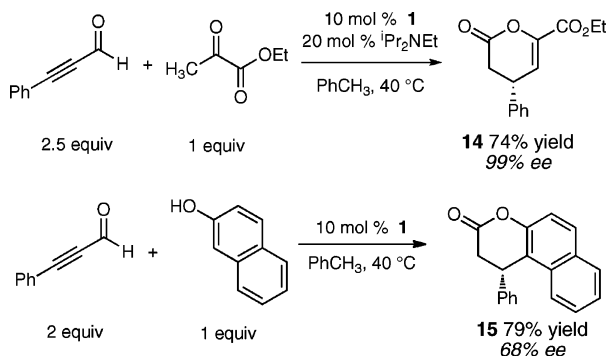


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adopted for product isolation (Table 1). A standard course of optimization identified the conditions shown in Table 1. The addition of a catalytic base (NEt_3 , *N*-Me-morpholine) increased the reaction rates but led to side products and a decrease in enantiopurity. In the absence of a triazolium salt, no reaction occurred regardless of whether or not base was present. Within our focus on reactions of kojic acid derivatives, the reaction proceeded with a broad range of ynals including both aromatic and aliphatic derivatives, all in good yield and with exceptional enantioselectivity.

Scheme 2. Azolium-Catalyzed Annulations of Ynals via Claisen Rearrangements



Although we have not exhaustively explored the scope of this reaction, we have found that many enolic compounds couple with ynals to give the expected products (Scheme 2). We were pleased to find that pyruvic esters are excellent substrates, provided that a weak amine base is added to promote enol formation. Phenolic compounds, such as naphthols, give Claisen products but with diminished levels of selectivity. The key α,β -unsaturated acyl triazolium **I** could be generated from other substrates, including α,β -unsaturated aldehydes via *in situ* oxidation.¹⁵

In all prior reports on the use of azolium salts as catalysts or precatalysts, including our own work, the addition of a base was required, presumably to generate the N-heterocyclic carbene, which is thought to be the active nucleophilic catalyst. This annulation proceeds smoothly in the absence of added base but is slower and counterion dependent; in contrast, NHC-catalyzed reactions in the presence of base show no counterion effects.¹⁶ In the absence of base, ^1H NMR investigations reveal no detectable loss of the azolium C-2 proton during the course of the reaction.¹⁷ While we cannot rule out alternative mechanisms at this time,¹⁸ our current understanding is that the chloride ion plays the role of base in generating a trace amount of the nucleophilic carbene, which quickly attacks the aldehyde to initiate the catalytic cycle. This is supported by comparing the reactivity of precatalysts bearing different counterions (Table 2). The acetate precatalyst is much more reactive than the chloride but led to product epimerization. Precatalysts with less basic counterions, such as SbF_6^- or ClO_4^- , are unreactive. The addition of a catalytic amount of a weak amine base restores the activity to levels similar to that observed with the chloride counterion.

During the preparation of this manuscript, Lupton reported a racemic dihydropyranone-forming annulation from enolates via α,β -unsaturated acyl azolium species, promoted by imidazolium-derived NHCs under basic conditions.¹⁹ Although the starting materials and reaction conditions are different from those for our process, the postulated intermediates are identical and the reactions are likely to be mechanistically related. Lupton proposes a direct Michael addition of an enolate to **I**, but our observations (*vide supra*) to date are more consistent with the Claisen mechanism shown in Figure 1.²⁰

We considered five possible rate-determining steps for the overall catalytic reaction, listed in red in Figure 1: (1) the initial redox reaction/protonation to form **I**; (2) the 1,2 addition of kojic acid to give

Table 2. Effect of Azolium Counterion on Conversion^a

X =	% conv 1 h	% conv 2.5 h	% conv 12 h
Cl^-	10	16	70
OAc^-	100	na	na
CF_3CO_2^-	7	10	20
ClO_4^-	0	0	trace
SbF_6^-	0	0	0
$\text{SbF}_6^- + \text{NMM}(30\%)$	30	35	86

^a Determined by ^1H NMR analysis against an internal standard.

hemiacetal **II**; (3) the conjugate addition of kojic acid to **III**; (4) the Claisen rearrangement of **II** to give **III**; (5) the lactonization of **III** to give **IV** and effect catalyst turnover. These mechanistic possibilities can be differentiated by analysis of the reaction kinetics. Kinetic studies of azolium-catalyzed processes such as the benzoin and Stetter reactions are often plagued by the presence of multiple rate-determining steps and catalyst inhibition;²¹ however, this system proved somewhat more tractable to analysis. We determined the empirical rate law for the reaction of kojic acid **17** with 2,4-dichlorophenyl substituted ynal **18** to be

$$\frac{d[\text{P}]}{dt} = k_{\text{obs}}[\text{I}]^1[\text{RCHO}]^{1/2}[\text{kojic acid}]^{-1/2} \quad (1)$$

From this experimental rate law, we also determined the activation parameters from the rate constant via an Eyring plot, which revealed an activation enthalpy of 15.3 kcal/mol and activation entropy of -25.5 cal/K·mol. The lactonization is excluded as the rate-limiting step by the activation parameters. The redox reaction–protonation step is excluded by isotopic labeling experiments, which show no kinetic isotope effect for the protonation.²² The 1,2-addition of kojic acid to **I**, as well as the 1,4-addition pathway, is excluded by the observed negative order of the reaction in kojic acid. These experimental results are consistent with a derived rate law (eq 2) for the Claisen rearrangement that takes into consideration generation of the NHC from the azolium, a steady-state approximation of the initial aldehyde–NHC adduct, and rapid formation of hemiacetal **II**.²³

$$\frac{d[\text{P}]}{dt} = k_2 \frac{[\text{I}]^1[\text{RCHO}]^1}{[\text{RCHO}] + \frac{k_2 + k_{-1}}{k_1} \left(1 + \frac{[\text{HX}]}{K_g[\text{X}^-]} \right)} \quad (2)$$

This rate law rationalizes the partial positive order of the reaction in aldehyde and the negative order of kojic acid, which inhibits generation of the N-heterocyclic carbene by acting as a general acid (HX in eq 2). It explains the observation that the reaction rate increases in the presence of added base by generating more of the NHC and provides a role for the counterion of the azolium salt as a general base to generate the active catalyst (X^- in eq 2).

Other observations are also most consistent with the Claisen pathway. All attempts to effect conjugate additions with nucleophiles that cannot undergo Claisen rearrangement, such as indoles or hydroxamic acids,²⁴ have failed; in most cases 1,2-adducts are obtained instead. The well-studied chemistry of acyl azoliums documents the rapid formation of hydrates and hemiacetals in their acylation

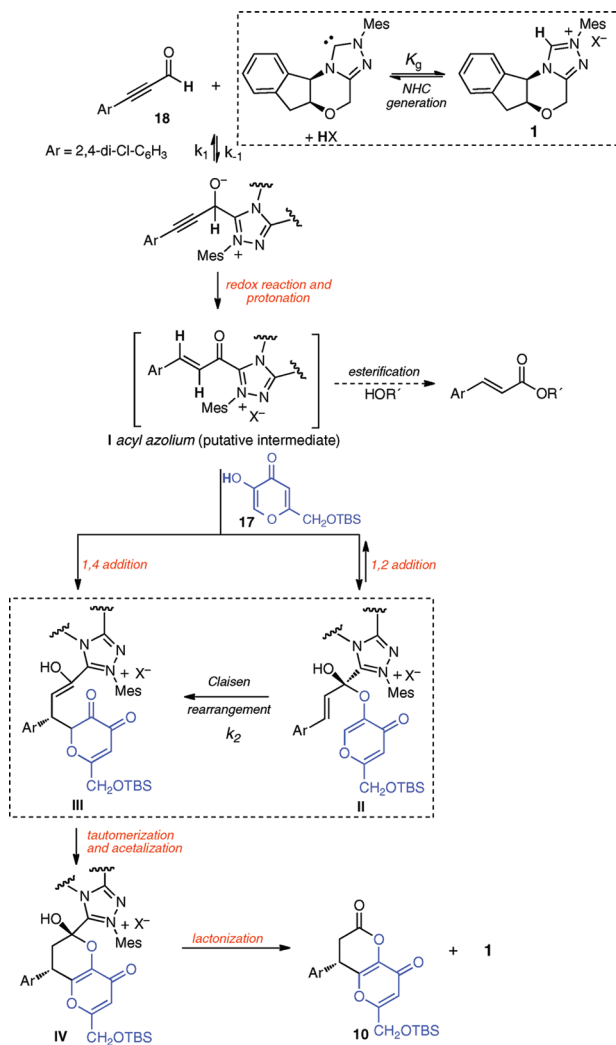


Figure 1. Possible mechanistic pathways for NHC-catalyzed annulation.

reactions.^{7,25} These hydrates are stable under acidic conditions and require general base catalysis to give hydrolysis products. This may explain the cleaner and higher yielding outcome of this reaction under our acidic conditions. The reaction is relatively insensitive to sterics; an *ortho,ortho*-dichloro derivative is competitive with its *ortho,para*-isomer, which would not be expected in the conjugate addition pathway (see Supporting Information).²⁶ Finally, the excellent enantioselectivity is best rationalized by a reversible, but stereochemically determining, 1,2-addition adjacent to the chiral triazolium to give the Claisen precursor. In contrast, a C–C bond forming conjugate addition would be an irreversible stereochemically determining step.

Although we cannot completely rule out a short-lived enolate–acyl azolium ion pair, our results, including the activation entropy, are consistent with the detailed studies of Coates and Curran on the related Claisen rearrangement of 2-alkoxy-substituted vinyl ethers. More importantly, these studies provide a new mode of substrate activation unique to chiral N-heterocyclic carbenes and, via their ability to access multiple catalytically generated reactive species in a tandem fashion,²⁷ a pathway to induce high levels of enantioselectivity and provide solution to catalyst turnover in a catalytic Claisen manifold.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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