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Asymmetric Multicomponent [C+NC+CC] Synthesis of Highly Functionalized Pyrrolidines Catalyzed by Silver(I)

Philip Garner,*,† H. Ümit Kaniskan,† Jieyu Hu,† Wiley J. Youngs,‡ and Matthew Panzner‡

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078, and Department of Chemistry, University of Akron, Akron, Ohio 44325
ppg@case.edu

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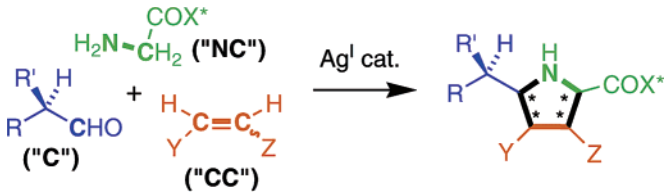
ABSTRACT



Highly functionalized pyrrolidines are obtained in a single chemical step via a mild, efficient, and selective Ag^{I}-catalyzed asymmetric [C+NC+CC] coupling process. Oppolzer's camphorsultam enables the desired reaction cascade and provides a reliable means to control the developing stereochemistry and purify the products. This three-component reaction provides unprecedented access to structurally diverse pyrrolidines for both target- and diversity-oriented syntheses.

The pyrrolidine ring is an important structural motif found in many bioactive molecules. Examples include the neuroprotective agent kaitocephalin,[1,2] the synthetic influenza drug A-192558,[3,4] and the antitumor antibiotic bioxalomycin β1 (Figure 1).[5,6] Pyrrolidines also serve as useful molecular scaffolds for the exploration and exploitation of pharmacophore space via diversity-oriented synthesis (DOS).[7−9] Such studies have resulted in new drug leads for the treatment of cancer[10] and hepatitis C viral infections.[11] Accordingly, there is a continued need for new reactions that provide stereocontrolled access to functionalized pyrrolidines.

Recently, we reported a simple synthesis of racemic functionalized pyrrolidines based on the union of an enolizable aliphatic aldehyde ("C"), an amino acid derivative

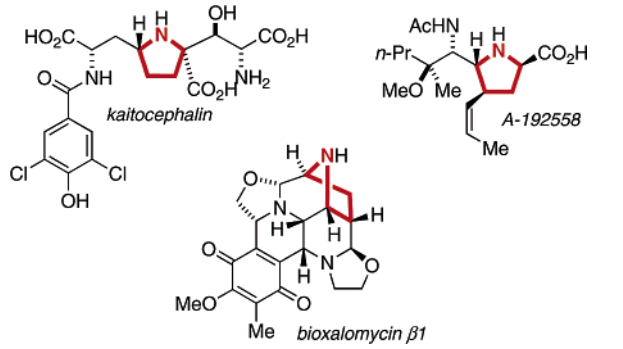


Figure 1. Representative pyrrolidine-containing targets.

† Case Western Reserve University.
‡ University of Akron.

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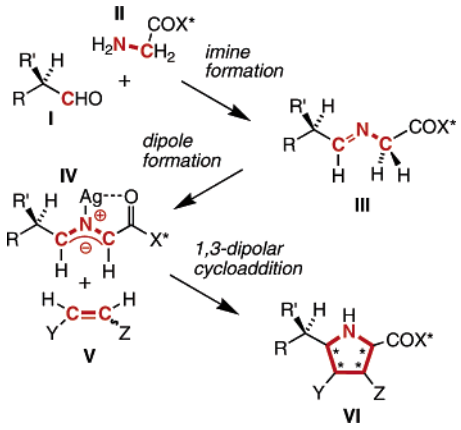
("NC"), and an electron-deficient alkene ("CC") in what may be termed a three-component [C+NC+CC] coupling reaction.[12] The underlying cascade of molecular events was built on the 1,3-dipolar cycloaddition of an azomethine ylide to an electron-deficient dipolarophile. This concerted process is a powerful synthetic transformation[13] that creates two new C−C bonds and up to four chiral centers in a single step. Absolute stereocontrol during the 1,3-dipolar cycloaddition has been achieved using either chiral, nonracemic substrates or auxiliaries. The latter approach is, of course, more general, but it still suffers from certain limitations. Catalytic asymmetric versions of this cycloaddition reaction that proceed via metalated azomethine ylides[14] have recently been developed.[15] However, this technology is still limited in terms of the structural variability of both the aldehyde (aromatic aldehydes are usually employed) and dipolarophile components.

We now report an exceedingly mild, efficient, and selective Ag^{I}-catalyzed asymmetric [C+NC+CC] synthesis of pyrrolidines. The method combines the advantages of a reliable multipurpose, reusable auxiliary and metal catalysis. A key feature of this reaction is the use of Oppolzer's chiral glycyl sultam as the amine component. The value of azomethine ylides incorporating this chiral auxiliary has been previously demonstrated with preformed aldimines using both thermal[16] and zinc-mediated[17] tautomerization. In the present case, the sultam facilitates the desired reaction cascade and provides a reliable means to control the absolute stereochemistry of the products independent of existing chirality. Grigg had previously noted the benefits of using silver(I) salts for the generation of metalloazomethine ylides from preformed enolizable aliphatic imines.[18] Significantly, the asymmetric three-component reaction[19] technology described herein permits unprecedented variation of the aldehyde component, enabling the synthesis of highly functionalized pyrrolidines.

Even though numerous examples of three-component reactions based on the cascade imine → azomethine ylide → 1,3-dipolar cycloaddition sequence have been reported (see ref 12 for a comprehensive listing), development of a general asymmetric [C+NC+CC] coupling reaction remains a challenging goal.[20] This is especially true in the case of enolizable aldehydes, where the following requirements must be met (Scheme 1). First, the aldehyde **I** must cleanly and quickly condense with the amine component **II** to give the intermediate imine **III**. The aldehydes and their imines must resist tautomerization to their corresponding enols and enamines, respectively. The amine component must not react in a nucleophilic sense with activated dipolarophiles **V**. Second, reactive azomethine ylide **IV** must be generated from the imine without any unwanted ancillary reactivity during the net tautomerization process. Third, the azomethine ylide **IV** must be efficiently trapped by the dipolarophile **V** to afford the pyrrolidine **VI**. Competitive heterocycloaddition to either the aldehyde (oxazolidine formation) or the imine (imidazolidine formation) must be minimized. After this gauntlet of potential side reactions is run, the goal of controlling both relative and absolute stereochemistry during the 1,3-dipolar cycloaddition reaction must be dealt with.

Scheme 1. Ag^{I}-Catalyzed Asymmetric [C+NC+CC] Coupling Reaction Cascade[a]



[a] X* = Oppolzer's D- or L-camphorsultam.

Simply mixing aldehyde **I**, chiral glycyl sultam **II** (X* = Oppolzer's camphorsultam),[21] and electron-deficient alkene **V** in THF in the presence of a catalytic amount of AgOAc resulted in the clean production of highly functionalized pyrrolidines **VI** (see Table 1). The reaction proceeds through

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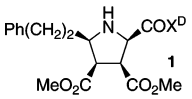
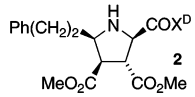
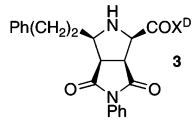
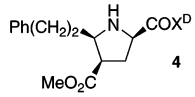
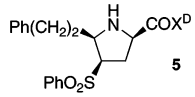
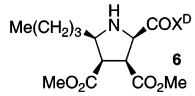
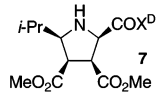
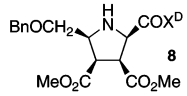
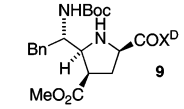
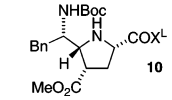
Table 1. Ag^{I}-Catalyzed Asymmetric [C+NC+CC] Synthesis of Pyrrolidines[a]

entry	aldehyde	amine	alkene	reaction time [h]	total yield [%]	isomer ratio	major cycloadduct
1	$Ph(CH_2)_2CHO$	$H_2NCH_2COX^D$	dimethyl maleate	4	63	15:1	 **1**
2	$Ph(CH_2)_2CHO$	$H_2NCH_2COX^D$	dimethyl fumarate	7	88	5:3:1	 **2**
3	$Ph(CH_2)_2CHO$	$H_2NCH_2COX^D$	N-phenyl maleimide	4	83	10:1[c]	 **3**
4	$Ph(CH_2)_2CHO$	$H_2NCH_2COX^D$	methyl acrylate	6	82	19:1	 **4**
5	$Ph(CH_2)_2CHO$	$H_2NCH_2COX^D$	phenyvinyl sulphone	5	94	8:1[c]	 **5**
6	$Me(CH_2)_3CHO$	$H_2NCH_2COX^D$	dimethyl maleate	6	59[b]	13:1	 **6**
7	*i*-PrCHO	$H_2NCH_2COX^D$	dimethyl maleate	overnight	76	13:1[c]	 **7**
8	$BnOCH_2CHO$	$H_2NCH_2COX^D$	dimethyl maleate	2	58	7:1	 **8**
9	(*S*)-BnCH(NHBoc)CHO	$H_2NCH_2COX^D$	methyl acrylate	2	86	*c*	 **9**
10	(*S*)-BnCH(NHBoc)CHO	$H_2NCH_2COX^L$	methyl acrylate	2	63[b]	*c*	 **10**

[a] Procedure: To a stirred mixture of glycyl sultam (0.37 mmol, 1.1 equiv) and AgOAc (5 mol %) in dry THF (1 mL) was added aldehyde (0.33 mmol, 1.0 equiv) followed by dipolarophile (3.0 equiv) at room temperature. The reaction was stirred in the dark under Ar for the indicated time (TLC monitoring of aldehyde and/or ^{1}H NMR monitoring of imine), at which point the mixture was partitioned between saturated aq NH_4Cl (5 mL) and DCM (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The cycloadducts were purified by flash chromatography and recrystallization as required. Minor products were tentatively assigned as diastereomers on the basis of characteristic ^{1}H NMR signals for H2 between δ4 and 5. [b] Yield of pure product after flash chromatography. [c] Minor amounts (<5%) of additional products were also detected.

the imine **III**, which forms very quickly in situ (NMR evidence) without the need for any special dehydrating additives. Because these reactions require Ag^{I} as the catalyst and result in the production of 2,5-cis disubstituted pyrrolidines, we surmise that they proceed via the intermediacy of a metalated (*E*,*E*)-azomethine ylide **IV**. No added base is necessary, an observation that is reminiscent of the bifunctional AgOAc-catalyzed [3+2] cycloaddition reported by Zeng and Zhou (ref 15g). Entries 1−5 show that the catalytic asymmetric [C+NC+CC] coupling reaction can be performed with a diverse set of mono- and 1,2-diactivated alkenes. Entries 6−10 show that the aldehyde component can be varied to include sterically hindered (entry 7), heteroalkyl-substituted (entries 8−10), and chiral (entries 9 and 10) aldehydes.

These Ag^{I}-catalyzed [3+2] cycloadditions are regioselective with monoactivated alkenes, and they exhibited high endo selectivity.[22] The kinetic diastereofacial selectivity of the 1,3-dipolar cycloadditions was typically good as judged by ^{1}H NMR analysis of the reaction at various times and of the crude products after workup. When flash chromatography failed to provide pure material, further purification of the major product could generally be accomplished by simple recrystallization. The relative stereochemical assignments for the major cycloadducts **1**−**10** are based on a combination of *J*-coupling data and NOE experiments (Supporting Information). The absolute stereochemistry of these cycloadducts is based on the X-ray crystallographic analysis of cycloadduct **4** (Figure 2).[23]

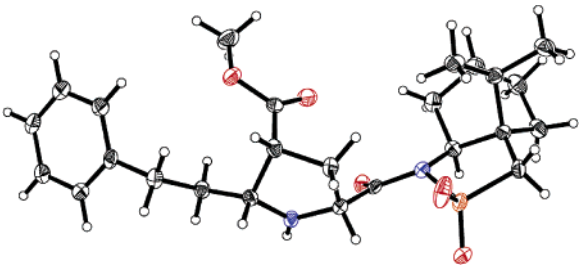


Figure 2. ORTEP diagram from the X-ray crystallographic analysis of cycloadduct **4**.

The readily available and reusable camphor-derived sultam serves five important roles in the asymmetric [C+NC+CC] coupling reaction sequence: (1) it reduces the nucleophilicity of the amine component, thus preventing unwanted Michael addition; (2) it facilitates azomethine ylide formation by enhancing the α-acidity of the intermediate imine; (3) it controls the diastereofacial selectivity of the 1,3-dipolar cycloaddition in a predictable manner via the (*E*,*E*)-azomethine ylide depicted in Figure 3; (4) it tends to make the

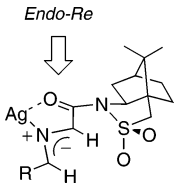
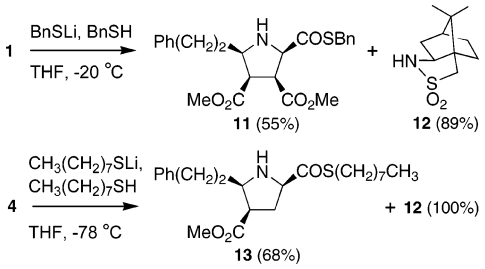


Figure 3. Rationale for auxiliary-controlled facial selectivity.

cycloadducts crystalline, facilitating their purification; and (5) it serves as a convenient handle for further synthetic transformations. The examples with *N*-Boc (*S*)-phenylalanal (entries 9 and 10) show that this chiral auxiliary can dominate the stereochemical outcome of the [C+NC+CC] process even with aldehydes possessing resident chirality. The reported methodology nicely complements the 1,3-dipolar cycloadditions of Williams' and Harwood's morpholin-2-one-derived azomethine ylides, which cannot involve N-metalated azomethine ylides and necessarily lead to 2,5-trans disubstituted pyrrolidines via (*E*,*Z*)-azomethine ylides (see ref 20).

To expand the practical utility of the Ag^{I}-catalyzed asymmetric [C+NC+CC] process, chemoselective removal of the chiral auxiliary was demonstrated. The use of buffered thiolate[24] for this purpose is particularly meritorious in that it enables the rapid and chemoselective conversion of the acylsultam moiety to a synthetically useful thiolester with minimal α-epimerization. The resulting thiol ester structures can be varied by employing different thiols to facilitate chromatographic separation of the products. The reactions shown below are illustrative, cleanly producing thiol esters **11** and **13** in the indicated yields.[25] We have previously shown that the removal of Oppolzer's sultam from similar 2-pyrrolidinyl acylsultams may also be accomplished via hydrolysis, transesterification, or reduction (see ref 16).



In summary, the Ag^{I}-catalyzed asymmetric [C+NC+CC] coupling reaction described herein provides convenient access to a variety of highly functionalized pyrrolidine structures at ambient temperature in a single chemical step. In addition to providing enantiomerically enriched products unavailable using existing 1,3-dipolar cycloaddition methodology, the process is unique in its ability to incorporate structurally diverse and enolizable aldehydes. Because the aldehyde component provides the most potential for introducing structural diversity into the [C+NC+CC] process, this mild reaction can serve as an asymmetric "linchpin" in the middle and latter stages of a synthesis. We anticipate that this reaction will be of considerable value for both target- and diversity-oriented syntheses.

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Supporting Information Available: Characterization data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Two stereoisomeric endo 1,3-dipolar cycloaddition transition states are possible with dimethyl fumarate.

(23) CCDC−614445 (cycloadduct **4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

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(25) **Auxiliary Removal:** To a stirred, cooled solution of thiolate (prepared by adding 1.5 equiv of *n*-BuLi to a cooled solution of 3 equiv of anhydrous thiol in THF) was slowly added a cooled solution of cycloadduct in dry THF (final concentration of cycloadduct is ~0.1 M). After confirming by TLC analysis that the starting material was consumed, the reaction mixture was partitioned between an aqueous buffer (pH 9−12) and DCM. The combined organic layers were dried over $MgSO_4$ and concentrated to yield a colorless oil, which was subjected to flash column chromatography to give the pure thiol ester and free camphorsultam.