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Stereocontrol in Asymmetric γ-Lactam Syntheses from Imines and Cyanosuccinic Anhydrides

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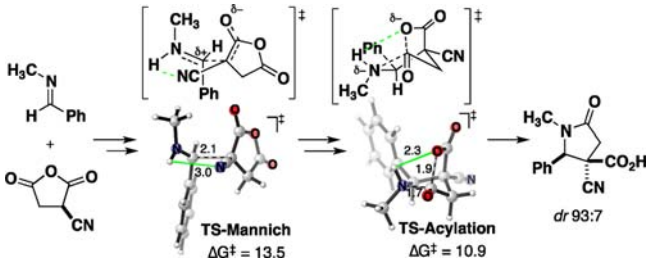
ABSTRACT



Computations (SCS-MP2//B3LYP) reveal that the asymmetric synthesis of highly substituted γ-lactams with three stereogenic centers, including one quaternary center, proceeds through a Mannich reaction between the enol form of the anhydride and the *E*-imine, followed by a transannular acylation. This new mechanistic picture accounts for both the observed reactivity and stereoselectivity. CH···O and hydrogen bonding interactions in the Mannich step and torsional steering effects in the acylation step are responsible for stereocontrol. It is demonstrated that this new mechanistic picture applies to the related reactions of homophthalic anhydrides with imines and presents new vistas for the design of a new reaction to access complex molecular architectures.

The prevalence of densely substituted γ-lactams (2-pyrrolidinones) and pyrrolidines in natural products and pharmaceutical compounds is striking.[1] γ-Lactams can be formed in a single step under mild conditions by direct reaction of imines with cyclic anhydrides.[2] The mechanism of this reaction, and related reactions of other anhydrides with imines, has never been elucidated. In this work, we disclose significant computational evidence that this reaction proceeds by a Mannich–acylation process, and we have also elucidated the factors responsible for the stereocontrol. We provide insight to explain over four decades of work in this area and a path forward for further development of the anhydride Mannich reaction (AMR).

The reactions of aliphatic anhydrides (e.g., succinic and glutaric) and imines were first discovered by Castagnoli[2f,g] and later expanded by Cushman to the homophthalic anhydride.[2h] Work in one of our groups (J.T.S.) began with the discovery of reactions employing thio-substituted anhydrides[2b] and the subsequent discovery of a new four-component reaction (4CR).[3] A remarkably high reactivity and stereoselectivity of α-cyanosuccinic anhydrides were discovered, and this prompted us to delve into the origins of stereocontrol and the mechanism for this useful reaction.

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(1) (a) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (b) Kogure, N.; Ishii, N.; Kitajima, M.; Wongseripipatana, S.; Takayama, H. *Org. Lett.* **2006**, *8*, 3085. (c) Tasker, A. S.; Sorensen, B. K.; Jae, H.-S.; Winn, M.; von Geldern, T. W.; Dixon, D. B.; Chiou, W. J.; Dayton, B. D.; Calzadila, S.; Hernandez, L.; Marsh, K. C.; WuWong, J. R.; Opgenorth, T. J. *J. Med. Chem.* **1997**, *40*, 322. (d) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236. (e) Kobayashi, J.; Inaba, Y.; Shiro, M.; Yoshida, N.; Morita, H. *J. Am. Chem. Soc.* **2001**, *123*, 11402.

(2) (a) Gonzalez-Lopez, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164. (b) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999. (c) Ng, P. Y.; Tang, Y. C.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5352. (d) Tan, D. Q.; Atherton, A. L.; Smith, A. J.; Soldi, C.; Hurley, K. A.; Fettinger, J. C.; Shaw, J. T. *ACS Comb. Sci.* **2012**, *14*, 218. (e) Tang, Y.; Fettinger, J. C.; Shaw, J. T. *Org. Lett.* **2009**, *11*, 3802. (f) Castagnoli, N.; Cushman, M. *J. Org. Chem.* **1971**, *36*, 3404. (g) Castagnoli, N. *J. Org. Chem.* **1969**, *34*, 3187. (h) Cushman, M.; Madaj, E. J. *J. Org. Chem.* **1987**, *52*, 907. (i) Kaneti, J.; Bakalova, S. M.; Pojarlieff, I. G. *J. Org. Chem.* **2003**, *68*, 6824.

(3) Wei, J. Q.; Shaw, J. T. *Org. Lett.* **2007**, *9*, 4077.

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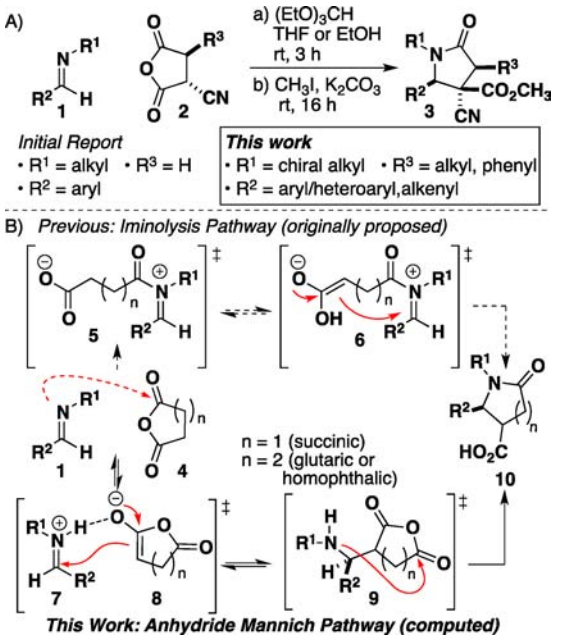
Scheme 1. (A) Reactions of Imines and Cyanosuccinic Anhydrides; (B) New Mechanistic Proposal for the Reactions of Imines with Anhydrides To Produce γ- or δ-Lactams



We recently reported a reaction of imines with cyanosuccinic anhydrides to produce tetrasubstituted γ-lactams.[2d] This reaction was examined for a single anhydride and achiral imines. The high reactivity and stereoselectivity (up to 95:5 *dr*) prompted us to explore this system broadly for the asymmetric synthesis of tetra- and pentasubstituted γ-lactams. These studies have revealed the first examples of stereocontrol from chiral imines and chiral anhydrides (Scheme 1A). Importantly, we disclose computational evidence that this reaction proceeds by a Mannich-type mechanism that explains both the relative reactivity and stereochemical outcome of this γ-lactam synthesis. These results suggest that related reactions of succinic, glutaric, and homophthalic anhydrides also proceed by a Mannich-type mechanism and set the stage for further development in this area, including the rational design of catalysts (Scheme 1B).

The mechanism and origins of stereocontrol were explored computationally. All computations were performed at the SCS-MP2[4]/def2-∞[5]//B3LYP/PCM (THF)/6-31G* level of theory.[6] Infinite basis set[5] energies were extrapolated from def2-TZVP and def2-QZVP.[6c] Solvation single point corrections were computed with PCM (THF) using B3LYP/6-31+G**.[6a] Manual, exhaustive conformational searches were performed to locate all relevant intermediates and transition structures. A stepwise Mannich–acylation process is operative (Scheme 1B, bottom), involving the enolate form **8** of anhydride **4**. Anhydride enol/enolates have been studied by Rappoport,[7] observed crystallographically, and have been suggested as key intermediates in a related lactone-forming reaction.[8] The iminium and the anhydride enolate form a pseudo-Zimmerman–Traxler transition state in which the instability of forming the zwitterionic intermediates are mitigated by hydrogen bonds.

This mechanism differs from previous hypotheses. Cushman favored an iminolysis mechanism in which the imine nitrogen is acylated by the anhydride, leading to a subsequent intramolecular Mannich with the enolate form of the pendant carboxylate (Scheme 1B, top).[2h] These zwitterionic intermediates have been computationally found to be unrealistically high in energy. Specifically, in cases involving the cyanosuccinic anhydrides, the anhydride acylated imine (25.3 kcal/mol) and the following iminium enolate complex (28.9 kcal/mol) are both higher than the upper estimate of the experimental barrier and the computed barrier of the Mannich–acylation mechanism (23 and 13.5 kcal/mol, respectively).

Our proposed mechanism is in agreement with the electronic trends observed by Cushman in a Hammett study of substituents on the aldehyde used to form imines, where electron withdrawing substituents accelerated the reaction.[2h] Kaneti showed computationally that small model substrates undergo a concerted (1,3)-cycloaddition process that favored *N*-acylation of the imine as the primary bond-forming event.[2i] We find that the electronic stabilizations afforded by substituents on the imine and the anhydride lead to a stepwise process in which the Mannich precedes the acylation. This is key to understanding the mechanisms of related reactions of imines and anhydrides, including variously substituted succinic as well as glutaric and homophthalic anhydrides.

The reaction coordinate of an achiral imine and a monosubstituted anhydride is shown in Figure 1. The rate-determining step (RDS) for the major diastereomeric product is the Mannich,[9] while the RDS for the minor is the acylation. The computed diastereoselectivity of 1.8 kcal/mol

(4) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095.

(5) (a) Neese, F.; Valeev, E. F. *J. Chem. Theory Comput.* **2011**, *7*, 33. (b) Zhong, S.; Barnes, E. C.; Petersson, G. A. *J. Chem. Phys.* **2008**, 129.

(6) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.1; Gaussian, Inc., Wallingford, CT, 2009. (b) TURBOMOLE V6.4 2012, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989–2007, TURBOMOLE GmbH, since 2007; available from www.turbomole.com. (c) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

(7) (a) Rappoport, Z.; Lei, Y. X.; Yamataka, H. *Helv. Chim. Acta* **2001**, *84*, 1405. (b) Song, J. H.; Lei, Y. X.; Rappoport, Z. *J. Org. Chem.* **2007**, *72*, 9152.

(8) (a) Cornaggia, C.; Manoni, F.; Torrente, E.; Tallon, S.; Connon, S. J. *Org. Lett.* **2012**, *14*, 1850. (b) Manoni, F.; Cornaggia, C.; Murray, J.; Tallon, S.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 6502.

(9) The *E*-imine is more stable than the *Z* by 5.2 kcal/mol. The computed barrier for the *E*/*Z* isomerization is 28.7 kcal/mol, or > 15 kcal/mol higher than the computed reaction barrier.

is in good agreement with experiment (1.5 kcal/mol). The computed free energies for all intermediates and TSs also are reasonable ($\Delta G \leq 15$ kcal/mol) and fall below the upper estimate for the experimental barrier of 23 kcal/mol.[10]

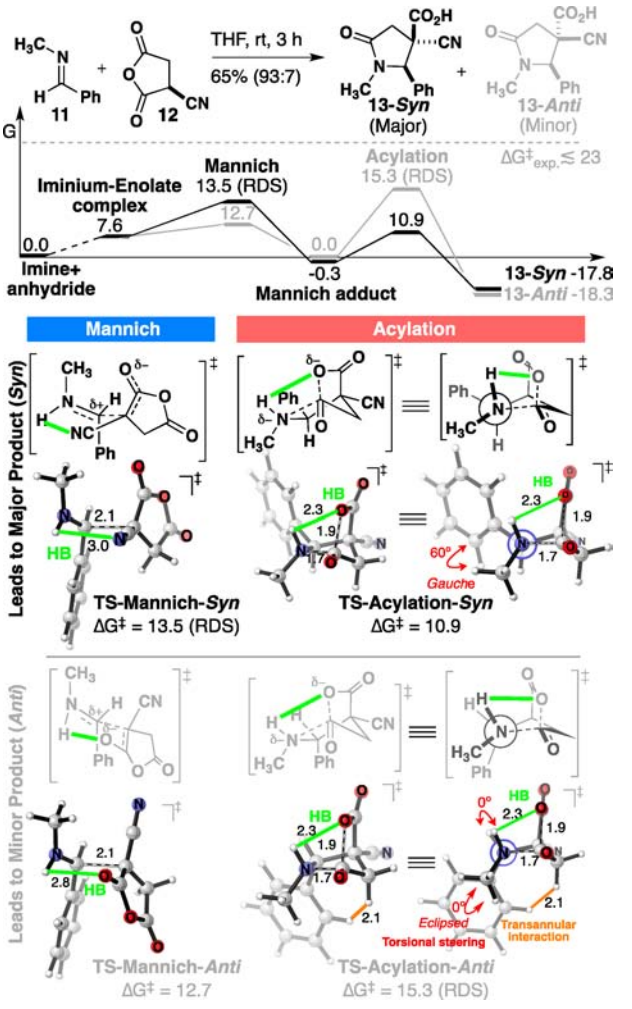


Figure 1. Reaction coordinate and TSs involving an achiral imine **11** and a monosubstituted anhydride **12**.[11−13]

In the Mannich step, there is a slight preference (0.8 kcal/mol) for the *anti* over the *syn*. This is due to the stronger hydrogen bond between the iminium proton and the enolate oxygen in the *anti* over the weaker hydrogen bond between the iminium proton and the cyano in the *syn* (Figure 1).[10] In contrast, the *anti* and *syn* preference in the acylation step is substantial at 4.4 kcal/mol.

The substantial instability of the minor *anti* acylation TS is key to the diastereocontrol. There are two causes:

(10) (a) See Supporting Information. (b) The reaction coordinates and the TSs for all four products are in the Supporting Information.

(11) Energies are in kcal/mol, distances in angströms, and torsions in degrees. All energies and thermal corrections are from SCS-MP2/def2-∞//B3LYP/6-31G* with PCM solvation corrections for THF.

(12) Legault, C. Y. *CYLview*, 1.0b; UCLA: Los Angeles, CA, 2007.

(13) The *syn*/*anti* refers to the relationship between the carboxyl and the γ-Ph groups. The *R*/*S* describes the absolute configuration of the carboxyl center in the lactam product.

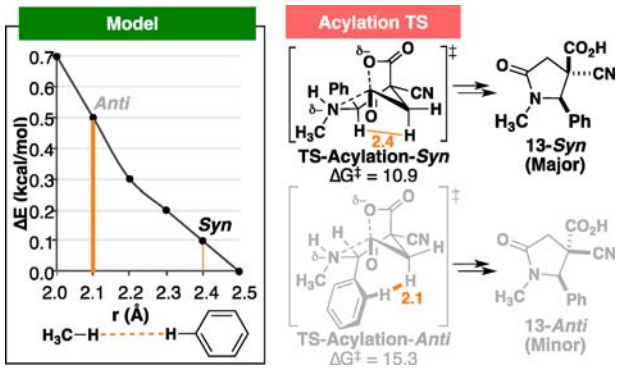


Figure 2. Magnitude of the transannular steric interactions.[11,13]

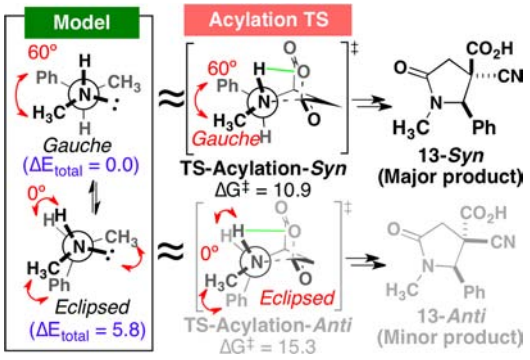


Figure 3. Magnitudes of torsional steering interactions.[11,13]

transannular steric interactions and torsional steering effects.[14] The transannular van der Waals interaction present in the minor *anti* acylation TS is between a lactam ring methylene and the γ-phenyl substituent, at 2.1 Å (indicated in orange in **TS-Acylation-*Anti***, Figure 2). We quantified the magnitude of this repulsive interaction using methane and benzene as a model system (Figure 2). At 2.1 Å, the model system reveals that this interaction contributes only ~0.4 kcal/mol to the selectivity.

The torsional steering effects are around the former imine C−N bond (Figure 3). In the major *syn*-TS, the substituents around this bond are staggered in a gauche conformation. In the minor *anti*-TS, these substituents are eclipsed. In order to quantify the magnitude of this effect, we computed the analogous conformations of a model system, *N*-methyl-1-phenylmethanamine (Figure 3). The model system reveals that the eclipsed interaction between the Ph and the vicinal *N*-methyl group is important and contributes significantly to the differentiation between the *syn*- and *anti*-acylation TSs (5.8 kcal/mol). The torsional steering effect in the model system is larger than in the real system due to diminished torsional effects in cyclopentane systems compared to the

(14) (a) Cheong, P. H. Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513. (b) Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchison, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J.; Wu, Y. D.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 2204.

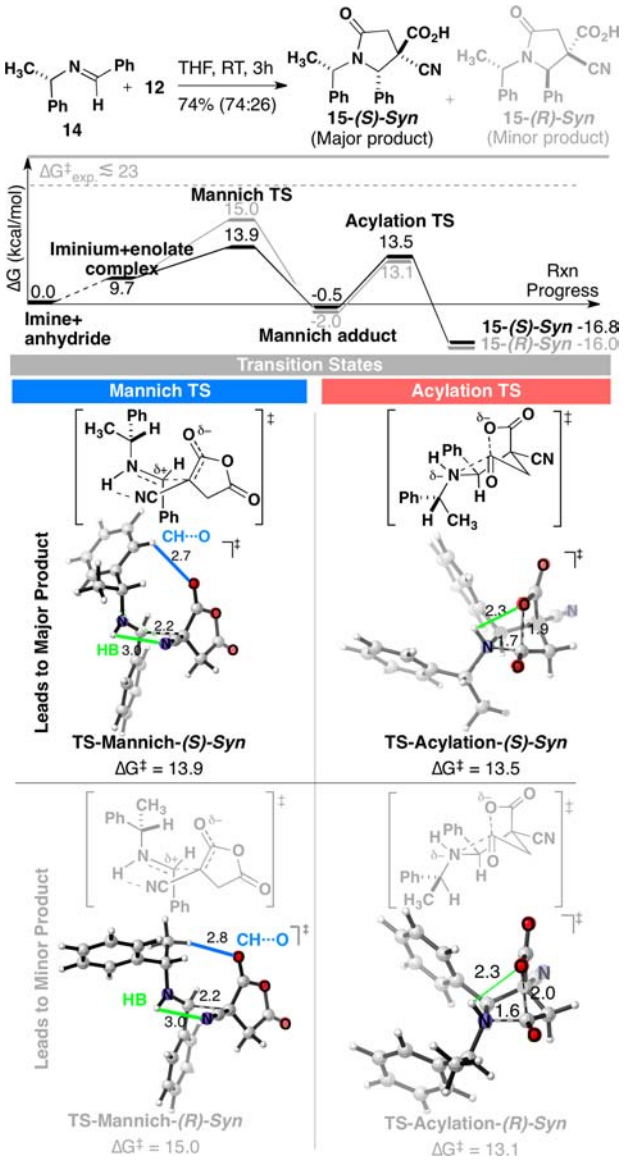


Figure 4. Reaction coordinate and TSs involving chiral imine **14** and anhydride **12**.[10b,11,12]

acyclic. Torsional steering is unambiguously responsible for the majority of diastereoselectivity in the acylation.[10]

The origins of stereocontrol in the disubstituted case were also investigated computationally.[10] Again, the overall factors that control the stabilities of the Mannich and acylation steps are the same: hydrogen bonding in the Mannich and torsional steering in the acylation. The chirality of the cyano center is lost in the tautomerization to form the anhydride enolate. However, the methyl group controls the facial approaches of the anhydride enolate. In the Mannich, the TSs with the methyl substituent *endo* to the forming bond are less stable (5−7 kcal/mol) than the *exo* due to the repulsive steric interaction between the Ph and

(15) (a) Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 7163. (b) Johnston, R. C.; Cheong, P. H.-Y. *Org. Biomol. Chem.* **2013**, *11*, 5057. (c) Pattawong, O.; Mustard, T. J. L.; Johnston, R. C.; Cheong, P. H.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1420.

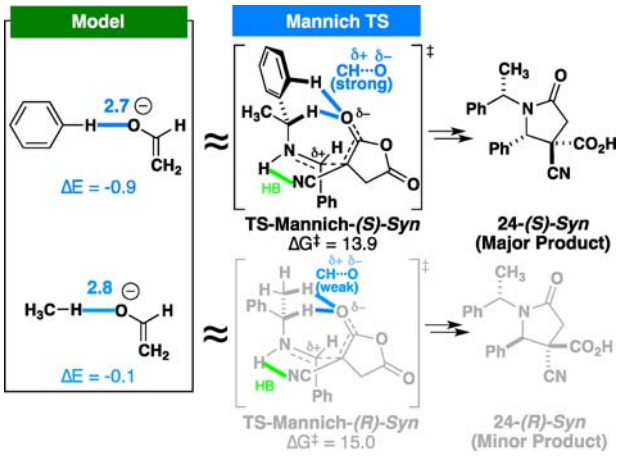


Figure 5. Magnitudes of CH···O interactions.[11]

Me groups. In the acylation, the TSs proceeding from the *exo* process are more stable than *endo* because the α-methyl group is in a stable pseudoequatorial configuration.

In contrast to all previous cases, the stereoselectivity in the reaction involving chiral imines (Figure 4) is determined exclusively by the Mannich step.[10] The selectivity here is governed by the strength of the CH···O interactions between the α-methylbenzyl group and the transient alkoxides in the various transition states.[15] In the major **TS-Mannich-(*S*)-*Syn***, the CH···O interaction is between the enolate and the more polar Ph C_{sp^2}−H, while, in the minor Mannich TS, it is with the less polar methyl C_{sp^3}−H. In Figure 5, the difference in energy between the two computed model systems of the relevant CH···O interactions match the selectivity found between the two Mannich TSs. Interestingly, the (*R*)- and (*S*)-acylation TSs are equally stable, owing to the great similarity in hydrogen bonding and CH···O interactions.[10b]

Computations reveal that the title reaction proceeds by a stepwise Mannich reaction of the enolate form of the anhydride followed by transannular acylation. Stereocontrol arises via a combination of electrostatic stabilizations and torsional steering. These discoveries enable the design of new reactions that exploit the unique reactivity of imines with enolizable anhydrides.

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Supporting Information Available. Additional figures, geometries, and energies of all structures considered. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.