

# Stereoselective Synthesis of $\gamma$ -Lactams from Imines and Cyanosuccinic Anhydrides

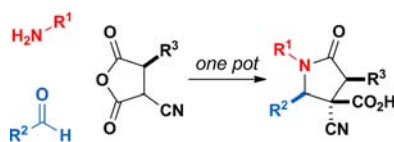
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## ABSTRACT



- 17 examples
- up to 95:5 dr & 98% yield
- 2 or 3 stereogenic centers (one quaternary)
- R<sup>1</sup> = chiral or achiral alkyl
- R<sup>2</sup> = aryl, heteroaryl
- R<sup>3</sup> = H, alkyl, phenyl

A reaction between imines and anhydrides has been developed with chiral disubstituted anhydrides and chiral imines. The synthesis of highly substituted  $\gamma$ -lactams with three stereogenic centers, including one quaternary center, proceeds at room temperature in high yield and with high diastereoselectivity in most cases. Enantiomerically pure alkyl-substituted anhydrides proceed with no epimerization, thus providing access to enantiomerically pure penta-substituted lactam products.

Densely substituted  $\gamma$ -lactams (2-pyrrolidinones) and pyrrolidines are found among natural products and pharmaceutical compounds (Figure 1).<sup>1</sup> The prevalence of these structural motifs has driven the development of new synthetic methodologies.<sup>2</sup> Although each of these methods offers certain advantages, drawbacks include limited substrate scope,<sup>2a,c,d</sup> expensive catalysts,<sup>2b</sup> and multistep processes.<sup>2a–c,h</sup>

The direct reaction of imines with cyclic anhydrides forms  $\gamma$ -lactams in a single step.<sup>3</sup> One consistent limitation

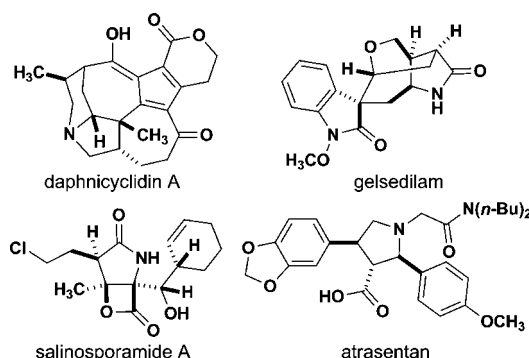


Figure 1. Examples of molecules with a  $\gamma$ -lactam or a pyrrolidine.

of this reaction has been the inability to produce enantiomerically enriched compounds. In the course of our studies directed toward the synthesis of diverse libraries of lactams, we recently reported the remarkably high reactivity and stereoselectivity of the reaction between  $\alpha$ -cyanosuccinic anhydride **3** and achiral imines formed from **1** and **2** for the formation of tetrasubstituted  $\gamma$ -lactams **4** (Scheme 1).<sup>3d</sup>

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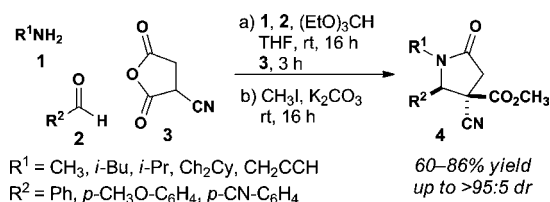
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These studies prompted us to explore fully the opportunities for further transformations of the lactam products and asymmetric synthesis. Herein we report the first examples of stereocontrol from chiral anhydrides and chiral imines in the formation of tetra- and pentasubstituted  $\gamma$ -lactams.

**Scheme 1.** Reactions of Achiral Imines and Cyanosuccinic Anhydride

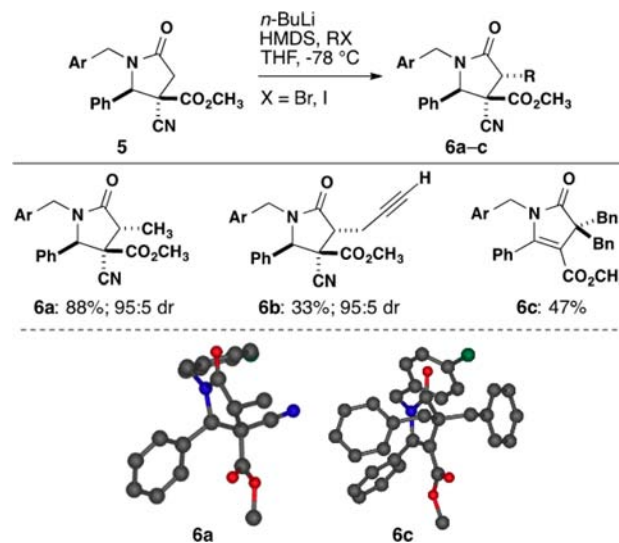


Our efforts in the development of asymmetric imine–anhydride reactions stemmed from our development of modifications to the  $\gamma$ -lactam products of the imine–anhydride reaction. We initially explored the preparation of  $\alpha$ -substituted  $\gamma$ -lactams through alkylation (Scheme 2). Lactam **5**<sup>3d</sup> was methylated using LHMDS to give **6a** with 95:5 diastereoselectivity, and X-ray crystallographic analysis<sup>4</sup> indicated that the incoming electrophile approached opposite to the adjacent carboxymethyl group. Unfortunately, other electrophiles (**6b–c**) gave poor yields. In the case of benzyl bromide, the gem-alkylated product **6c**, which was determined by X-ray analysis,<sup>4</sup> resulted from the elimination of the cyano group. The limited scope of alkylating the lactam compounds led us to pursue the use of disubstituted anhydrides and the possibility of forming enantiopure compounds.

We synthesized disubstituted succinic anhydrides for use in imine–anhydride reactions (Scheme 3). Following literature conditions, diester **8a** was synthesized in two steps from ethyl lactate.<sup>5</sup> Subsequent hydrolysis and cyclization gave anhydride **9**. In order to explore the scope and diastereoselectivity of the disubstituted anhydrides, the isobutyl, benzyl, and phenyl analogs (**10–12**) were also prepared.

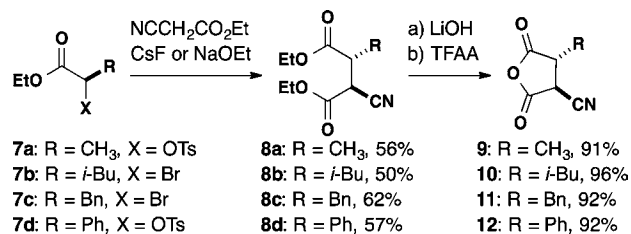
We explored the scope of the imine–anhydride reaction with respect to various imines and chiral disubstituted succinic anhydrides (Scheme 4). Using methyl-substituted cyanosuccinic anhydride **9**, the reaction produced **13a–f** in 82–98% yield and up to 95% selectivity for the formation

**Scheme 2.** Alkylation at the  $\alpha$ -Carbon<sup>a</sup>



<sup>a</sup> Reaction conditions: 1 equiv of **5**, 2.5 equiv of *n*-BuLi, 3.0 equiv of hexamethyldisilazane, and 2.6 equiv of the alkyl halide in tetrahydrofuran (0.6 M). Ar = 4Cl-C<sub>6</sub>H<sub>4</sub>.

**Scheme 3.** Synthesis of 3,4-Disubstituted Succinic Anhydrides



of one major product out of the four possible diastereomers. The products (**13g–i**) from **10–12** gave similarly high selectivities. The analogous reaction of enantiomerically pure **9**, prepared from (*S*)-ethyl lactate, demonstrated that the stereogenic center was preserved through the lactam-forming reaction.<sup>6</sup> X-ray crystallographic analysis<sup>4</sup> (Figure 2) revealed that the major isomer is **13f-syn**, complementing the outcome of the alkylation reaction. The stereochemistry of the major diastereomer of **13a–h** was assigned by comparing <sup>1</sup>H NMR coupling constants. For product **13i**, X-ray analysis showed a different major diastereomer from **13a–h**. Furthermore, when (*S*)-ethyl mandelate was used to make anhydride **12**, chiral HPLC analysis of the resulting **13i** showed a racemic mixture of products. Although the synthesis of pentasubstituted  $\gamma$ -lactams is suitable for various alkyl substituents, the increased acidity of the  $\alpha$ -H of **8d** from the anion-stabilizing phenyl group makes this substrate susceptible to racemization.

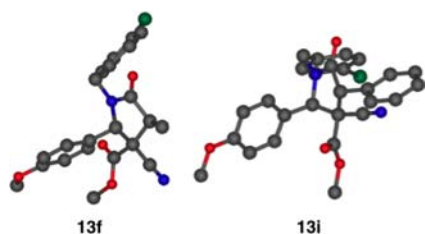
We next examined the possibility of asymmetric induction from imines derived from chiral amines to synthesize

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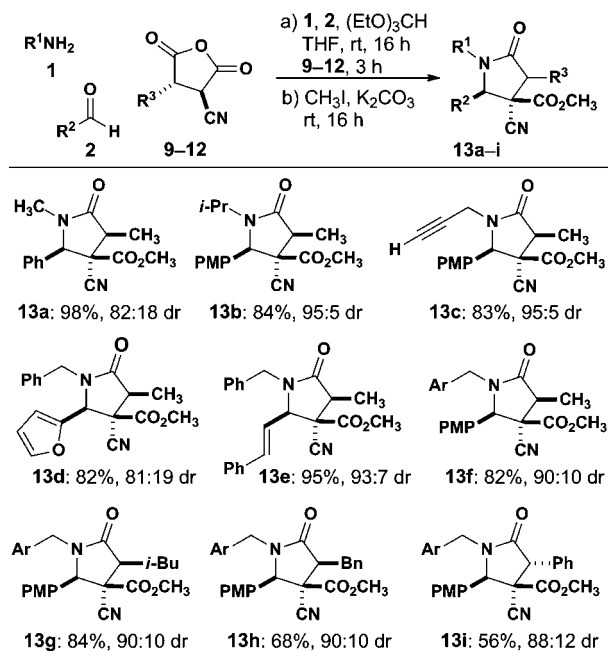
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(6) See Supporting Information.



**Figure 2.** X-ray crystal structures of lactams **13f** and **13i**.

**Scheme 4.** Reaction of Disubstituted Anhydrides and Imines<sup>a</sup>



<sup>a</sup> Reaction conditions: 1 equiv of **1**, 1 equiv of **2**, 1 equiv of **9–12**, and 1.6 equiv of (EtO)<sub>3</sub>CH in THF (0.2 M) at 23 °C. After the removal of solvent, 4 equiv of CH<sub>3</sub>I and 4 equiv of K<sub>2</sub>CO<sub>3</sub> were added in acetone (0.05 M) at 23 °C. The dr is the ratio of the major diastereomer to the sum of the minor diastereomers. Ar = *p*-Cl–C<sub>6</sub>H<sub>4</sub>; PMP = *p*-CH<sub>3</sub>O–C<sub>6</sub>H<sub>4</sub>.

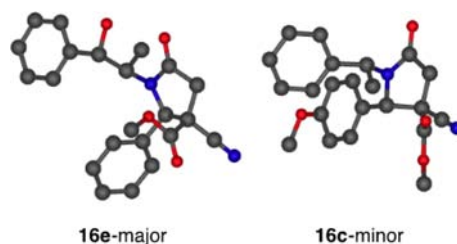
enantiopure  $\gamma$ -lactams. A range of solvents was screened to identify conditions for the reaction using cyanosuccinic anhydride **3** and the imine derived from (*R*)-phenylglycinol (**14**) and benzaldehyde (**15**) (Table 1). Although moderate yields and diastereomeric ratios (dr) of **16a** were observed, only two out of the four possible products can be detected by <sup>1</sup>H NMR analysis. This is consistent with the high diastereoselectivity of the imine–anhydride reaction even though the chiral induction of the imine *N*-substituent is variable. Further screening revealed that DMF and ethanol provided the highest selectivities and yields. Additional experiments using lower temperatures did not lead to improved dr.

We determined the scope of the enantiopure synthesis of  $\gamma$ -lactams (Scheme 5). Using an (*S*)- $\alpha$ -methylbenzyl group on the nitrogen (**16b–c**), we observed a range of 74:26 to

**Table 1.** Screening Reaction Conditions for Chiral Imines and Cyanosuccinic Anhydride<sup>a</sup>

entry	solvent	isolated yield	dr <sup>b</sup>
1	THF	54%	65:35
2	CH <sub>3</sub> CN	30%	76:24
3	CHCl <sub>3</sub>	39%	64:36
4	toluene	40%	58:42
5	DMF	68%	79:21
6	ethanol	69%	75:25

<sup>a</sup> Reaction conditions: see Scheme 4. <sup>b</sup> The dr is the ratio of the major diastereomer to the sum of the minor diastereomers.



**Figure 3.** X-ray crystal structure analyses of products **16e**-major and **16c**-minor from chiral imines.

81:19 dr. We found that, in the absence of the alcohol moiety, the reaction proceeds in good yields and dr (**16b–d**) when tetrahydrofuran is used as the solvent. Other cleavable auxiliaries and larger groups (**16e–h**) gave similar yields and diastereoselectivities. The NH lactam can be obtained in high yield by cleaving the  $\alpha$ -methyl-*p*-methoxybenzyl<sup>7</sup> or 2-phenylethanol groups.<sup>8</sup> Previous to these results, one example of asymmetric induction had been documented in the related synthesis of a substituted 2-quinolone from homophthalic anhydride.<sup>9</sup> The absolute and relative stereochemistries of the diastereomers were unambiguously assigned by X-ray analyses<sup>4</sup> of compounds **16e**-major and **16c**-minor (Figure 3). The stereochemistry of products **16a**, **16b**, and **16d–h** has been assigned by comparing the <sup>1</sup>H NMR coupling constants.

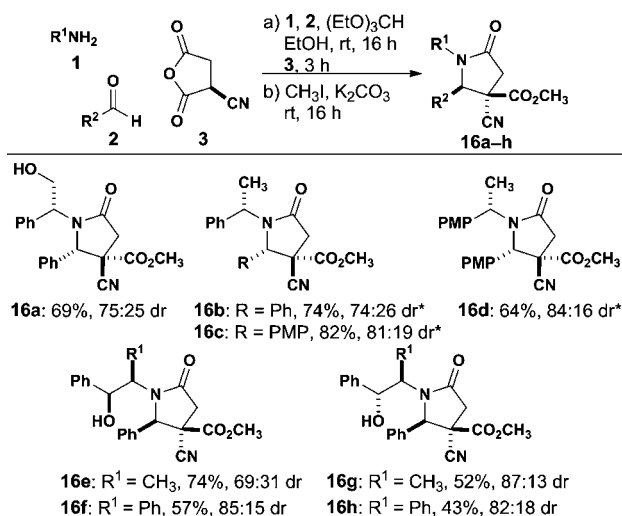
Unlike the previously proposed mechanisms of related imine–anhydride reactions which describe an iminolysis pathway,<sup>3b,i</sup> our current mechanistic hypothesis involves a

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**Scheme 5.** Reaction of Chiral Imines and Cyanosuccinic Anhydride<sup>a</sup>



<sup>a</sup> Reaction conditions: see Scheme 4. The dr is the ratio of the major diastereomer to the sum of the minor diastereomers. \* marks the reactions performed with THF as solvent instead of ethanol. PMP = *p*-CH<sub>3</sub>O-C<sub>6</sub>H<sub>4</sub>.

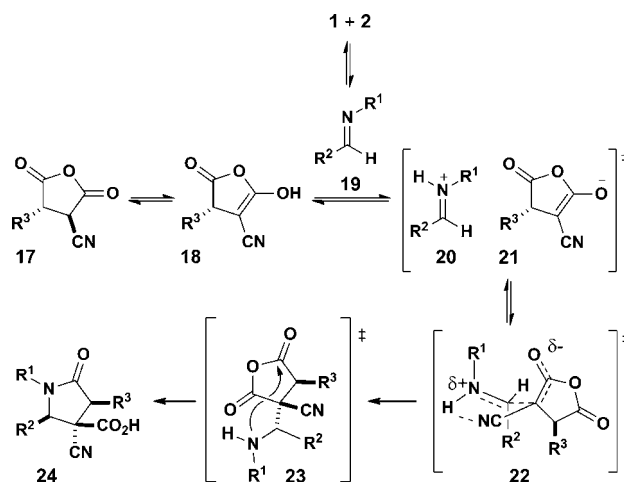
stepwise Mannich–acylation process (Scheme 6), involving the enol form **18** of the anhydride **17**. Although there are only a few examples where anhydride enols have been reported as reactive intermediates,<sup>10</sup> they have been studied computationally,<sup>11</sup> observed crystallographically,<sup>12</sup> and suggested as key intermediates in a related lactone-forming reaction.<sup>13</sup> A proton transfer leads to the reactive iminium **20** and enolate **21** intermediates. The Mannich step occurs with high diastereoselectivity through the pseudo-Zimmerman–Traxler transition state **22** with intermolecular hydrogen bonding complexation. The formation of the Mannich adduct **23** is followed by a transacylation to form the  $\gamma$ -lactam product **24** with a  $\beta$ -carboxylic acid. This mechanistic picture emanates from extensive computational investigations.<sup>14</sup>

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**Scheme 6.** Proposed Mechanism for the Diastereoselective Reaction of Cyanosuccinic Anhydrides and Imines



In conclusion, we have demonstrated that the imine–anhydride reaction using cyanosuccinic anhydrides is a robust method for the synthesis of a wide variety of highly substituted  $\gamma$ -lactams. The formation of the two new stereogenic centers can be controlled by chiral amines and chiral anhydrides, the latter leading to exquisite diastereoselectivity in three contiguous stereogenic centers.

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**Supporting Information Available.** Experimental procedures, compound characterization data for all new compounds, X-ray data, and HPLC analysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.