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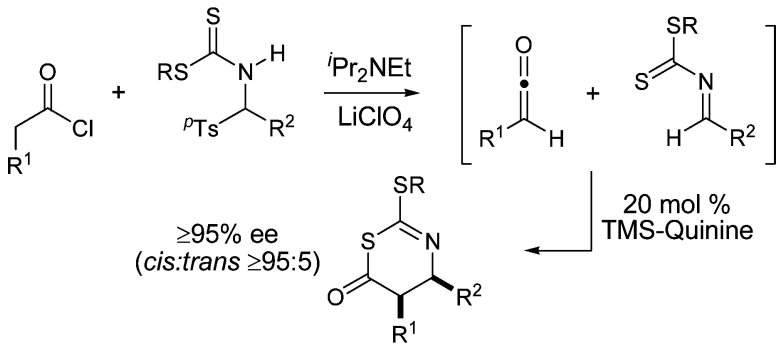

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Catalytic Asymmetric [4 + 2] Cycloadditions of Ketenes and *N*-Thioacyl Imines: Alternatives for Direct Mannich Reactions of Enolizable Imines

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Mannich reactions are attractive and versatile strategies for establishing nitrogen-bearing stereocenters with concomitant C−C bond construction.[1] Accordingly, there have emerged a variety of highly successful solutions to stereoselective Mannich additions, including asymmetric catalytic variants.[2] However, the inherent incompatibility of reaction conditions that affect enolate formation with enolizable imine electrophiles has functioned to limit the number of successful direct Mannich processes useful for aliphatic imines.[3] Indeed, direct catalyzed Mannich reactions affording α,*β*-disubstituted Mannich adducts with high absolute and relative stereocontrol are especially rare. As one solution to Mannich reactions adhering to these design criteria, we describe the utility of cinchona alkaloid (**1** or **2**)-catalyzed cyclocondensations of acid chlorides and α-amido sulfones as effective surrogates for catalytic asymmetric Mannich addition reactions (Figure 1). These reactions deliver enantioenriched Mannich adducts masked as *cis*-4,5-disubstituted thiazinone heterocycles that exhibit useful behavior as activated ester equivalents.

Direct Mannich additions necessarily incorporate mechanisms for in situ formation of the requisite enolate nucleophile. Aliphatic imine Mannich substrates are subject to thermodynamically driven imine-to-enamine tautomerization under the basic reaction conditions necessary for enolate formation. Enolizable imines, therefore, are generally poor substrates for catalyzed direct Mannich processes. Based on our success developing acyl halide−aldehyde cyclocondensations as surrogates for direct catalytic asymmetric aldol additions, we were interested whether a similar reaction design would yield Mannich-type reactions compatible with enolizable, unactivated imines.[4] Accordingly, in situ ketene generation would replace the typical enolization event in the Mannich reaction sequence (Figure 2). Concomitant in situ imine generation, via base-mediated elimination of α-amido sulfone **3**, provided a mechanism for affording the maximum kinetic advantage to the catalyzed ketene−imine addition reaction relative to competing tautomerization.[5,6] Presuming imine formation would not be instantaneous, we expected the reaction of the ketene-derived enolate **4** with low concentrations of imine **5** to minimize the enamine formation that would accompany extended exposure of **5** to the reaction conditions. Successfully realizing this reaction design proved to be critically dependent on utilizing *N*-thioacyl imine electrophiles that afforded formal [4 + 2] cycloadducts **6** with ketene reaction partners.[7,8]

Establishing the veracity of this reaction design followed from the experience we gained developing alkaloid-catalyzed ketene−aldehyde cycloadditions.[4] Thus, a catalyst system composed of *O*-trimethylsilylquinine (**1**) and $LiClO_4$ was evaluated in the condensation of α-amido sulfone **3a**, used as a representative enolizable imine precursor, and propionyl chloride.[9] Reacting **3a** with propionyl chloride in the presence of 10 mol % of **1**, $LiClO_4$, and *i*-Pr_2NEt (9:1 CH_2Cl_2/Et_2O, −78 °C) afforded the *cis*-disubstituted thiazinone **6a** with near perfect enantioselection

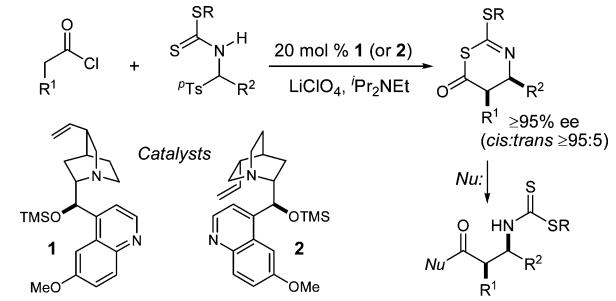


Figure 1. Alkaloid-catalyzed ketene-*N*-thioacyl imine cycloadditions.

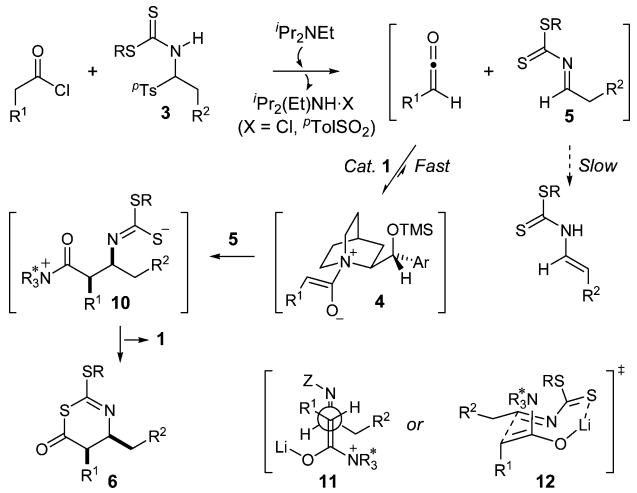
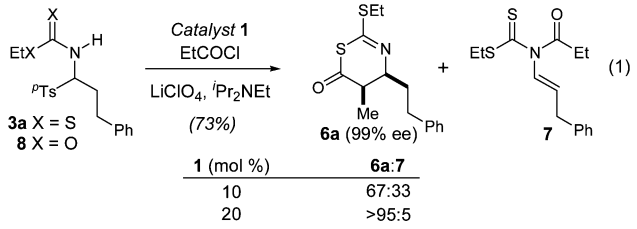


Figure 2. Mechanism for ketene-*N*-thioacyl imine [4 + 2] cycloadditions.

(>98% ee, 95:5 *cis*:*trans*) along with ∼20% of the N-acylated enamine **7** (eq 1).



1 (mol %)	**6a**:**7**
10	67:33
20	>95:5

The enamine byproduct **7** could be eliminated by using 20 mol % of catalyst that, presumably, increases the cycloaddition reaction rate relative to catalyst-independent imine tautomerization. Indeed, enhanced reaction fidelity offsets the need for higher catalyst loadings as the basic alkaloid is efficiently recovered from the reaction mixtures by standard acid−base extraction techniques. The critical role in situ imine generation played in the success of these reactions was evident from attempts to utilize pregenerated imines

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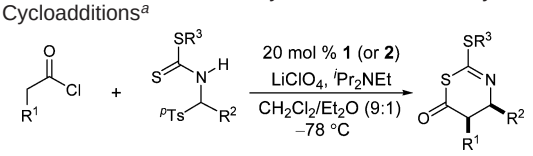
Table 1. Cinchona Alkaloid-Catalyzed Ketene-*N*-Thioacyl Imine [4 + 2] Cycloadditions[a]

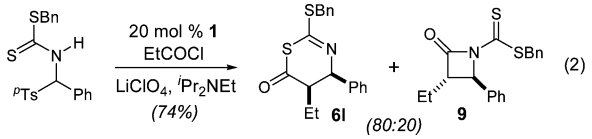


entry	R^1	R^2	R^3	yield[b] **6** (%)	% ee (*cis*:*trans*)[c,d]
a	Me	CH_2CH_2Ph	Et	76 (**6a**)	>98 (95:5)
b	Me	C_6H_{11}[c]	Et	75 (**6b**)	>98 (95:5)
c	Me	CH_2OBn	Et	51 (**6c**)	>98 (>97:3)
d	Et	CH_2CH_2Ph	Et	68 (**6d**)	>98 (>97:3)
e	CH_2Ph	CH_2CH_2Ph	Et	65 (**6e**)	>98 (>97:3)
f	Me	C_6H_5	Et	59 (**6f**)	>98 (>97:3)
g	Me	$CH_2CH_2CH_3$	Bn	67 (**6g**)	98 (>97:3)
h	Me	$CH_2CH(CH_3)_2$	Bn	74 (*ent*-**6h**)	95 (>97:3)
i	Et	$CH_2CH(CH_3)_2$	Bn	72 (**6i**)	>98 (>97:3)
j	^{n}Pr	CH_2CH_2Ph	Bn	58 (**6j**)	>98 (>97:3)
k	^{i}Pr	CH_2CH_2Ph	Bn	63 (**6k**)	>98 (>97:3)
l	Et	C_6H_5	Bn	59 (*ent*-**6l**)	>98 (>97:3)

[a] Catalyst (20 mol %): **1**, entries a−g, i−k; **2**, entries h, l. [b] Isolated yield. [c] Enantiomeric excess determined by chiral HPLC; minor enantiomer not observed for values >98. [d] Diastereomer ratios determined by ^{1}H NMR analysis of crude product mixtures; minor diastereomer not observed for values >97:3.

(e.g., **5**) that afforded exclusively enamine **7**. Similarly, attempts to employ the carbamate-derived sulfone **8** as the proelectrophile afforded no cycloaddition, suggesting that the nucleophilicity of the thiocarbonyl moiety was critical to the success of this reaction.

The alkaloid-catalyzed ketene-*N*-thioacyl imine cycloadditions proved to be generally effective for a variety of alkyl-substituted ketenes and unactivated imine electrophiles (Table 1). Cycloadditions involving α-amido sulfones bearing straight chain or branched alkyl substituents uniformly proceed with nearly complete control of absolute and relative stereochemistry in affording the 4,5-*cis*-disubstituted 1,3-thiazin-6-one derivatives **6a**−**l** (≥95% ee, ≥95:5 *cis*:*trans*).[10] These formal [4 + 2] cycloadditions are similarly accommodating of substituted ketenes incorporating aliphatic and branched alkyl substituents with no deviation in stereoselectivity. Cycloadditions involving aryl α-amido sulfones (entries f and l) afford modestly attenuated reaction yields due to competing formation of the *β*-lactam adducts (e.g., **9**), possessing the unanticipated *trans* diastereoselection that was not observed for alkyl imine electrophiles (eq 2).

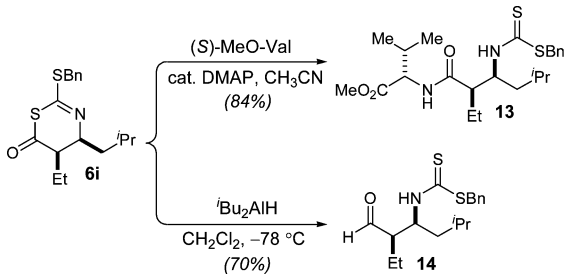


(2)

Stereoselectivity in the ketene−imine cycloadditions was consistent C−C bond formation proceeding via the quinine-derived enolate **4**; imine approach to the exposed *si* enolate face would deliver the carbamodithioate anion **10** (Figure 2).[11] The high *syn* selectivity characterizing these reactions can be attributed to enolate−imine addition proceeding through either open or lithium-coordinated, closed transition states **11** or **12**, respectively. Sulfur's enhanced nucleophilicity relative to nitrogen dictates that **10** collapses by sulfur addition to the acyl ammonium ion to generate the formal [4 + 2] cycloadduct **6**.

The utility of the enantioenriched cycloadducts as surrogates for traditional Mannich products was revealed by the ring opening processes available to the thiazinone heterocycles (Scheme 1). Amine-mediated ring opening of thiazinone **6i** with valine methyl

Scheme 1



ester provided the α,*β*-dipeptide derivative **13** (84%), suggestive of the thiazinone's function as an activated ester surrogate.[12] Hydride-mediated thiazinone reduction led directly to the enantioenriched *β*-amino aldehyde derivative **14** (70%).

Cinchona alkaloid-catalyzed ketene−imine cycloadditions offer useful alternatives to traditional asymmetric Mannich reactions. The ketene−imine cycloadditions are mechanistically distinct and, in several aspects, complementary to existing direct Mannich reactions. These reaction attributes are expected to make these ketene−imine cycloadditions useful alternatives for executing Mannich-type C−C bond constructions.

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

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