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A stereodivergent cascade imine → azomethine ylide → 1,3-dipolar cycloadditive approach to α-chiral pyrrolidines

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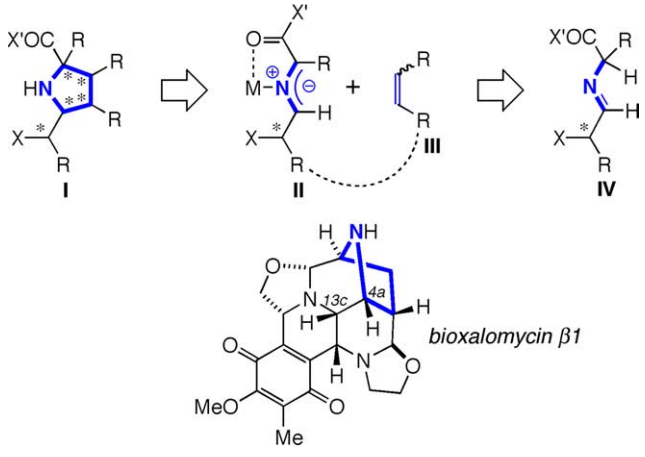
Abstract—Stereodivergent [3+2] cycloadditions of chiral α-amino azomethine ylides leading to highly functionalized pyrrolidines are reported. The marriage of substrate conformational preferences and either an inter- or intramolecular cycloaddition manifold leads to either the *l* (*syn*) or *u* (*anti*) relationship between the pyrrolidine and α-stereocenters. The latter result may be applicable to a new approach to the bioxalomycin family of antibiotics.

Pyrrolidine rings are found in many bioactive natural products and their synthetic analogs. The synthesis of α-chiral pyrrolidine systems (see structure **I** in Scheme 1) is a particularly challenging goal. We became interested in this general problem in the context of a total synthesis of complex bioactive alkaloids such as bioxalomycin β1[1,2] using a strategy that employs a 1,3-dipolar cycloaddition reaction to assemble the pyrrolidine D-ring core of this molecule.[3] In this particular scenario, a complex pyrrolidine corresponding to **I** (X = NH_2) would make a very attractive structure-goal. The required all *cis*-2,4,5-trisubstituted pyrrolidine **I** can be assembled in one step by the *endo*-selective [3+2] cycloaddition of azomethine ylide **II** (M = metal or proton) and dipolarophile **III** (acrolein equivalent).[4] Both inter- and intramolecular cycloaddition manifolds may be envisioned for this process. This approach directly addresses the significant challenge posed by the *anti*-disposed C13c and C4a amino functions in the target molecule. The problem, then, reduces to controlling which diastereoface of the dipole will be attacked by the chiral azomethine ylide.



Scheme 1. α-Chiral pyrrolidines via cascade imine-azomethine ylide-1,3-dipolar cycloaddition.

Before embarking on a program to explore such [3+2] cycloadditions, the α-amino azomethine ylide corresponding to **II** must be accessed via its precursor α-amino imine **IV**. Although there was evidence that α-amino iminium species could be trapped in an intramolecular, nucleophilic sense without competing enamine formation,[5] the issue was certainly not secure for the case at hand. We were aware of a few examples of such a reaction and none of them successfully addressed the stated problem. Both Grigg et al.[6] and Alcaide et al.[7] had reported cycloadditions of α-chiral azomethine ylides derived from *N*-PMP-4-formyl-2-azetidinones to give pyrrolidines related to **I** (X = N). These systems are inherently resistant to enamine formation because of the angle strain that would result due to the azetidinone ring. Cheng et al. reported the microwave-induced intramolecular [3+2] cycloaddition of a serine-derived azomethine ylide.[8] Similarly, Chiacchio et al. reported the intramolecular cycloaddition of an α-sulfonamido

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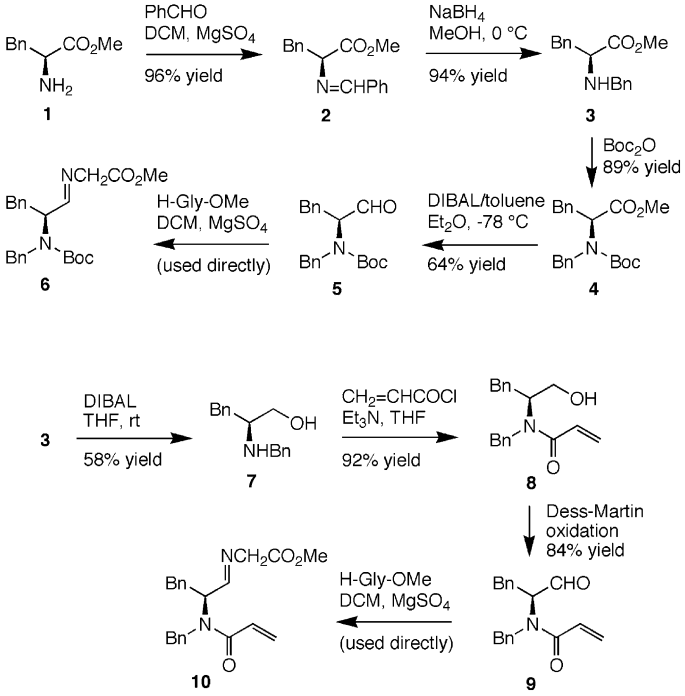
azomethine ylide but found that the products were racemic.[9] This result underscored the problem of facile and reversible enamine formation. Recently, [3+2] cycloadditions of azomethine ylides corresponding to **II** (X = O, R = riboside) were reported.[10] More often than not, the diastereoselectivity of these dipolar cycloadditions was not very good. We now report a solution to the problem outlined in Scheme 1 that provides stereocontrolled access to either *syn*- or *anti*-diastereomers corresponding to **I** (X = N).

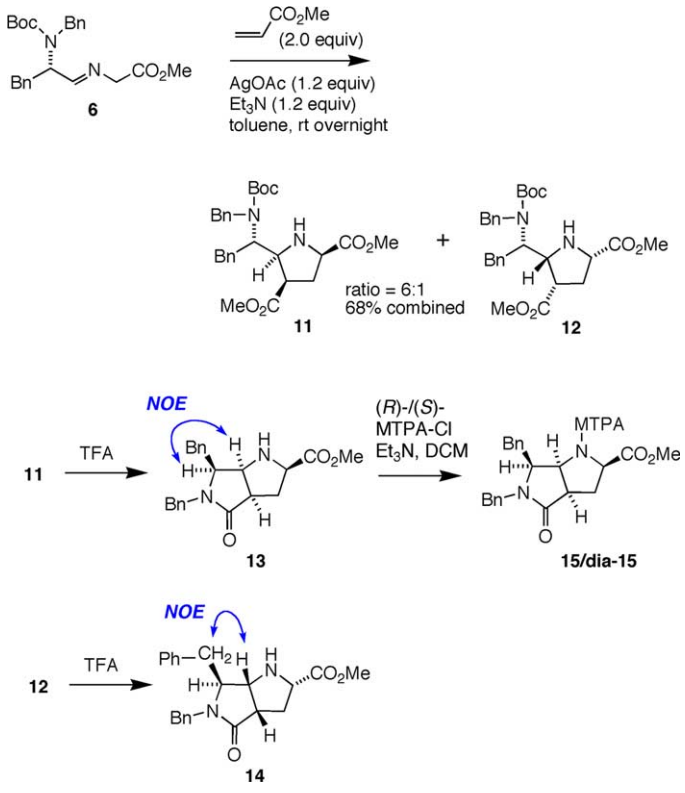
We first examined the model α-amino imine substrate **6**, the synthesis of which is shown in Scheme 2. The sequence began with the condensation of free phenylalanine methyl ester (**1**) with benzaldehyde to give imine **2** in 96% yield. The imine structure was clearly evident from characteristic C^{13} (δ 163.7) and H^1 (δ 7.90) NMR signals. This compound was reduced with $NaBH_4$ to give the *N*-benzylated derivative **3** in 94% yield. The *N*-benzylamine function was then protected with a Boc group to give **4** in 89% yield. Partial reduction of the ester with DIBAL at −78 °C led to the corresponding aldehyde **5** in 64% yield. This *N*-diprotected α-amino aldehyde was then condensed with glycine methyl ester to give desired α-amino imine **6** [NMR data: C^{13} (δ 168.6) and H^1 (δ 7.69)]. In keeping with Grigg's observations with a glycine-derived imine,[11] disubstitution of the α-amino group was found to be crucial for the success of this condensation reaction.

As shown in Scheme 3, imine **6** reacted smoothly with methyl acrylate in the presence of a stoichiometric amount of AgOAc and Et_3N (Grigg's conditions) to give a 6:1 mixture of cycloadducts **11** and **12** in 68% combined yield. These isomeric (by HRMS) compounds were isolated as oils but did not give very definitive ^1H NMR spectra—even upon heating. This was presumably due to rotamer populations with high interconversion barriers. Somewhat surprisingly,[12] the major product of this reaction was found to possess the *like* (*l*)[13] or *syn*-stereochemistry. This conclusion was reached after separately converting **11** and **12** into their respective bicyclic γ-lactams **13** and **14** with TFA and then performing a series of NOE difference NMR experiments on these conformationally constrained bicyclic molecules. The diagnostic NOE correlations are indicated in the scheme. Furthermore, Mosher amide experiments on **13** indicated a 90% ee for this material, demonstrating that the α-stereocenter had remained largely intact throughout the process.

The [3+2] cycloaddition reaction of a chiral azomethine ylide derived from *N*-Boc-serinal acetonide[14] was also examined next (Table 1). The results of these experiments with imine **16** and *tert*-butyl acrylate mirrored those obtained with the phenylalaninal imine. Both stoichiometric (entry 1) and achiral catalytic conditions (entry 2) produced the undesired diastereomer **17** as the major cycloadduct. The stereochemistry of **17** was assigned based on a combination of *J*-coupling and NOE data. The preference for this diastereomer with this substrate is consistent with analogous nitrone-derived azomethine ylide cycloadditions reported in the literature.[15] In an effort to overturn the substrate's preference for the *syn*-diastereomer, we also tried the asymmetric catalytic protocol of Schreiber using the (*R*)-QUINAP ligand (entry 3).[16] This resulted in a definite increase in the percentage of the *unlike* (*u*) or *anti*-diastereomer **18**, but ligand control was still not dominant in this stereochemically mismatched case. Once again, no evidence of enamine formation or β-elimination was observed.

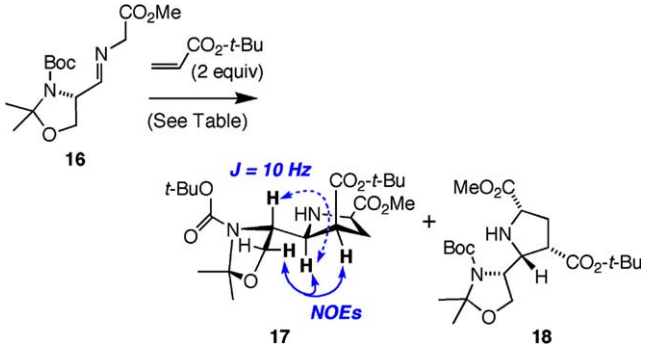


Scheme 2. Synthesis of phenylalanine-derived imine substrates.



Scheme 3. Intermolecular cascade 1,3-dipolar cycloaddition with phenylalanine-derived α-amino imine.

Table 1. Intermolecular cascade 1,3-dipolar cycloadditions with *N*-Boc-serinal acetonide imine



Entry	Reaction conditions	Combined yield (%)	Diastereomer ratio
1	AgOAc (1.2 equiv) Et_3N (1.2 equiv) toluene, rt overnight	64	10:1
2	AgOAc (10 mol%) Ph_3P (20 mol%) Et_3N (10 mol%) toluene, rt overnight	51	4.5:1
3	AgOAc (3 mol%) (*R*)-QUINAP (3 mol%) Et_3N (10 mol%) toluene, rt overnight	62	1:1

The diastereoselectivity of the intermolecular cycloaddition reactions of azomethine ylides derived from imines **6** and **16** can be rationalized by the pre-TS conformations **A** and **B** that minimize A-strain between the α-stereocenter and the azomethine moiety (Fig. 1). In both cases, this conformational preference forces the Boc (or possibly the Bn group in the case of **6**) to block the *Re*-face of the azomethine ylide, leading to *Si*-attack. We reasoned that one might be able to turn this conformational preference to our advantage by tethering the dipolarophile to the α-amino group as in pre-TS conformation **C** (R = H). In such a case, the resulting (*E*,*E*)-azomethine ylide would undergo intramolecular dipolar cycloaddition to the acrylamide dipolarophile to give the bicyclic lactam **14** directly.

Accordingly, we set out to examine the intramolecular version of the cascade imine → azomethine ylide → 1,3-dipolar cycloaddition with the phenylalanine-derived model substrate **10** (Scheme 2). This compound was readily prepared from amino ester **3** in four steps via a sequence that began with reduction of the ester to give the aminoalcohol **7**. The amine was condensed with acryloyl chloride to give the protected acrylamide **8**, and then subjected to Dess–Martin oxidation to produce the α-acrylamido aldehyde **9** in 45% overall yield.

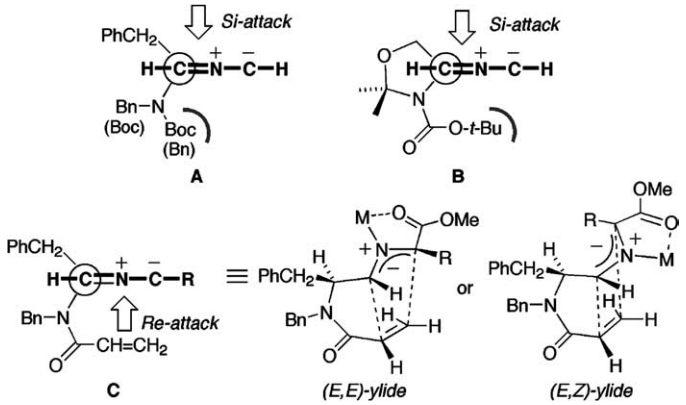
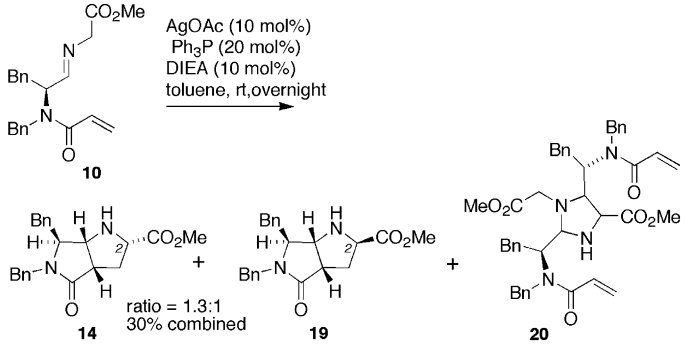


Figure 1. Rationale for stereodivergent intermolecular and intramolecular [3+2] cycloadditions.

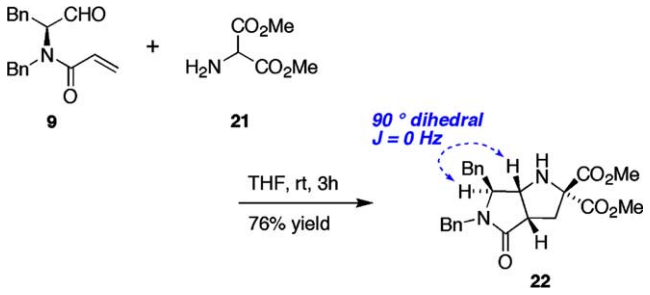
Significantly, this sequence proceeded without interference by the potentially reactive acrylamide moiety. The aldehyde was condensed with glycine methyl ester to give the imine **10**, which was used directly. Exposure of this compound to catalytic Ag(I) conditions resulted in formation of two cycloadducts (Scheme 4). Gratifyingly, the major product was identical to compound **14** that had been obtained from the minor product in the intermolecular cycloaddition sequence. A second isomeric compound, tentatively identified as the corresponding epimeric methyl ester **19**, was also obtained. This cyclo- adduct could result from cycloaddition to the isomeric (*Z*,*E*)-azomethine ylide or epimerization of **14**. Unfortunately, the combined yield of these two cycloadducts was never above 30%. A compound that we believe to be imidazolidine **20** (stereochemistry unassigned) was also found as a by-product and its formation provided us with a hint to the way around this problem.

We reasoned that imidazolidine **20** was formed because of ineffective trapping of the azomethine ylide **C** by the acrylamide dipolarophile. One possible explanation for attenuated reactivity was that the higher energies of the acrylamide versus acrylate π molecular orbitals resulted in a larger dipole$_{HOMO}$–dipolarophile$_{LUMO}$ frontier molecular orbital (FMO) energy gap.[17] This led to competitive intermolecular [3+2] cycloaddition to the imine double bond.[18] The rate of azomethine cycloaddition could be accelerated by either reducing the FMO gap or increasing the concentration of the reactive dipole. One or both of these conditions could be met by replacing H–Gly–OMe with dimethyl 2-aminomalonate (**21**).[19] Note also that, in this case, the same product would form irrespective of azomethine ylide geometry. The optimal conditions for this [3+2] cycloaddition involved simply mixing the aldehyde **9** and amine **21** together in THF. The reaction proceeded rapidly at room temperature to give good yields of a single cycloadduct, identified as compound **22** (Scheme 5). The *u* (*anti*) stereochemistry of **22** was readily ascertained by the absence of *J*-coupling between the pyrrolidine H-5 and α-proton. This situation is the consequence of a 90° dihedral angle, that is only possible with this diastereomer. Thus, the desired cascade imine → azomethine ylide → 1,3-dipolar cycloaddition sequence occurred sequentially and selectively in one-pot.

In conclusion, we have defined a new approach to either *l* (*syn*) or *u* (*anti*) configured α-chiral pyrrolidines based on stereocontrolled [3+2] cycloadditions of chiral α-amino azomethine ylides. Both inter- and intramolecular [3+2] cycloadditions reactions of potentially labile α-amino azomethine ylides proceed selectively without significant α-racemization. The intermolecular [3+2] cycloaddition leads to the *l* (*syn*) diastereomeric relationship whereas the intramolecular cycloaddition manifold provides the *u* (*anti*) diastereomeric series. This intramolecular cascade imine → azomethine ylide → 1,3-dipolar cycloaddition proceeds efficiently in one-pot under very mild



Scheme 4. Intramolecular cascade [3+2] cycloaddition of glycine-derived azomethine ylide.



Scheme 5. One-pot intramolecular cascade [3+2] cycloaddition of amino malonate derived azomethine ylide.

reaction conditions. The intramolecular [3+2] cycloaddition forms the basis for a new synthetic approach to the bioxalomycin family of antibiotics.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.119. General experimental procedures and characterization for all new compounds are provided.

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