

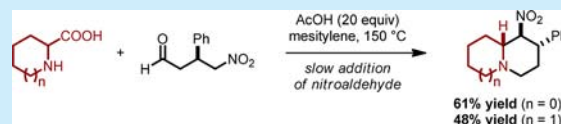
# Decarboxylative Annulation of $\alpha$ -Amino Acids with $\gamma$ -Nitroaldehydes

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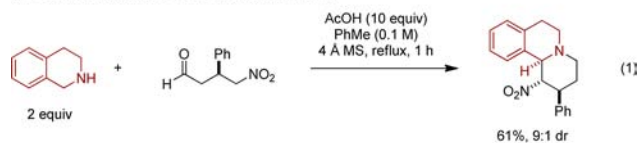
## S Supporting Information

**ABSTRACT:** Indolizidine and quinolizidine derivatives are readily assembled from proline or pipecolic acid and  $\gamma$ -nitroaldehydes by means of a decarboxylative annulation process. These reactions are promoted by simple acetic acid and involve azomethine ylides as reactive intermediates. The method was applied to the synthesis of an epiquinamide analog.

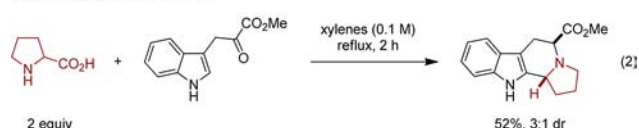


As part of our ongoing studies to develop redox-neutral methods for the C–H functionalization of amines,<sup>1</sup> we recently reported the synthesis of fused tricyclic ring systems via redox-neutral annulation of cyclic amines with a range of substituted  $\gamma$ -nitrobutyraldehydes (e.g., eq 1).<sup>2</sup> While this

### Redox-annulation via C–H functionalization:



### Decarboxylative annulation:



method proved valuable in rapidly accessing relatively complex products in highly enantioenriched form, the method has remained limited to relatively activated amines such as 1,2,3,4-tetrahydroisoquinoline and tryptoline. More challenging amines such as pyrrolidine and piperidine did not form the corresponding annulation products under a variety of conditions. However, the use of pyrrolidine and piperidine would be particularly attractive as an entry to substituted indolizidines and quinolizidines, core structures of a significant number of natural products.<sup>3</sup> Here we report a simple decarboxylative annulation approach to the synthesis of substituted indolizidines and quinolizidines utilizing cyclic amino acids (proline and pipecolic acid) and  $\gamma$ -nitroaldehydes.

Based on the computationally delineated mechanism of the redox-annulation shown in eq 1,<sup>2</sup> we speculated that the failure of pyrrolidine and piperidine to undergo this transformation might be due to a higher barrier for azomethine ylide formation,<sup>4</sup> a crucial early step in the pathway toward product. Given the well-known propensity of amino acids such as proline and pipecolic acid to undergo azomethine ylide formation upon decarboxylative condensation with an aldehyde,<sup>5,6</sup> we proposed that these readily available amino

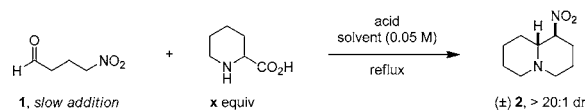
acids may be used as surrogates for pyrrolidine and piperidine in the desired annulation process. Indeed, we and others have shown that azomethine ylides obtained via the decarboxylative route can undergo a range of nonpericyclic transformations including annulations.<sup>7–10</sup> The majority of these reactions, however, are limited to the use of nonenolizable aldehydes. The condensation of an indole-containing, highly activated enolizable ketone with proline is the only example of a decarboxylative annulation with an enolizable species (eq 2).<sup>7e</sup> To our knowledge, no examples of decarboxylative annulations with enolizable aldehydes have been reported.

In order to test the feasibility of the proposed decarboxylative annulation, parent  $\gamma$ -nitrobutyraldehyde (**1**) was allowed to react with pipecolic acid under a range of conditions.<sup>11</sup> Key findings of this survey are summarized in Table 1. Under reflux in toluene, no product was observed in the absence of acetic acid (entry 1) or even with up to 10 equiv of acetic acid (entries 2, 3). No improvement was seen upon raising the reaction temperature (reflux in xylenes, entry 4). Slow addition of nitroaldehyde **1** was found to be a strict requirement in order to observe any of the desired product **2** (entry 5). A reduction in addition time from 15 to 2 h resulted in a slight increase in yield (entry 6). The yield of **2** could be further improved to 28% upon increasing the amount of acetic acid to 20 equiv (entry 7). At this point, the addition time of **1** was lowered from 2 to 1 h, without detrimental effect (entry 8).

An increase in the amount of pipecolic acid to 2 equiv led to a noticeable increase in yield (entry 9), as did the addition of 4 Å molecular sieves (entry 10). A further increase to 4 equiv of pipecolic acid allowed for the isolation of product **2** in 51% yield (entry 11). However, a significant reduction in yield was observed with 6 equiv of pipecolic acid (entry 12). Benzoic acid and 2-ethylhexanoic acid (2-EHA) performed similarly or equally well to acetic acid but offered no further improvements (entries 13, 14). Use of *o*-xylene or mesitylene as solvents led to inferior results (entries 15, 16). Interestingly, the conditions of

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Table 1. Reaction Development<sup>a</sup>


| entry             | x   | acid (equiv)             | solvent          | time [h] <sup>b</sup> | yield (%) |
|-------------------|-----|--------------------------|------------------|-----------------------|-----------|
| 1                 | 1.1 | —                        | PhMe             | 0 + 2                 | complex   |
| 2                 | 1.1 | AcOH (1)                 | PhMe             | 0 + 2                 | trace     |
| 3                 | 1.1 | AcOH (10)                | PhMe             | 0 + 2                 | trace     |
| 4                 | 1.1 | AcOH (10)                | xylenes          | 0 + 2                 | complex   |
| 5                 | 1.1 | AcOH (10)                | xylenes          | 15 + 1                | 17        |
| 6                 | 1.1 | AcOH (10)                | xylenes          | 2 + 1                 | 22        |
| 7                 | 1.1 | AcOH (20)                | xylenes          | 2 + 0.5               | 28        |
| 8                 | 1.1 | AcOH (20)                | xylenes          | 1 + 0.5               | 27        |
| 9                 | 2   | AcOH (20)                | xylenes          | 1 + 0.5               | 34        |
| 10 <sup>c</sup>   | 2   | AcOH (20)                | xylenes          | 1 + 0.5               | 41        |
| 11 <sup>c</sup>   | 4   | AcOH (20)                | xylenes          | 1 + 0.5               | 51        |
| 12 <sup>c</sup>   | 6   | AcOH (20)                | xylenes          | 1 + 0.5               | 34        |
| 13 <sup>c</sup>   | 4   | PhCO <sub>2</sub> H (20) | xylenes          | 1 + 0.5               | 41        |
| 14 <sup>c</sup>   | 4   | 2-EHA (20)               | xylenes          | 1 + 0.5               | 51        |
| 15 <sup>c</sup>   | 4   | AcOH (20)                | <i>o</i> -xylene | 1 + 0.5               | 32        |
| 16 <sup>c,d</sup> | 4   | AcOH (20)                | mesitylene       | 1 + 0.5               | 16        |

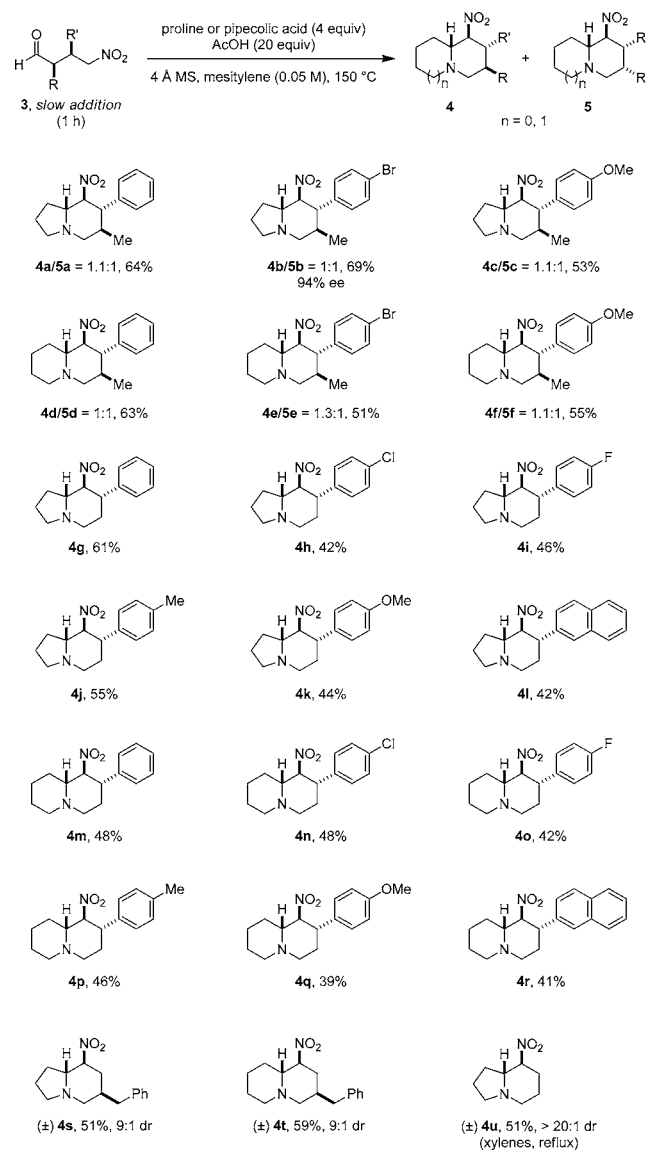
<sup>a</sup>Reactions were performed with 0.5 mmol of 4-nitrobutyraldehyde. Yields are isolated yields of chromatographically purified compounds. <sup>b</sup>Addition time for 4-nitrobutyraldehyde + additional reaction time after completed addition. <sup>c</sup>With 4 Å MS. <sup>d</sup>Reaction was performed at 150 °C.

entry 16 proved optimal for substituted analogs of  $\gamma$ -nitrobutyraldehyde 1 (vide infra).<sup>12</sup>

The scope of the decarboxylative annulation reaction was explored as summarized in Scheme 1. Both proline and pipecolic acid readily underwent decarboxylative annulations with highly enantioenriched 2,3-disubstituted 4-nitrobutyraldehydes<sup>11</sup> to provide the corresponding products in moderate to good yields. Consistent with the intermediacy of enamines and the corresponding epimerization of the 2-position of the nitroaldehyde starting materials, annulation products were obtained as mixtures of diastereomers 4 and 5. In the absence of a substituent in the 2-position of 3, products 4 were isolated as essentially single diastereomers. Interestingly, 4-nitrobutyraldehyde bearing a benzyl substituent in the 2-position but no substituent in the 3-position allowed for the formation of products 4s and 4t in good diastereoselectivities. These compounds were obtained in racemic form. Finally, proline readily underwent the title reaction with  $\gamma$ -nitrobutyraldehyde 1 under the conditions optimized in Table 1 to provide product 4u in highly diastereoselective fashion.<sup>13</sup> Acyclic amino acids such as sarcosine failed to undergo decarboxylative annulations with  $\gamma$ -nitrobutyraldehydes 3.

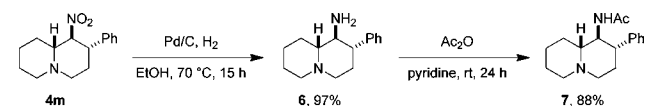
Following the simple two-step procedure outlined in Scheme 2, nitroamine 4m was readily converted to product 7. This compound represents an epimeric analog of epiquinamide,<sup>14</sup> a natural product that has been the focus of intense interest in the synthetic community.<sup>15</sup>

In summary, we have achieved the first decarboxylative annulations of proline and pipecolic acid with enolizable  $\gamma$ -nitrobutyraldehydes. While the yields are only moderate in many cases, this method allows for rapid access to underexplored chemical space.

Scheme 1. Scope of the Decarboxylative Annulation<sup>a</sup>

<sup>a</sup>Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields of purified products.

Scheme 2. Synthesis of an Epiquinamide Analog



## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02020.

Experimental procedures and characterization data (PDF)

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## Notes

The authors declare no competing financial interest.

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