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Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene−Aldehyde Cycloadditions

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In 1982, Wynberg reported an extraordinary example of asymmetric Lewis base catalysis in the context of cinchona alkaloid-catalyzed ketene−chloral cycloadditions (Figure 1).[1] Wynberg's pioneering investigations undoubtedly provided inspiration to recent reports of asymmetric alkaloid-catalyzed ketene−imine cycloadditions,[2] ketene dimerizations,[3] and intramolecular ketene−aldehyde cycloadditions.[4] The success of these latter investigations, however, serves to emphasize the absence of a ketene−aldehyde cycloaddition based on the Wynberg model addressing the original transformation's severe substrate limitations. Successfully extending the Wynberg ketene−aldehyde cycloadditions to structurally diverse aldehydes would afford access to versatile enantioenriched β-lactones using a commercially available catalyst.[5] Herein, we report asymmetric cinchona alkaloid (**1** or **2**)-catalyzed acid chloride−aldehyde cyclocondensation (AAC) reactions applicable to a range of structurally diverse aldehydes. These reactions are characterized by exceptionally high enantio- and diastereoselection and the operational simplicity derived from using commercially available reaction catalysts and in situ ketene generation.

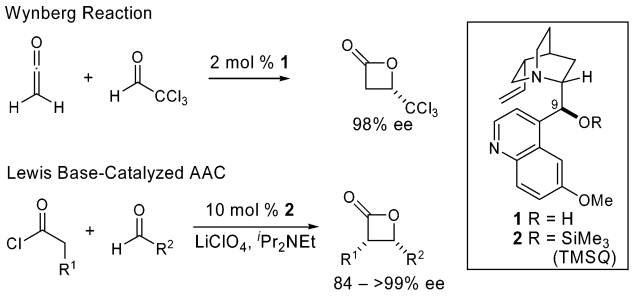


Figure 1. Alkaloid-Catalyzed Ketene−Aldehyde Cycloadditions.

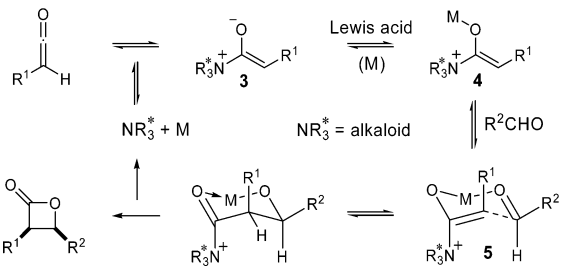
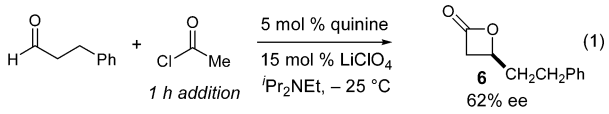


Figure 2. Postulated Mechanism for Alkaloid-Catalyzed AAC Reactions.

Alkaloid additives catalyze ketene−aldehyde additions through nucleophilic addition to ketene, generating the acylammonium enolate **3** responsible for mediating C−C bond construction (Figure 2).[6] The specificity of Wynberg's original cycloaddition for highly electrophilic aldehydes (e.g., chloral) suggested that these enolates possess relatively limited nucleophilicity. In considering strategies for generalizing the alkaloid-catalyzed ketene−aldehyde additions, Lewis acid activation of the aldehyde electrophile emerged as an alternative for eliciting the requisite nucleophilicity from the ammonium enolates.[7] Furthermore, alkaloid-mediated enolate formation in the presence of metallic Lewis acid cocatalysts (M) was considered a plausible conduit to metal-stabilized ammonium enolates **4**. Such enolates could be expected to mediate aldehyde addition through a metal-templated, closed transition state **5**, providing both enthalpic and entropic activation to the ensuing enolate−aldehyde addition.

Preliminary reaction development emphasized the identification of cinchona alkaloid-Lewis acid combinations that would allow in situ ketene generation to be integrated with the catalyzed ketene−aldehyde cycloadditions. Our prior success in merging tertiary amine-mediated dehydrohalogenation of acyl halides with asymmetric ketene−aldehyde cycloadditions led us to explore the $^{i}Pr_2$-NEt-acid chloride combination as the ketene source.[8,9] Quinine was employed initially as the requisite Lewis base catalyst (5 mol %) for evaluating various Lewis acid cocatalysts (15 mol %) in the reaction of acetyl chloride/$^{i}Pr_2$NEt (ketene) with hydrocinnamaldehyde as a representative unactivated aldehyde (eq 1). Among the various Lewis acids examined, lithium perchlorate emerged as a uniquely effective cocatalyst for mediating the desired AAC reaction.[10] The catalyst system composed of 5 mol % quinine and 15 mol % $LiClO_4$ in the standard acetyl chloride-hydrocinnamaldehyde test reaction afforded the first indication of this reaction design's validity, delivering the desired β-lactone **6** in 62% ee.



Success in this preliminary reaction provided a platform for evaluating the impact of Lewis base (alkaloid) structure, solvent composition, and catalyst stoichiometry on the alkaloid/$LiClO_4$-catalyzed AAC reactions. Lewis base catalyst candidates were drawn from easily accessed cinchona alkaloid derivatives differing in C_9 oxygen substitution. Systematically investigating AAC efficiency as a function of the quinidine *O*-protecting group revealed that the *O*-trimethylsilyl derivative (**2**, TMS*Q*) afforded optimum reaction yields while enantioselection was relatively insensitive to oxygen substitution.[11,12] Catalytic competency of the pseudoenantiomeric Lewis base catalyst *O*-trimethylsilyl quinine (TMS*q*) paralleled closely that of TMS*Q* and, thus, provided convenient access to the enantiomeric β-lactone series. Solvent systems for the TMS*Q*/$LiClO_4$-catalyzed AAC reactions composed predominately of methylene chloride but containing sufficient diethyl ether to ensure solubility of the $LiClO_4$ at low temperatures delivered optimum reaction yields and stereoselection. Lewis acid stoichiometry emerged as a crucial variable that could be conveniently modulated to maximize reaction efficiency depending on aldehyde structure. Thus, slow addition of acid chloride (2 equiv over ~1−4 h) to a CH_2Cl_2/Et_2O (2:1) solution containing TMS*Q* (10 mol %)/

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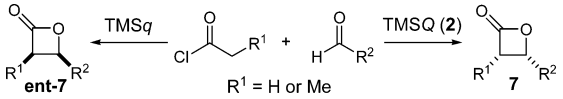
Table 1. Cinchona Alkaloid/$LiClO_4$-Catalyzed AAC Reactions

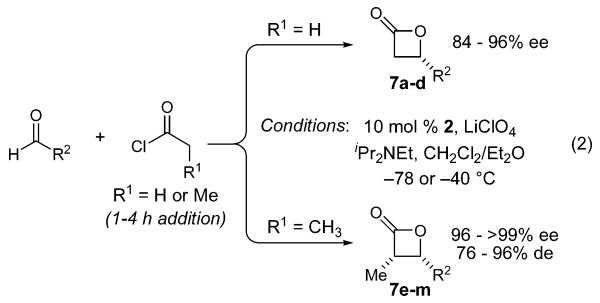


TMS*Q* = *O*-trimethylsilylquinidine; TMS*q* = *O*-trimethylsilylquinine

entry	product	R^1	R^2	% ee[a,b]	% de[c]	% yield
a	**7a**	H	$^cC_6H_{11}$	94[d]	–	85
b	**7b**	H	CMe_3	96[e]	–	71
c	**7c**	H	CH_2CH_2Ph	92	–	80
d	**ent-7d**	H	CH_2OBn	84	–	70
e	**ent-7e**	Me	CH_2CH_2Ph	>99	96	84
f	**ent-7f**	Me	$(CH_2)_8CHCH_2$	99	90	74
g	**ent-7g**	Me	CH_2OBn	99	76	68
h	**ent-7h**	Me	$CH_2CH(CH_3)_2$	99	90	72
i	**7i**	Me	$^cC_6H_{11}$	97[f]	>96	74
j	**ent-7j**	Me	C_6H_5	>99	96	78
k	**ent-7k**	Me	$^pC_6H_4F$	>99	>96	85
l	**7l**	Me	$^oC_6H_4Cl$	>99	96	80
m	**ent-7m**	Me	$^oC_6H_4CH_3$	>99	>96	76

[a] Enantiomer ratios determined by chiral GLC or HPLC. [b] Minor enantiomer not observed for values >99%. [c] Diastereomer ratios determined by ^1H NMR of crude product mixtures. [d] 90% ee using TMS*q* as catalyst. [e] 95% ee using TMS*q* as catalyst. [f] 96% ee using TMS*q* as catalyst.

$LiClO_4$ (30−300 mol %) and $^iPr_2NEt$ (2.5 equiv) provided the optimized conditions for AAC reactions employing a range of structurally diverse aldehydes (eq 2).[13]



While these alkaloid-catalyzed AAC reactions are superficially related to the Al(III)-catalyzed variants developed previously, the quinidine-$LiClO_4$ catalyst system offers several notable advantages.[8] In reactions involving acetyl chloride-derived ketene, the TMS*Q*/$LiClO_4$ system renders α-branched and sterically hindered aldehydes as effective AAC substrates, providing the cyclohexanecarboxaldehyde- and pivaldehyde-derived β-lactones **7a** and **7b** in 94 and 96% ee, respectively (Table 1, entries a and b). Similar α-branched aldehydes are unreactive under the Al(III) catalyst conditions. Unbranched aldehydes also afford useful levels of enantioselection in the ketene AAC reactions (92% and 84% ee for entries c and d, respectively). From an operational perspective, it is noteworthy that, except for the simple one-step preparation of TMS*Q*,[3a] these results are obtained using commercially available, inexpensive reagents and catalysts.

Methylketene is also an effective AAC reaction partner using the TMS*Q* (or TMS*q*)/$LiClO_4$ catalyst system. In fact, enantioselection in AAC reactions employing propionyl chloride-derived methylketene improves dramatically relative to their simple ketene counterparts (Table 1). Thus, adding propionyl chloride (over 1−4 h) to a mixture of hydrocinnamaldehyde, $^iPr_2NEt$, and TMS*q* (10 mol %)-$LiClO_4$ (50 mol %) at −78 °C afforded the 3,4-cis-disubstituted β-lactone **ent-7e** with near perfect absolute and relative stereocontrol (>99% ee, 96% de). Other enolizable aldehydes afforded similarly high absolute and relative stereocontrol under analogous conditions and, when necessary, using increased amounts of $LiClO_4$ for aldehydes affording sluggish reaction rates (e.g., the sterically hindered aldehyde pivaldehyde requires 3 equiv $LiClO_4$; entry b). As observed in the ketene cyclocondensations, the α-branched aldehyde cyclohexanecarboxaldehyde delivers the cis-disubstituted β-lactone **7i** in good yield and with very high enantio- and diastereoselection (entry i; 97% ee, >96% de). Modulating Lewis acid loading also succeeded in rendering aryl aldehydes (entries j−m), including ortho-substituted derivatives, as useful AAC substrates, delivering the *cis*-4-aryl-3-methyl-2-oxetanones in >99% ee (≥96% de, 76−85% yield).

Cinchona alkaloid-Lewis acid-catalyzed AAC reactions dramatically expand the scope of Wynberg's original ketene−aldehyde cycloadditions. These reactions are mechanistically distinct and, in several important aspects, directly complement the asymmetric Lewis acid-catalyzed reaction variants. In particular, the TMS*Q*/$LiClO_4$ catalyst system relieves the limitation α-branched aldehydes previously imposed on AAC reactions and engages methylketene in exceptionally stereoselective cyclocondensations. These reaction attributes combined with the ready availability of the necessary reaction components promise to further expand the scope and utility of the AAC reaction technology.

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Supporting Information Available: Experimental procedures, stereochemical proofs, and representative ^1H and ^{13}C spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Slow addition of the acid chloride was employed to maintain relatively low ketene concentrations, thereby minimizing competing ketene dimerization.

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