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Stereoselective Synthesis of Highly Substituted Δ^1-Pyrrolines: *exo*-Selective 1,3-Dipolar Cycloaddition Reactions with Azlactones

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Δ^1-Pyrrolines are found in nature as biosynthetic intermediates and as a part of pheromones, alkaloids, steroids, hemes, and chlorophylls.[1] In addition to having a wide range of biological activities, Δ^1-pyrrolines are important synthetic intermediates because they have three contiguous stereogenic centers and one prochiral center as part of a cyclic imine, which is amenable to further stereoselective synthetic manipulation with nucleophiles.[2] A stereoselective and efficient preparation of a general Δ^1-pyrroline template would provide rapid access to a range of biologically active natural products including the myosmines, amathaspiramides, and kaitocephalin-type alkaloids.[3] Although there have been several reports for the synthesis of simple Δ^1-pyrrolines, cycloaddition reactions of münchnones and alkenes have not been fruitful as a synthetic method to generate these compounds.[4,5] A few examples include the use of azomethine ylides or cyclopropanes to gain access to di- or trisubstituted Δ^1-pyrrolines.[6] However, the primary cycloadducts that are formed in the cycloaddition reaction with münchnones readily eliminate carbon dioxide, resulting in the formation of pyrroles, or isomerize to the Δ^2-pyrroline, resulting in a loss of stereochemistry.[5,7−9] A notable exception was reported by Padwa and co-workers who successfully isolated and characterized the primary adducts from intramolecular cycloadditions of münchnones to terminal alkenes.[10] In addition, Turchi and co-workers described the isolation of a Δ^1-pyrroline-5-carboxylic acid from the intermolecular cycloaddition of 1,2-dicyanocyclobutene to a münchnone.[9] Our recently reported trimethylsilyl chloride-mediated intermolecular 1,3-dipolar cycloaddition of an in situ generated münchnone and imine yielded the primary imidazoline adduct containing a four-point diversity and two new stereogenic centers (Scheme 1).[11] We report herein an *exo*-selective synthesis of highly substituted Δ^1-pyrroline scaffolds from amino acid-derived münchnones. After screening a variety of Lewis acids[12] we found that silver acetate successfully catalyzed the cycloaddition reaction of azlactones with alkenes, generating Δ^1-pyrrolines in very good yields without isomerization to the Δ^2-pyrrolines or decarboxylation to the corresponding pyrroles.[8,13]

Scheme 1. Lewis Acid-Mediated Synthesis of Δ^1-Pyrrolines

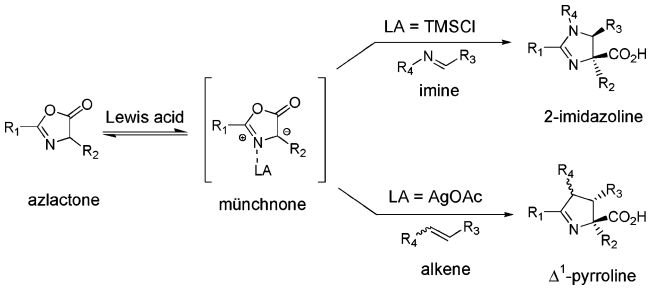
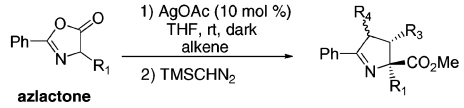
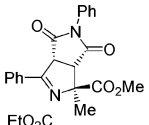
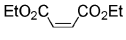
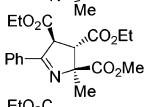
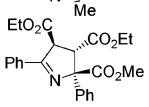
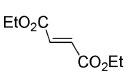
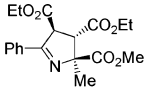
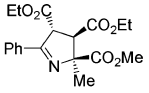
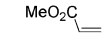
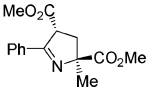
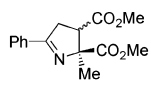


Table 1. Cycloaddition with Various Alkenes



	R_1	alkene	% yield a:b	Δ^1-pyrroline a	b
1	Me		78		
2	Me		75		
3	Ph		15		
4	Me		75 (2:1)		
5	Me		95 (1:1)		

The cycloaddition reactions proceed well with electron-deficient alkenes and 10 mol % silver acetate in THF at room temperature to provide the highly substituted Δ^1-pyrrolines, often in good yields. Only the *exo* adducts of the Δ^1-pyrrolines were observed with *cis*-olefins as determined by NOE experiments and X-ray crystallography[12] in accordance with observations by other groups.[14] However, *trans*-diethyl fumarate resulted in 2:1 ratio of *exo*-/*endo*-diastereomers (entry 4, Table 1). Diethyl fumarate and diethyl maleate provided both a 3,4-*trans* relationship of the ethoxycarbonyl groups. This is likely the result of the isomerization of the 3,4-*cis*-substituted Δ^1-pyrroline obtained from diethyl maleate to the thermodynamically more stable 3,4-*trans* product through an intermediate enolate ion (Table 1, entry 2 versus 4).[12] The *exo* preference is in contrast to the *endo* preference observed in the synthesis of pyrrolidines from acyclic azomethine ylides.[12,13] A notable exception to this is the ligand-induced *exo* selectivity described by Komatsu.[15]

Acyclic azomethine ylides have been proposed to adopt a *syn* orientation in the prescence of a Lewis acid, whereas the münchnones are locked in *anti* orientation. This could be a possible basis for obtaining opposite diastereoselectivity in the resulting product for the same orientation of alkene.[12] Electronic effects were suggested to play a dominant role in favoring the *exo* product in intermolecular cycloaddition reactions.[10,16] Turchi and co-workers have carried out extensive MO calculations to rationalize the stereochemical outcome.[17] AM1 calculations for additions of 1,2-dicyanocyclobutene to münchnones indicated that the cycloaddition is a concerted but nonsynchronous process. Semiempirical calculations have not been successful in explaining the regiochemical and

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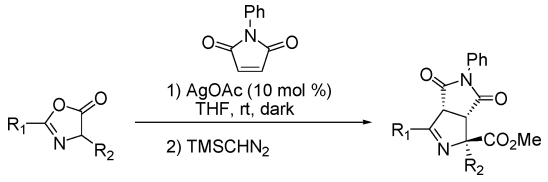
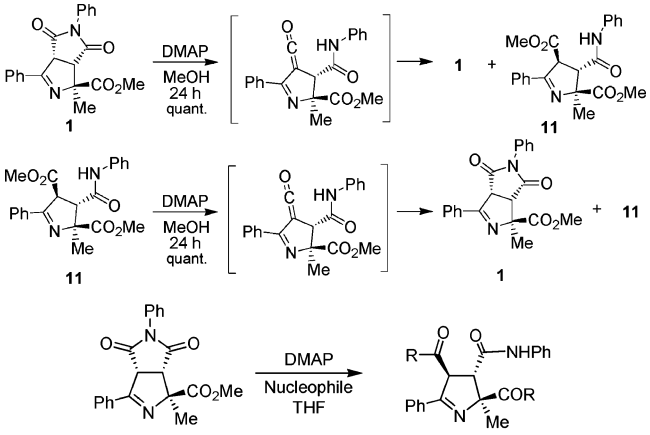
Table 2. Variation of Substituents at 2- and 5- Positions



	azlactone		
entry	R_1	R_2	% yield
6	Ph	Ph	0
7	Ph	Bn	67
8	Ph	3-indolylmethyl	70
9	Me	Me	59
10	Bn	Me	75

Scheme 2. Ring Opening and Isomerization of Cycloadducts



Entry	Nucleophile	R	% Yield
11	MeOH	OMe	50 %
12	NH_2Bn	NHBn	76 %

stereochemical outcome of cycloadditions with münchnones. Inspection of electrostatic isopotential surfaces, however, revealed that the *exo* transition state shows attractive stabilizing interactions between the CH−NH−CH portion of dipole and the nitrile groups.[12] In fact, it was found that the *exo* adduct is also electrostatically favored over the *endo* adduct.[17] This may provide a rationale for the formation of the *exo* cycloadduct with this in situ generated münchnone−alkene cycloaddition reaction.

Efforts to introduce alkyl or aryl substituents in the 4-position with crotonic or cinnamic esters were not successful. Electron-rich alkenes such as vinyl trifluoroacetate were also unreactive in the cycloaddition with münchnones under these conditions. Good yields were obtained with benzyl and indolylmethyl substituted azlactones (entries 7 and 8, Table 2). The 2-position on the Δ^1-pyrroline scaffold is also amenable to different substituents including the 2-methyl and 2-benzyl (entries 9 and 10, Table 2). The phenyl glycine-derived azlactone reacted with diethyl maleate to afford the Δ^1-pyrroline in a modest 15% yield (entry 3, Table 1) and was unreactive toward maleimide (entry **6**, Table 2).

Isomerization of the bicyclic *cis* Δ^1-pyrroline carboxylate to the thermodymanically more stable ring-opened *trans* product can be accomplished upon exposure of the cycloadduct to mild base. Of the various bases screened to convert **1** to **11**, DMAP resulted in clean conversion and afforded a 50:50 mixture of **1** and **11** in quantitative yields. Treatment of the isolated 3,4-*trans*-Δ^1- pyrroline methyl ester (**11**) with DMAP in methanol re-established the 1:1 ratio of **1** and **11**, indicating that the interconversion of **1** and **11** most likely proceeds via a common ring-opened ketene intermediate (Scheme 2). We were successful in selectively trapping the ketene intermediate with benzylamine to afford the *trans* amide in good yield (entry 12, Scheme 2). This selective ring-opening reaction provides another opportunity to expand on the stereochemical diversity of the scaffolds.

In conclusion, we have developed a diastereoselective and efficient synthesis of highly substituted Δ^1-pyrroline-5-carboxylic acid scaffolds via a silver(I)-catalyzed [3 + 2] cycloaddition reaction. The *exo* selectivity complements the *endo*-selective cycloaddition of related acyclic azomethine ylides very well. Diastereocontrol can be extended to the three stereogenic centers by appropriate choice of substrates and isolation conditions.

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Supporting Information Available: Full experimental protocols, crystallographic tables, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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