

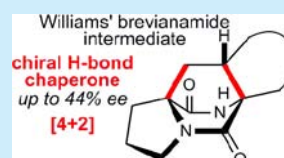
Adaptation of a Small-Molecule Hydrogen-Bond Donor Catalyst to an Enantioselective Hetero-Diels–Alder Reaction Hypothesized for Brevianamide Biosynthesis

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S Supporting Information

ABSTRACT: Chiral diamine-derived hydrogen-bond donors were evaluated for their ability to effect stereocontrol in an intramolecular hetero-Diels–Alder (HDA) reaction hypothesized in the biosynthesis of brevianamides A and B. Collectively, these results provide proof of principle that small-molecule hydrogen-bond catalysis, if even based on a hypothetical biosynthesis construct, holds significant potential within enantioselective natural product synthesis.



Scientists have long wondered whether the Diels–Alder cycloaddition, a [4 + 2] pericyclic reaction used extensively in laboratory chemical synthesis, might also occur in nature along biosynthetic pathways as a means to build natural product structure. Furthermore, speculation that enzymes, dubbed Diels–Alderses,¹ might exist for the purpose of catalyzing the reaction has not only driven a search for existing species^{2–7} but has also inspired an intensive effort to develop non-natural variants that catalyze non-physiological [4 + 2] cycloadditions.^{8–13} Enantioselective hetero-Diels–Alder reactions catalyzed by hydrogen-bond organocatalysts^{14,15} have been developed for heterocycle synthesis, particularly piperidines^{16–20} and tetrahydroquinolines,^{18,21–29} largely driven by the now-privileged³⁰ chiral phosphoric acid motif.^{31,32}

One might naturally wonder, therefore, whether hydrogen-bond catalysis might be applied to hetero-Diels–Alder reactions hypothesized within the context of biomimetic natural product synthesis. Leveraging the unique virtues of chemical synthesis and biosynthesis has demonstrated value, and a balance between speculation and experimental evidence, however circumstantial, has long driven the search for reagent-controlled selectivity in hypothesized biomimetic transformations.³³

Williams' application of the intramolecular hetero-Diels–Alder reaction to prepare numerous members of the brevianamide and related natural products (e.g., Figure 1A)³⁴ is fertile ground on which to merge enantioselective hydrogen-bond catalysis and complex natural product total synthesis. Porter and Sammes first postulated a biogenetic hetero-Diels–Alder reaction in brevianamide A, B biosynthesis (Figure 1B),³⁵ and Williams has since accumulated considerable support for its chemical feasibility.³⁴ A common feature of the hetero-Diels–Alder step in these syntheses was noncatalyzed conversion at room temperature and low relative stereocontrol. Given this backdrop, we asked whether hydrogen bonding, a biologically pervasive interaction, might be used as the sole directing element for stereocontrol in this [4 + 2] cycloaddition.

Bis(AMidine)-based ligands have been used to create chiral proton complexes that effect highly enantioselective additions to

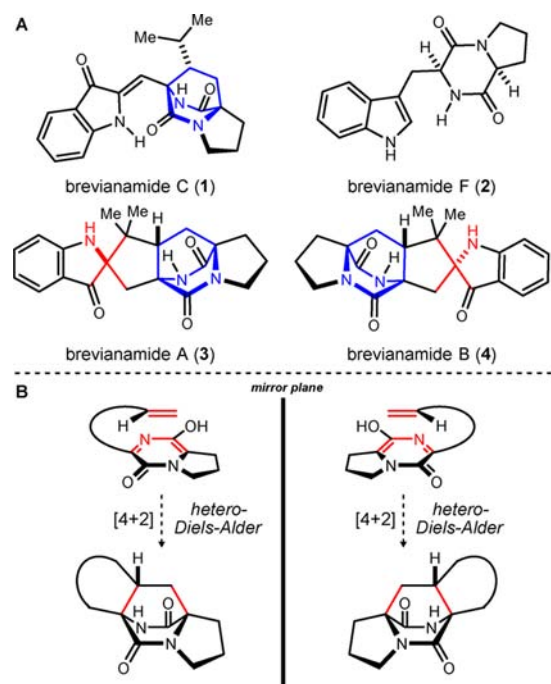


Figure 1. Representative members of the brevianamide class of natural products (A) and Sammes' postulated biogenetic hetero-Diels–Alder reaction to create the diazabicyclooctane core (B).

N-Boc-imines,³⁶ and recently *N*-TMS-imines,³⁷ using nitroalkane pronucleophiles. By analogy, we speculated that these same complexes might engage Williams' hetero-Diels–Alder substrate through a two-point binding interaction as outlined in Figure 2. Binding to the tertiary amide, however, remained a possibility despite its hindered nature as a hydrogen-bond acceptor. In direct contrast to the aza-Henry precedent wherein

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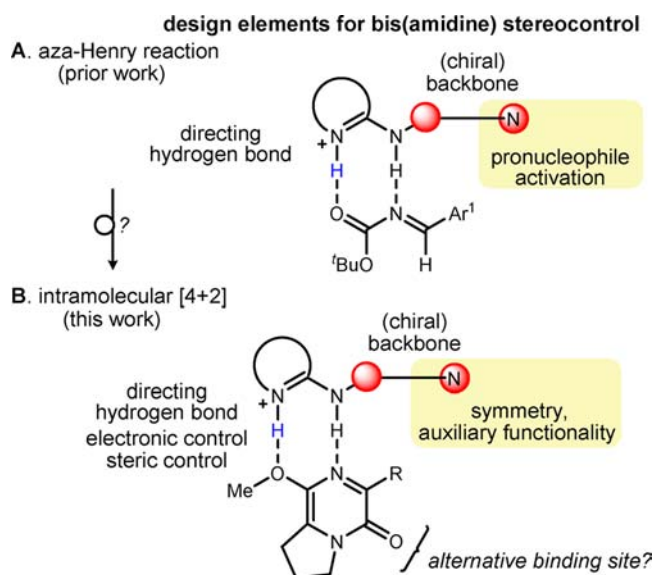


Figure 2. Lateral application of bis(amidine) catalyst design features to a hetero-Diels–Alder reaction.

both substrates are activated by the catalyst, the intramolecular [4 + 2] cycloaddition with methoxy pyrimidone **6** would be oriented (but not necessarily activated) by hydrogen bonding with the chaperone. It was anticipated that the chaperone design elements might ultimately differ greatly, particularly in unanticipated ways, so our approach reflected a combination of hypothesis-driven experiments and general screening. Although the goal was not to investigate the legitimacy of natural Diels–Alderase enzymes, we did intend to establish precedent in the use of a small-molecule hydrogen-bond catalyst to promote enantioselective [4 + 2] cycloadditions with an unusually complex substrate.

Preparation of intermediate **5** was achieved using the protocol developed by Williams, who also established its intramolecular cycloaddition to bicyclodiketopiperazine **7** after base-induced isomerization to **6** (Figure 3). This was the starting point for our studies, since a [4 + 2] cycloaddition proceeding at significant

rate at ambient temperature was an important feature. The cycloaddition rate was studied by sampling the reaction to determine conversion by ^1H NMR spectroscopy. The kinetics of cyclization are consistent with a unimolecular reaction, leading to full conversion at 43 h (25 °C). Knowing more precisely the time to completion, we established 48 h as the standard experiment time, since any conversion during the workup procedure would lead to racemic product.

Numerous attempts were made initially to chaperone the cycloaddition in solution in the presence of a chiral Brønsted acid catalyst, such as **9b**. These experiments uniformly provided racemic cycloaddition product. Since the solvent is a matter of convenience in reaction setup and analysis, a protocol was developed that involved the preparation of **6** at low temperature, division of a batch into 2–4 separate experiments, addition of the chaperone and solvent, mixing, and then solvent removal in vacuo, all at low temperature. The resulting film containing a 1:1 mixture of **6**/chaperone was maintained at 25 °C for 48 h prior to workup and analysis. In this way, an equimolar mixture of substrate and organocatalyst could convert to product as a (neat) residue.

This protocol resulted in two distinct outcomes: (1) the expected formation of the intramolecular Diels–Alder product **7**, along with the organocatalyst, or (2) a complex mixture of products sometimes devoid of the desired cycloaddition product. A summary of key results belonging to the first outcome, using amidine-based catalysts, is provided in Table 1 and is drawn from a broader exploration that generally included both protonated and free base forms of a particular chaperone. The parent bis(amidine) (H,Quin-BAM (**9a**)) contains two potential polar covalent hydrogen-bond conduits for stereocontrol but provided results identical to the thermal cycloaddition. Use of its triflic acid complex (**9b**) revealed a subtle, but detectable, increase in both diastereomeric (dr) and enantiomeric (er) ratios. On the basis of the similarity in size between the catalyst and substrate and the assumption that the substrate-binding site would be at the aminopyridinium, H,⁵ Me-BAM-HOTf (**9c**) was evaluated for its more open binding area. Unfortunately, this led to nearly racemic product.

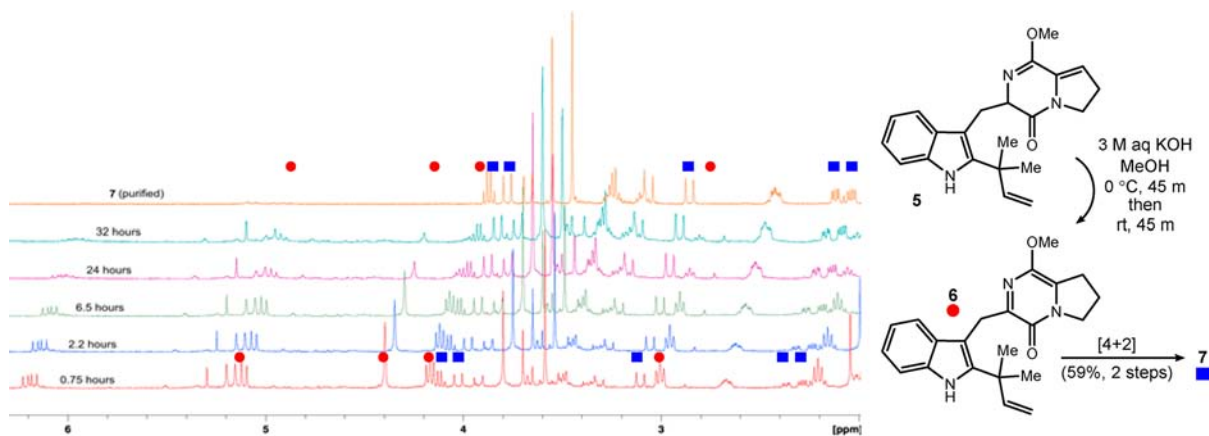
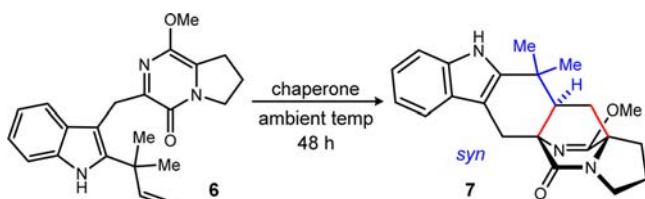


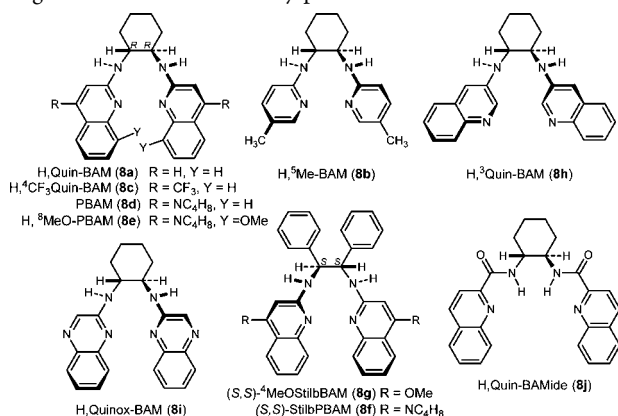
Figure 3. Preparation of **6**³⁴ and study of its thermal (25 °C) cycloaddition rate to **7**. Isomerization of purified **5** was effected by treatment with base in two temperature stages, followed by a careful workup procedure at low temperature to minimize thermal [4 + 2] cycloaddition prior to a specific experiment. These conditions were developed to minimize formation of **7**, but at the expense of residual **5** carried through (**6**:**5** ≈ 9:1). Time: $t = 0$ established as time of first analysis by ^1H NMR for this experiment. Selected peaks labeled for **6** (red circle) and **7** (blue square). Residual CH_2Cl_2 (5.3 ppm) used as an internal standard and reference point. See the Supporting Information for complete details. Composition calculated using integrations of **6** and **7**, defined as $7/(6 + 7)$.

Table 1. Application of Chiral Hydrogen-Bonding Small Molecules to the Intramolecular Hetero-Diels–Alder Cycloaddition of **6**



entry ^{a,b}	free base (8)	chaperone (9)	dr ^c	er ^d
1		none	1.3:1	50:50
2	a	H ₂ Quin-BAM	a 2:1	50:50
3	a	H ₂ Quin-BAM-HOTf	b 2.8:1	54:46
4	b	H ₂ ³ Me-BAM-HOTf	c 1.3:1	53:47
5	c	H ₂ ⁴ CF ₃ Quin-BAM-HOTf	d 1.9:1	54:46
6	d	PBAM-HOTf	e 1.6:1	53:47
7	e	H ₂ ⁸ MeO-PBAM-HOTf	f 1.7:1	54:46
8	f	(<i>S,S</i>)-StilbPBAM-HOTf	g 2:1	49:51
9	g	(<i>S,S</i>)- ⁴ MeOStilbBAM-HOTf	h 1:1.1	43:57
10	h	H ₂ ³ Quin-BAM-HOTf	i 3.5:1	64:36
11	i	H ₂ Quinox-BAM-HOTf	j 3.5:1	67:33
12	j	H ₂ Quin-BAMide-HOTf	k 2.1:1	72:28
13	h	H ₂ ³ Quin-BAM	l 1.3:1	45:55
14	ent-h	<i>ent</i> -H ₂ ³ Quin-BAM-HOTf	m 4.2:1	38:62
16	h	H ₂ ³ Quin-BAM-HO ₂ CCF ₃	n 1.9:1	50:40
17	h	H ₂ ³ Quin-BAM-HCl	o 2.5:1	57:43
18	h	H ₂ ³ Quin-BAM-HBF ₄	p 2.7:1	59:41
19	h	H ₂ ³ Quin-BAM-HSbF ₆	q 2.9:1	66:34

^aThe substrate was prepared as described in Figure 3, combined with the chaperone in dichloromethane, and concentrated to a neat film, all at 0 °C or below until final warming to room temperature for the chaperoned reaction. Isolated yields generally ranged from 50% to 70%. Absolute configuration as depicted is arbitrary, relative stereochemistry reported as *syn:anti*. ^bResults are reported as an average of reactions. See the Supporting Information for complete experimental details. ^cDetermined by relative integration of MeO methyls (¹H NMR of crude reaction mixture). ^dDetermined by HPLC using Chiralcel OD-H stationary phase.



Attempts to modulate the polarity of the hydrogen bond by substitution of the aminoquinoline at its 4-position with either trifluoromethyl (**9d**) or pyrrolidine (**9e**) groups led to equally nonselective reactions. One case represents an attempt to affect the coordination chemistry of the key hydrogen bond by a proximal oxygen (MeO at the quinoline 8-position) (**9f**), although this crowds the putative binding pocket as well. This

chaperone produced a product with selectivity similar to that for the thermal case. Another attempt to rationally and modestly change the angles within the binding pocket involved the use of the stilbene diamine backbone alternative to cyclohexane diamine.³⁸ The pyrrolidine variant delivered results similar to its counterpart (**9g**), but the 4-methoxy-substituted variant (**9h**) effected an interesting change in diastereoselection, with a preference, albeit small, for the minor diastereomer produced under all conditions to this point.

Significant improvement in selectivity was ultimately achieved by more profound changes in ligand structure, if even less rational in overall design.³⁹ For example, a regioisomeric ligand in which the diamine is connected via C3 of the quinoline rather than C2 led to as high as 3.5:1 dr and 64:36 er (**9i**). The hydrogen-bond-donating ability of this aminoquinoline regioisomer is quite different, and the possibility of intramolecular hydrogen bonding is limited. A quinoxaline ligand (**9j**) was then examined, as it combined both 2- and 3-aminoquinoline substructures. This chaperone was more selective, at 3.5:1 dr and 68:32 er. Ultimately, a ligand that combined both quinolinium and amide functional groups provided the maximum enantioselection observed during these studies, with H₂Quin-BAMide (**9k**) leading to the cycloadduct in 2.1:1 dr and 72:28 er (44% ee). As expected, the preparation and use of an enantiomeric chaperone resulted in the same diastereo- and enantiomeric ratios but opposite enantioselectivity (Table 1, entry 14).

A final study was undertaken to more clearly establish the influence of the polar ionic hydrogen bond on the levels of enantioselection observed. A series of acid salts prepared from the H₂³Quin-BAM free base were deployed in parallel experiments (Table 1, entries 10, 13, 16–19).⁴⁰ Compared to the free base which exhibited selectivity, albeit low, for the opposite enantiomer normally observed (entry 13, 45:55 er), use of acid salts bearing increasingly less-coordinating character displayed a trend of increasing enantiomer ratio, in the order: HO₂CCF₃, HCl, HBF₄, HOTf, HSbF₆. The diastereomeric ratios also tracked higher along this order. This behavior might be interpreted to further highlight the importance of the proton's coordination sphere for its influence on both relative and absolute stereocontrol.⁴¹ Increasing *syn* diastereoselection that tracks with increasing enantioselection is consistent with the hypothesis advanced in Figure 2B, wherein catalyst binding as depicted would sterically disfavor *anti*-diastereomer formation.

Collectively, these studies establish the ability to modulate diastereo- and enantioselectivity using a collection of small molecule chaperones functioning solely by the principles of hydrogen bond donor/acceptor interactions. It was not possible to determine whether these chaperones accelerated the rate of cycloaddition relative to thermal energy alone,⁴² but their ability to control stereoselection using hydrogen bonding at ambient temperature does provide a discrete chemical context for the proposal that certain enzymes chaperone [4 + 2] cycloadditions.⁴³ This catalyst class is a basis for rendering Williams' total synthesis enantioselective. Further improvements in enantioselection might be achieved by increasing the size of the chaperone, which is currently quite similar in size to its substrate ([ligand-H]⁺ ~425 MW vs [5] ~363 MW). In principle, tools are in place to achieve this using short peptide catalysis,⁴⁴ enzyme evolution techniques,⁴⁵ or the tools of calculation in silico and the strategy of enzyme repurposing.^{46,47} The *chemical feasibility* of an enantioselective Brønsted acid catalyzed hetero-Diels–Alder reaction for brevianamide syn-

thesis is established for the first time through this study. There is great potential in the development of a small molecule Diels–Alderase and its application in a biosynthesis-inspired natural-product total synthesis, whether or not a brevianamide-class Diels–Alderase is ever discovered.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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