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Synthesis of Amino Acid Derived Enaminones via Wolff Rearrangement Using Vinylogous Amides as Carbon Nucleophiles

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Abstract: Cyclic enaminones were synthesized in high yields from amino acids in two steps via Wolff rearrangement. The cyclization represents a rare 6-*exo-dig* cyclization involving a ketene as an electrophile. No racemization was observed during this reaction.

Piperidine, indolizidine, and quinolizidine alkaloids (Figure 1) display important biological properties and therefore have been frequent targets for synthetic chemistry efforts.[1] It is well-known that monocyclic and bicyclic enaminones (2,3-dihydropyridin-4(1*H*)-ones) can serve as versatile intermediates for their synthesis.[2]

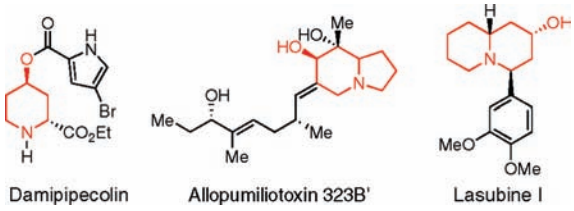
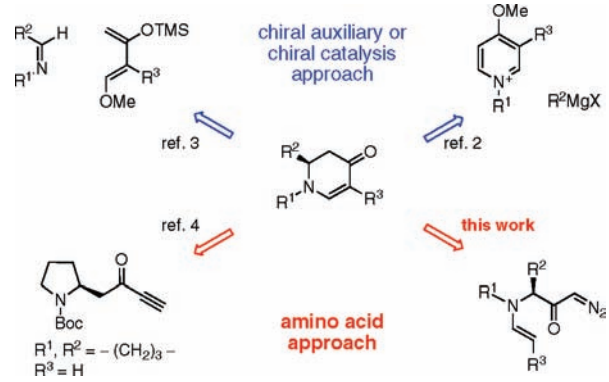


Figure 1. Examples of biologically active molecules containing piperidine, indolizidine, and quinolizidine core structures.

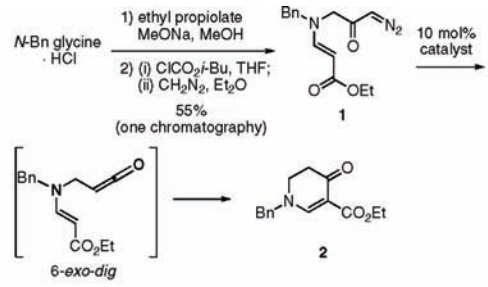
The most common synthetic strategies (Scheme 1) to obtain enaminones in optically active form are (1) the hetero Diels−Alder reaction and (2) the nucleophilic addition to pyridinium salts utilizing chiral auxiliaries or chiral catalysts.[2,3] In 2006 we reported a concise method that relies on the cyclization of amino acid derived amino ynones to prepare enantioenriched enaminones under very mild conditions.[4] In some instances, however, partial racemization of the reaction products was observed during these reactions.[4] To address this issue a different disconnection, which retained the use of amino acids, was sought. We hypothesized that enaminones could be derived from diazoketones carrying a pendant enamine moiety that could trap the ketene generated by a Wolff rearrangement (Scheme 2).[5]

The Wolff rearrangement and its ketene intermediate have been studied extensively. Reactions involving the reactive ketene species are classified as either cycloaddition or nucleophilic addition reactions, exemplified by the Staudinger reaction and the Arndt−Eistert homologation.[6,7] While a C−C bond is formed in cycloadditions, C−C bond formation in nucleophilic addition reactions of ketenes are less common. Although ketenes have been investigated in reactions with organolithium and magnesium reagents, other types of carbon nucleophiles have been studied less frequently[8] and typically involve intermolecular reactions. Only a few reports have appeared where a carbon nucleophile was employed in an intramolecular fashion.[9] Herein, we detail our new synthetic strategy to

Scheme 1. Various Approaches for Enaminone Syntheses



Scheme 2. Optimization of Reaction Conditions



entry[a]	catalyst	isolated yield (%)
1	Ag_2O	90
2	CF_3CO_2Ag	82
3	AcOAg[b]	97
4	$PhCO_2Ag$	99

[a] Reaction conditions: diazoketone **1** in CH_2Cl_2 (0.2M), 24 h, dark
[b] Sonication was used.

prepare enaminones from amino acids via Wolff rearrangement using vinylogous amides as carbon nucleophiles. The cyclization represents a rare example of a 6-*exo-dig* cyclization involving a ketene as the electrophile.[10]

Our efforts started with the synthesis of diazoketone **1** as a starting material for the reaction in order to test the feasibility of our hypothesis (Scheme 2). *N*-Benzylglycine readily underwent Michael addition to ethyl propiolate, and the acid group of the reaction product was subsequently converted into a diazo moiety. With diazoketone **1** in hand, we embarked on screening reaction conditions. A variety of silver salts, known to induce the Wolff rearrangement, as well as other reaction conditions were tested. We found that the use of halogenated solvents, $PhCO_2Ag$,

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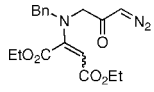
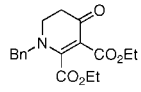
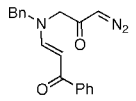
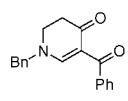
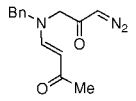
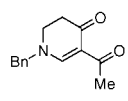
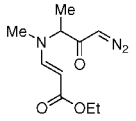
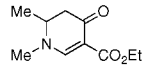
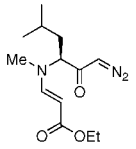
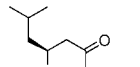
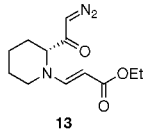
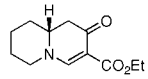
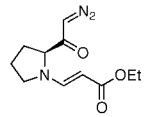
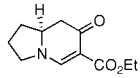
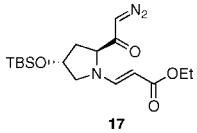
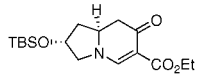
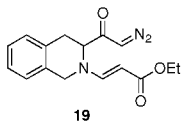
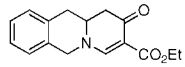
CF_3CO_2Ag, and AcOAg readily facilitated the rearrangement to furnish the desired product in excellent yields. The presence of triethylamine, which is often used in Arndt−Eistert homologations as an additive, however diminished the yield. As a result of this study, we selected $PhCO_2Ag$ as the catalyst and CH_2Cl_2 as the solvent for further studies of this method. With optimized reaction conditions in hand, we investigated the scope of the reaction (Table 1). First, diazoketones **3**, **5**, and **7** (entries 1−3) were synthesized from *N*-benzylglycine and the corresponding alkynes. Upon treatment with $PhCO_2Ag$, the desired enaminones **4**, **6**, and **8** were obtained in good yields. Next, α-substituted diazoketone **9** and **11** (entries 4−5) were prepared from *N*-methylalanine and *N*-methylleucine respectively, which underwent cyclization to afford *β*-alkyl enaminones **10** and **12**. ^{19}F NMR analysis of the Mosher ester of (*S*)-**12** in comparison to the Mosher esters of (±)-**12** revealed that only a single diastereoisomer of the (*S*)-**12** Mosher ester had formed (see Supporting Information (SI)).[11] Diazoketones **13**, **15**, **17**, and **19** (entries 6−9) derived from cyclic amino acids afforded bicyclic enaminones **14**, **16**, **18**, and **20** in good yields. These derivatives are known to be excellent intermediates for indolizidine, and quinolizidine syntheses.[2] Mosher ester derivatives of **14** and **16** showed single diastereoisomers by HPLC analysis (see SI).[11] (2*R*,8a*S*)-**18** was formed as a single diastereoisomer as determined by ^1H NMR.

Table 1. Substrate Scope of the Reaction[a]

entry	substrate	product	isolated yield (%)
1	 **3**	 **4**	80
2	 **5**	 **6**	88
3[b]	 **7**	 **8**	93
4	 **9**	 **10**	93
5	 **11**	 **12**	76[c]
6	 **13**	 **14**	93[c]
7[d]	 **15**	 **16**	86[c]
8	 **17**	 **18**	79[e]
9	 **19**	 **20**	81

[a] Reaction conditions: diazoketone and $PhCO_2Ag$ (10 mol %) in CH_2Cl_2 (0.2 M). [b] 20 mol % of $PhCO_2Ag$ was used. [c] *ee* was determined by ^{19}F NMR (Mosher ester derivatives); only one isomer was observed. [d] Ag_2O (10 mol %) and $C_2H_4Cl_2$ (0.2 M) were used. [e] *dr* was determined by ^1H NMR; only one isomer was observed.

In summary, we have developed a novel enantiospecific synthetic method to obtain monocyclic, bicyclic, and tricyclic enaminones from amino acids in two steps. Due to the lack of racemization, a simple nucleophilic 6-*exo*-*dig* cyclization is a plausible mechanism, which is a favorable transformation according to Baldwin's rules.[10] Further investigation regarding the synthetic utility of this methodology is ongoing.

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

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