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Mechanistic alternatives in Lewis acid-catalyzed acyl halide–aldehyde cyclocondensations

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Abstract

An investigation of the operative reaction mechanisms in Lewis acid-catalyzed acyl halide–aldehyde cyclocondensations is presented. Aluminum-based catalysts promote cyclocondensation via a ketene-dependent reaction pathway while acyl halide enolates are implicated as reactive intermediates in Ti(IV)-catalyzed reactions.

Aluminum-catalyzed acyl chloride–aldehyde cyclocondensation (AAC) reactions have recently been developed as a strategy for executing catalyzed chemospecific crossed aldol reactions.[1] These Al(III)-catalyzed acyl halide–aldehyde cyclocondensations were postulated to proceed via amine-mediated ketene generation with ensuing Lewis acid-catalyzed [2+2] cycloaddition affording the desired β-lactone adducts **1** (Fig. 1, path a).[2] However, the AAC reaction conditions closely parallel the Lewis acid-tertiary amine base 'soft enolization' conditions used extensively in stoichiometric aldol reactions, causing us to consider acid chloride enolates **2** as potential reaction intermediates.[3] Intervention of an acyl halide enolate-dependent reaction pathway in the AAC reactions would be indistinguishable from the [2+2] cycloaddition mechanism as cyclization of the aldolate intermediate **3** emerging from the enolate–aldehyde addition process would afford the analogous β-lactone adduct (Fig. 1, path b). Either of these reaction mechanisms would place considerably different constraints on the design and development of effective chiral reaction catalysts. To expedite the development of asymmetric catalytic variants of the AAC reactions, we were interested in defining the reaction mechanism operating in these transformations. The results of these investigations and their implications for the development of asymmetric AAC reactions are detailed herein.

Preliminary investigations directed toward developing catalyzed AAC reactions provided evidence suggesting the intermediacy of acid chloride-derived enolates under certain reaction conditions. For example, while using $Al(SbF_6)_3$ as the reaction catalyst afforded exclusively β-lactone **1**, the $Cl_2Ti(O\textit{i}\text{-}Pr)_2$-catalyzed (10 mol%) reaction of acetyl chloride with cyclohexane carboxaldehyde selectively afforded dioxanone **4** and only small quantities of β-lactone **1** (Eq. 1).[4]

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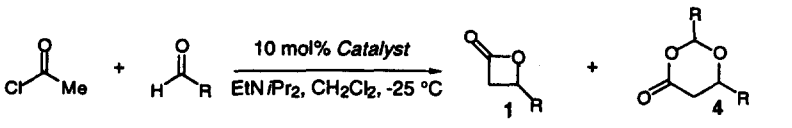
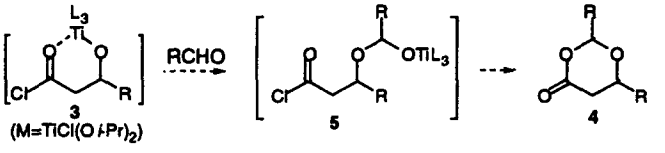


Catalyst	1:4 (% yield)
$Al(SbF_6)_3$	>95:<5 (≥81%)
$Cl_2Ti(O\textit{i}Pr)_2$	10:90 (53%)

(1)

To establish that dioxanone **4** was not derived from further reaction of the β-lactone adduct, isolated lactone **1** was resubjected to the cyclocondensation reaction conditions. No dioxanone formation was observed in this reaction, indicating that dioxanone products result from a reaction pathway independent of any [2+2] cycloaddition mechanism responsible for β-lactone formation. Thus, contrary to initial expectations, these investigations revealed that ketene-dependent reaction mechanisms did not adequately describe all of the available reaction pathways for the catalyzed cyclocondensation reactions. In fact, the formation of dioxanone **4** is best accommodated by a reaction mechanism involving acyl halide deprotonation to engender a reactive acid chloride enolate **2** and ensuing aldehyde addition affording aldolate **3** (Fig. 1). Intermolecular reaction of **3** with another equivalent of aldehyde and cyclization of the resulting metallo hemiacetal **5** would deliver the observed dioxanone product **4** (Eq. 2).[5]



(2)

These observations raised doubts that the Al(III)-catalyzed AAC reactions that afforded exclusively β-lactone products could be uniformly categorized as ketene–aldehyde cycloadditions. To verify the operative mechanism under these reaction conditions, the elemental steps involved in the Lewis acid-catalyzed AAC reactions were examined using ^{13}C NMR. Lewis acid-mediated deprotonation of $^{13}C_1$-labeled acetyl chloride with di(isopropyl)ethylamine (DIEA) was monitored by low-temperature (–78°C) ^{13}C NMR (Eq. 3); at –78°C, acid chloride deprotonation in the presence of 10 mol% $Al(SbF_6)_3$ is rapid with the C_1-ketene resonance (δ 194) appearing within 5 min (unreacted acetyl chloride is also observed).[6] No ^{13}C resonances indicative of enolate-like structures were observed. Evidence for acylammonium ion formation was also absent indicating that amine acylation is not significant under these reaction conditions. Adding cyclohexanecarboxaldehyde to the NMR tube and warming to –30°C, the optimal temperature for executing the catalyzed AAC reactions, resulted in the appearance of the β-lactone C_2 resonance (δ 168) with a corresponding decrease in the ketene resonance intensity.

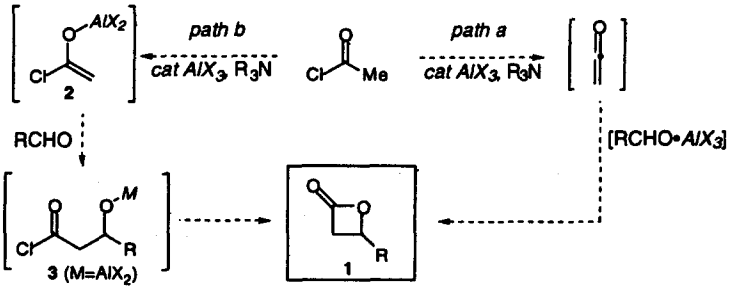
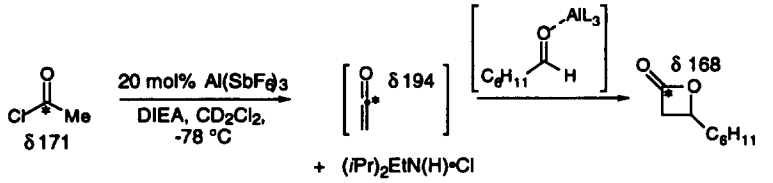


Figure 1. Potential reaction pathways for catalyzed AAC reactions

Treating acetyl chloride with DIEA at −78°C in the absence of Lewis acid also generates ketene; however, aldehyde addition to this reaction and warming to −30°C affords only the appearance of resonances consistent with diketene (C_2 δ 166 and C_4 δ 148) and no detectable β-lactone product. These observations strongly support a ketene–aldehyde cycloaddition reaction pathway as being the operative mechanism in the Al(III)-catalyzed acid chloride–aldehyde cyclocondensations.



(3)

Verifying a Lewis acid-catalyzed ketene–aldehyde cycloaddition as an integral component of the Al(III)-catalyzed AAC reactions has critical implications for the design of asymmetric reaction variants. The nature of the stereochemically defining C–C bond construction and the role of the metal complex in this process are now elucidated. The reactive Lewis acid–aldehyde complex involved in the ketene addition, therefore, emerges as a strategic platform for effecting absolute stereocontrol within these catalyzed C–C bond constructions. These mechanistic insights in conjunction with structural data of relevant Al(III)-derived Lewis acid–base complexes should accelerate the development of effective asymmetric reaction variants.

Acknowledgements

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