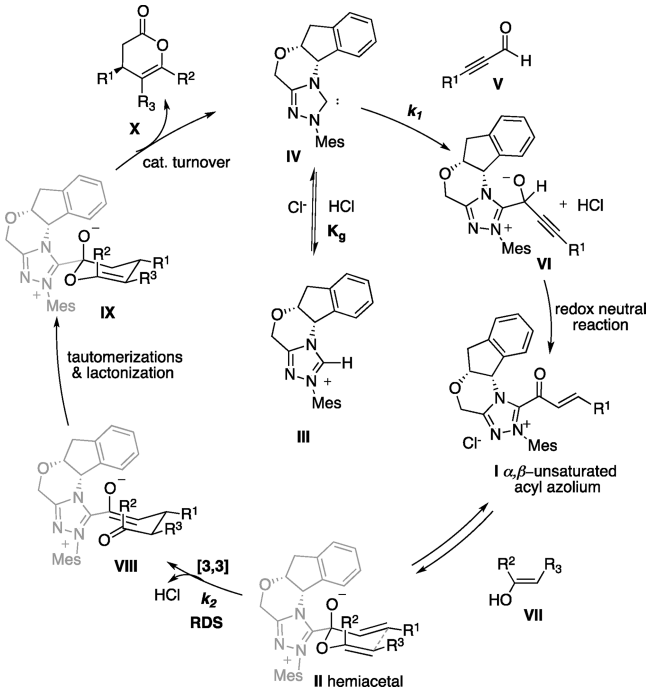


Figure 2. The catalytic cycle for NHC-catalyzed Claisen rearrangement from ynal and an enol.

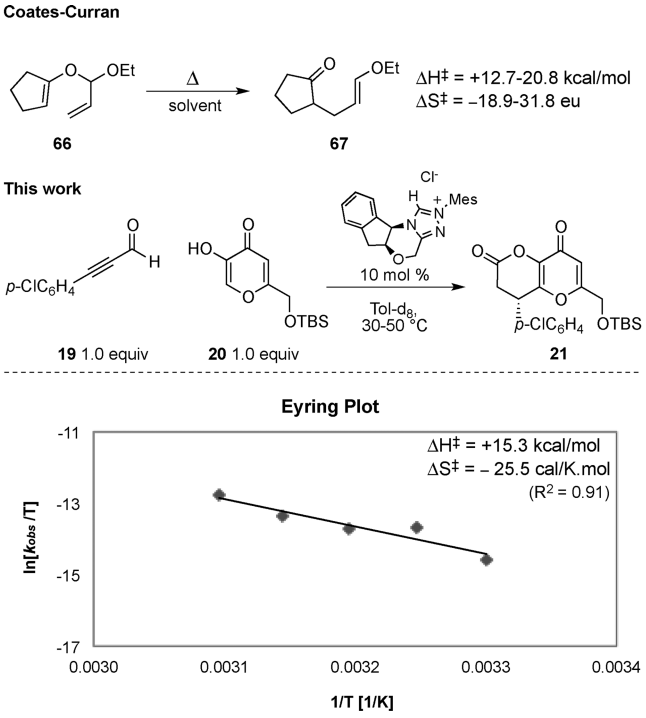
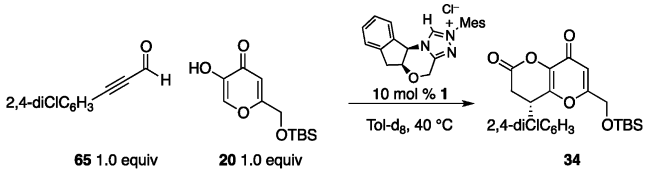


Figure 3. The activation parameters for Coates–Claisen reaction and the NHC-catalyzed variant.

Table 6. Rate Laws for NHC-Catalyzed Claisen Rearrangement



Empirical rate law (from above):

$$rate = k_{obs}[1]^{1}[65]^{1/2}[20]^{-1/2}$$

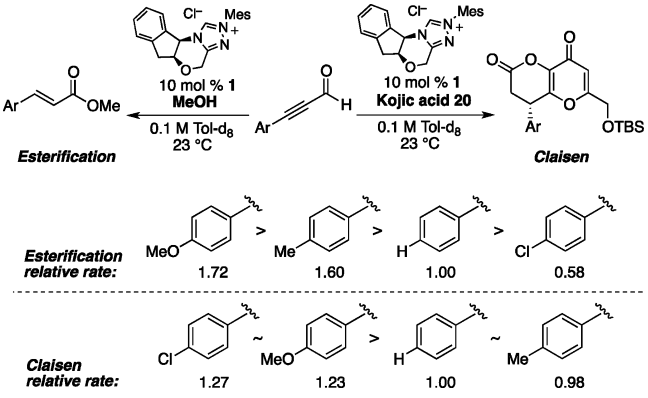
Derived rate law (from Figure 2):

$$rate = k_2 \frac{[IV]_0[V]}{[V] + \frac{k_2 + k_{-1}}{k_1}\left(1 + \frac{[HX]}{K_g[X^-]}\right)}$$

process that involves similar intermediates as this annulation, it was proposed that the NHC activated the alcohol toward nucleophilic attack.[66,87] This implies that two molecules of the catalyst would be involved in the key bond-forming step. To test this, we briefly examined our annulation reaction for nonlinear effect using precatalyst **1** with varying degrees of enantiopurity. No such effect was observed, suggesting a single role for the catalyst in this reaction (Figure 4).

The last remaining question, which cannot be directly answered by kinetic studies, concerns the nature of the catalytic Claisen rearrangement. Does the *N*-mesityl triazolium catalyst play a role in lowering the activation barrier to the sigmatropic rearrangement, or does it simply serve as a chiral auxiliary for controlling the stereochemistry of the rearrangement? From our initial catalyst screening, we found intriguingly that the

Scheme 8. Ynals Reactivity Comparison



aminoindanol-derived triazolium salt **1** bearing the *N*-mesityl group affected the desired annulation cascade but the otherwise identical triazolium salt **11** bearing an *N*-C_6F_5 group cleanly afforded ester **69** as the sole product via a redox-neutral reaction (Scheme 9). On the basis of this finding, we propose that the mesityl moiety of the catalyst raises the activation barrier of the competing esterification and effectively prolongs the lifetime of the hemiacetal **II**, and the chiral aminoindanol moiety induces enantioselectivity by favoring one of the possible diastereomeric transition states for the Claisen rearrangement. In contrast, the *N*-C_6F_5 group made its corresponding carbene a better leaving group, accelerating the C–C bond cleavage during catalyst turnover (by lowering its energetic barrier). This mechanistic bifurcation was observed for the coupling of ynals with both kojic acid derivative **20** and 2-naphthol **6** (Table 1). The origin of these two catalysts' divergence has been extensively investigated.[88]

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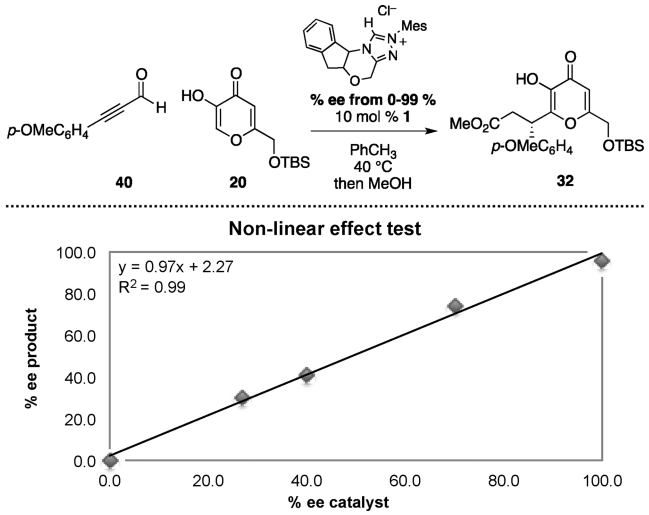
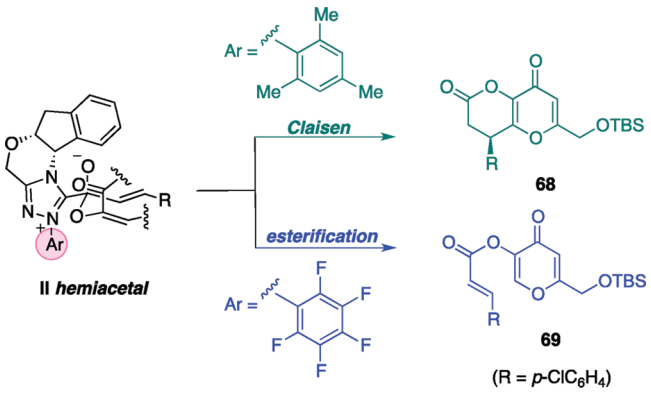


Figure 4. Investigation of nonlinear effect.

Scheme 9. Catalyst-Controlled Product Selectivity: Claisen Reaction vs Esterification



CONCLUSION

We have reported herein the development of a chiral N-heterocyclic carbene catalyzed Coates–Claisen rearrangement. This reaction generally proceeded with a broad substrate scope and in many cases with a very high level of enantioselectivity. The key α,β-unsaturated acyl azolium intermediate was accessible via a NHC-catalyzed redox neutral reaction of ynals or oxidative reaction of enals. The synthetic utility of this methodology has also been demonstrated in the context of the functionalization of kojic acid derivatives, ready for further elaboration into compounds of contemporaneous interest. Detailed kinetic analysis provided insights into the nuances and the complex nature of the mechanism of this NHC-catalyzed annulation reaction.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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