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### Authors

Laws, Stephen W  
Moore, Lucas C  
Di Maso, Michael J  
[et al.](#)

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## Diastereoselective Base-Catalyzed Formal [4 + 2] Cycloadditions of *N*-Sulfonyl Imines and Cyclic Anhydrides

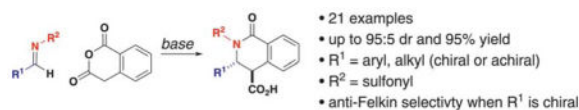
Stephen W. Laws, Lucas C. Moore, Michael J. Di Maso, Q. Nhu N. Nguyen, Dean J. Tantillo, and Jared T. Shaw\*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States

### Abstract

A diastereoselective base-catalyzed Mannich reaction of cyclic, enolizable anhydrides and *N*-sulfonyl imines for the synthesis of  $\delta$ -lactams is reported. This anhydride Mannich reaction tolerates imines derived from aryl and enolizable aldehydes. A base-catalyzed product epimerization pathway ensures high anti diastereoselectivity in aryl and achiral enolizable imines.

### Graphical abstract



Substituted  $\gamma$ -lactam (2-pyrrolidinone) and  $\delta$ -lactam (2-piperidinone) ring systems are core structures featured in numerous natural products that exhibit interesting biological activities (Figure 1).<sup>1,2</sup> As part of a longstanding interest in accessing such lactam cores, our group has developed new methods for the formal [4 + 2] cycloaddition of imines and cyclic, enolizable anhydrides based on the foundational work of Castagnoli<sup>3,4</sup> and Cushman.<sup>5</sup> To this end, our group has previously contributed to advances in mechanistic understanding of the Castagnoli–Cushman reaction,<sup>6,7</sup> which we now call the anhydride Mannich reaction (AMR), developed a novel four-component reaction<sup>8–14</sup> (4CR), and reported the first base-promoted AMR variant using *N*-sulfonyl imines in the synthesis of bisavenanthramide B-6.<sup>15</sup> While the AMR has proven a powerful means of synthesizing complex lactams in diversity-oriented and natural product syntheses, most reports of such reactions employ *N*-

\*Corresponding Author: jtshaw@ucdavis.edu.

#### ORCID

Dean J. Tantillo: 0000-0002-2992-8844

Jared T. Shaw: 0000-0001-5190-493X

#### Notes

The authors declare no competing financial interest.

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00468.

X-ray data for compound **16e** (CIF)

X-ray data for compound **16f** (CIF)

Structures of obtained compounds (MOL)

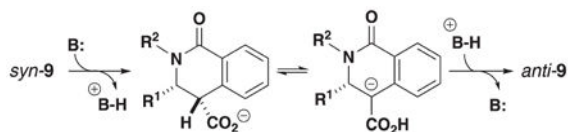
Experimental details, compound characterization, and NMR spectra (PDF)

alkylimines, which react readily with many anhydrides in the absence of catalyst.<sup>9</sup> Several reports of catalysis do not clearly show acceleration relative to the known background rate. One recent report uses *N*-sulfonyl imines in reactions with homophthalic anhydride to form lactams in moderate stereoselectivity and yields ranging from 12 to 65%.<sup>16</sup> More recently, high enantioselectivity was achieved in reactions of homophthalic anhydride and *N*-arylimines.<sup>17</sup> Herein, we report the development of a highly diastereoselective and catalytic AMR for the synthesis of  $\delta$ -lactams from cyclic anhydrides and *N*-sulfonyl imines derived from aryl and enolizable aldehydes. Notably, this reaction is only the second reported use of imine substrates derived from chiral aldehydes in the AMR.<sup>18</sup>

Mechanistic understanding of the AMR suggests that the inherent reactivity observed in reactions of *N*-alkyl- and *N*-arylimines can be attributed to a crucial proton transfer from anhydride (**1**) to imine (**2**), which leads to the formation of enolate **3** and iminium ion **4** (Figure 2A).<sup>6,7</sup> Following this key step, Mannich addition to **5** and subsequent acylation rapidly forms lactam product **6**. Based on this understanding, we first reported the suppressed reactivity of *N*-sulfonyl imines to enolizable anhydrides as well as their base-mediated reactivity in the anionic AMR.<sup>15</sup> From that report, we formed the general hypothesis that a reduction in imine nitrogen basicity through thoughtful substitution would prevent enolate formation in the absence of exogenous base (Figure 2B). In such a catalytic system, imine **7** and anhydride **8** cannot form lactam **9** alone. Instead, added base **10** would generate the requisite enolate (**11**), which would then undergo Mannich addition to **12** and subsequent transannular acylation through intermediates **13** and **14** to form lactam product **9** and regenerate base **10**.

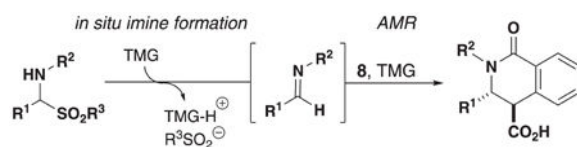
Initial investigation of the catalytic AMR focused on the reactivity of homophthalic anhydride, a readily enolizable substrate containing the aromatic core of the Amaryllidaceae alkaloids. This anhydride was shown to be unreactive when paired with *N*-sulfonyl, benzaldehyde-derived imine (**15a**) in the absence of base. Furthermore, addition of stoichiometric quantities of Hünig's base to the same reaction mixture yielded the desired lactam product in excellent conversion and diastereoselectivity (Table 1). A series of catalyst loading experiments confirmed that the originally observed conversion and selectivity could be repeated with as little as 10 mol % base loading.

The diastereoselectivity of this process was observed as a function of reaction time using <sup>1</sup>H NMR spectroscopy with modest anti/syn diastereomeric ratios at early time points leading to a single, anti diastereomer after 20–24 h. This observation suggested a base-catalyzed epimerization process for converting the syn lactam to the thermodynamically favored anti diastereomer, which was supported by kinetic studies (eq 1). Optimization of reaction conditions for each substrate pairing allowed for the isolation of a single lactam diastereomer in 20–24 h reaction times in all cases through the use of a stronger base, more polar solvent, or both (Scheme 1). The structures of **16d** and **16e** were confirmed by X-ray crystallography and established the *anti* configuration as the observed product. In the remainder of products, the chemical shifts and coupling constants of the diagnostic lactam protons were consistent with those in **16d** and **16e**.



(1)

Although many imine substrates were readily formed in condensation reactions between aldehydes and arylsulfonamides,<sup>19</sup> several substrates necessitated the use of  $\alpha$ -aminosulfones<sup>20</sup> as imine precursors. In some cases, these isolable intermediates could be treated with aqueous base to eliminate arylsulfinate and produce the desired imine. Other aminosulfones readily degraded in the elimination conditions. We recognized that the aminosulfones could be used to generate imines in situ, albeit with the addition of stoichiometric base (eq 2).<sup>21–25</sup>



(2)

A short series of base-loading experiments was conducted to determine the feasibility of a catalytic AMR using aminosulfones in place of imines. Hydrocinnamaldehyde-derived aminosulfone **15j** was combined with homophthalic anhydride and varying concentrations of TMG (Table 2). While substoichiometric TMG facilitated conversion to product with excellent diastereoselectivity, loadings of less than 50 mol % failed to show the catalytic activity of the analogous reaction with imines. Presumably, liberated phenylsulfonic acid protonates the base, decreasing activity. Although the use of aminosulfones as in situ imine precursors requires stoichiometric base, they enable a significant expansion of substrate scope.

Direct introduction of aminosulfones into the AMR allowed for a significant scope expansion (Scheme 2). Hydrocinnamaldehyde- and isobutyraldehyde-derived aminosulfones, when combined with homophthalic anhydride and TMG, produced AMR products in moderate yields and excellent diastereoselectivities. Additionally, chiral-pool derived enolizable imines and aminosulfones containing stereogenic centers readily produced AMR products.

Although four possible diastereomers of product could be formed in the reaction of chiral pool-derived imines or aminosulfones, only two were observed. The relative stereochemistry of the three stereogenic centers was assigned by computational NMR (see the Supporting Information). Curiously, the major diastereomers are consistent<sup>18</sup> with a chelation-controlled, or anti-Felkin, initial addition of homophthalic anhydride enolate to imine (Scheme 3), in spite of the lack of a chelating Lewis acid. We initially predicted that the

addition would be governed by the polar Felkin–Anh model,<sup>26–30</sup> consistent with two reports of homophthalic anhydride enolate additions to alkyl imines.<sup>31,32</sup> However, we know of only two examples of nucleophilic addition to  $\alpha$ -chiral *N*-sulfonyl imines without addition of exogenous chelating agent; one was governed by the Cornforth–Evans model,<sup>33</sup> and the other, a Grignard addition, did not give the expected chelation-controlled product.<sup>34</sup> With the steric bulk of the sulfonyl group in play, the classic polar Felkin–Anh and Cram chelation addition models may not adequately describe additions to *N*-sulfonyl imines.

Evaluations of anhydride scope revealed that other enolizable anhydrides were also capable substrates for this reaction (Scheme 4). With the exception of lactam **16u**, which could only be isolated in low yield after spontaneous decarboxylation<sup>35</sup> in the AMR reaction conditions, all lactams were formed as a single diastereomer. The lactam product of methyl homophthalic anhydride was formed as a single diastereomer without any evidence of epimerization by NMR spectroscopy over time, suggesting excellent kinetic selectivity in this case. Lactam **16t** contains the dihydroisoquinolone core of 7-deoxypancratistatin, a bioactive Amaryllidaceae alkaloid, and is structurally similar to Souchet and Clark’s proposed synthetic precursor to that natural product.<sup>18</sup>

In summary, we have discovered a base-catalyzed variant of the anhydride–Mannich reaction between cyclic anhydrides and imines. Although isolated imines require as little as 10 mol % base, for many reactions a stoichiometric quantity of base is operationally convenient. For cases in which imines were difficult or impossible to prepare, aminosulfones could be employed directly. This innovation enabled us to document significant levels of stereocontrol with chiral substrates, albeit with products inconsistent with addition by the Felkin–Anh model.

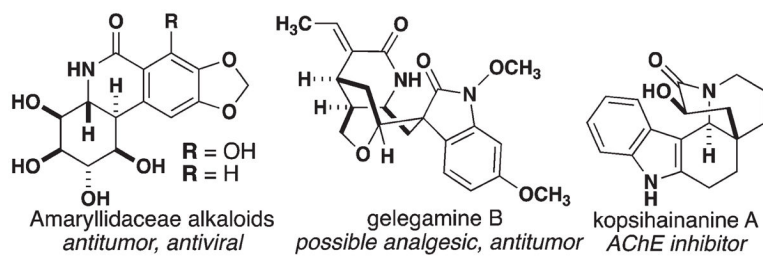
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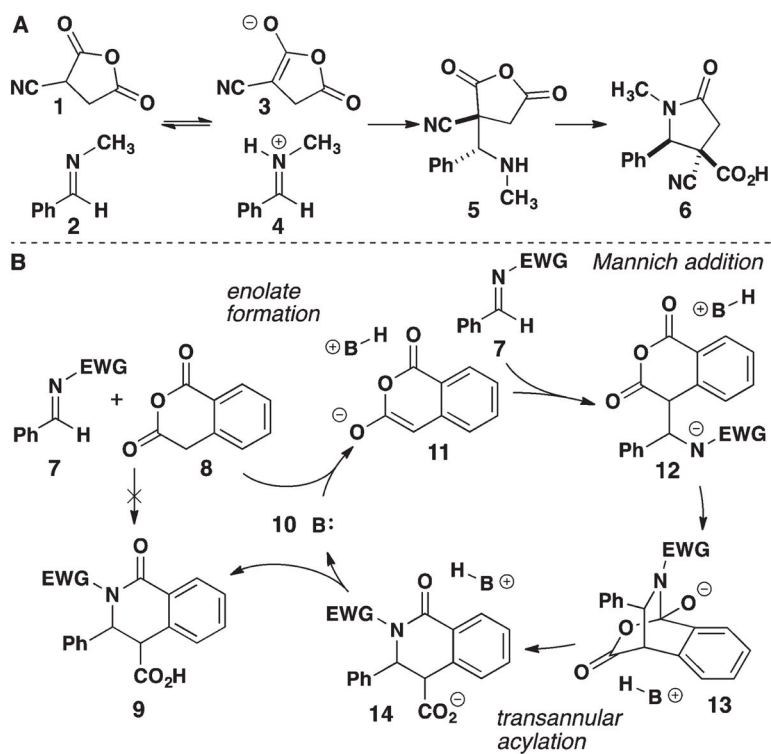
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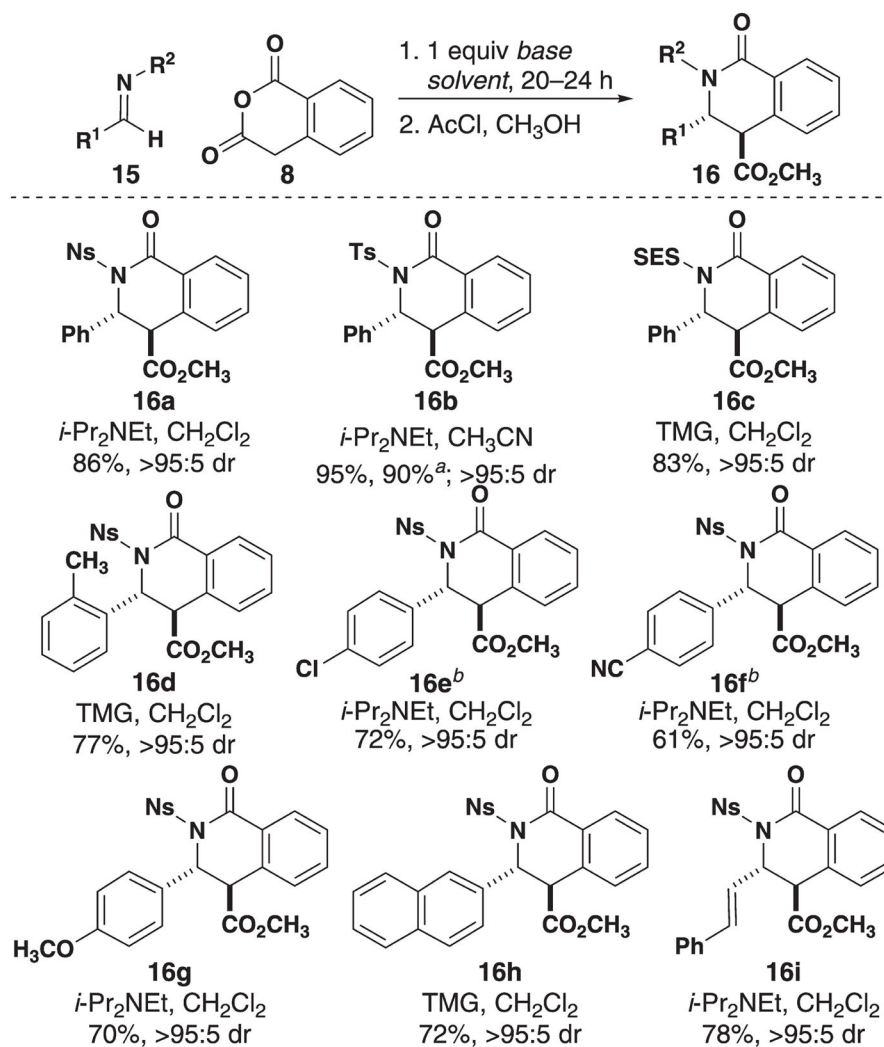


**Figure 1.**  
Select bioactive lactam natural products containing the  $\delta$ -lactam core motif.

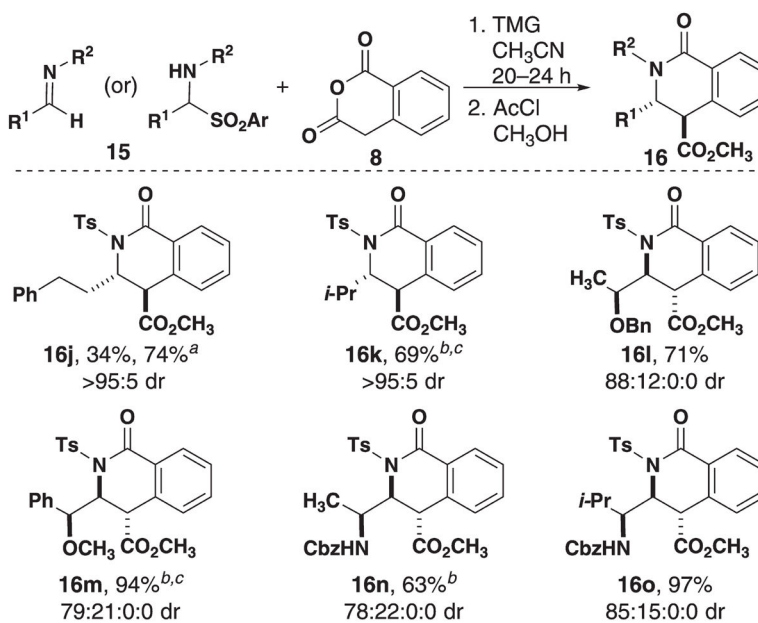


**Figure 2.**  
 (A) Proposed catalyst-free AMR mechanism. (B) Proposed catalytic cycle of the base-promoted AMR.



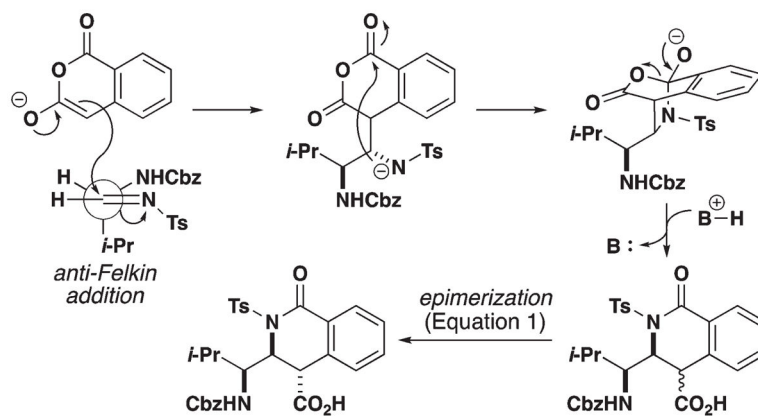


**Scheme 1. Aryl Aldehyde Derived *N*-Sulfonyl Imine Scope of the Base-Mediated AMR**  
<sup>a</sup>1.3 mmol scale, 20 mol % base. <sup>b</sup>Relative configuration confirmed by X-ray crystallography.

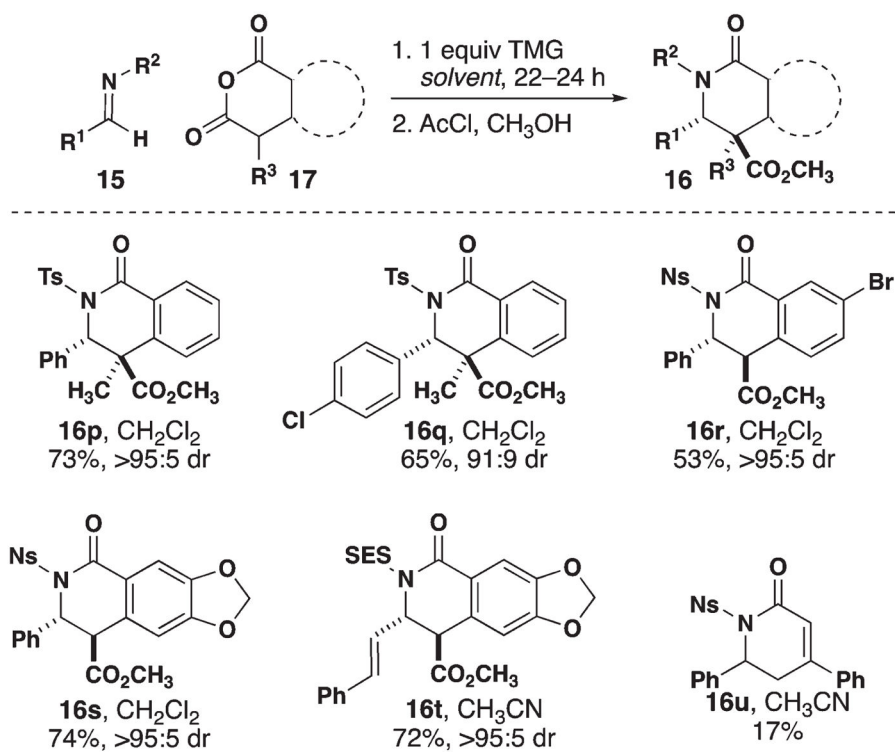


**Scheme 2. Enolizable Imine Scope of the TMG-Mediated AMR**

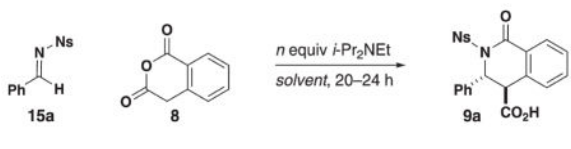
<sup>a</sup>NMR yield. <sup>b</sup>Aminosulfone used as substrate. <sup>c</sup>2 equiv of TMG.



**Scheme 3.**  
Plausible Anti-Felkin-Anh Addition and Epimerization Mechanisms

**Scheme 4.**

Anhydride Scope of the Achiral Base-Mediated AMR

**Table 1**Base-Loading Screen for Reaction of the *N*-Nosyl Imine of Benzaldehyde and Homophthalic Anhydride

The reaction scheme shows the reaction of *N*-nosyl imine of benzaldehyde (15a) and homophthalic anhydride (8) to form product 9a. The reagents are *n* equiv *i*-Pr<sub>2</sub>NEt, solvent, 20–24 h.

equiv	solvent	% conv	dr
n/a	CH <sub>2</sub> Cl <sub>2</sub>	0	n/a
0.10	CD <sub>2</sub> Cl <sub>2</sub>	100	>95:5
1.00	CD <sub>2</sub> Cl <sub>2</sub>	100	>95:5

**Table 2**

Base-Loading Screen for the Reaction of Cinnamaldehyde-Derived Aminosulfone and Homophthalic Anhydride

The reaction scheme shows the reaction of compound 15j (a cinnamaldehyde-derived aminosulfone) with compound 8 (homophthalic anhydride) in the presence of *n* equivalents of TMG in CH<sub>3</sub>CN for 20–24 h to form product 16j (a diastereomeric amide).

equiv	% conv	dr
0.10	<5	n/a
0.25	23	>95:5
0.50	69	>95:5