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Scandium triflate and secondary amine promoted *AA′B* 2:1 coupling and formal inverse electron demand Diels–Alder reactions of dienals

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Abstract

Reaction prospecting studies resulted in the discovery of a $Sc(OTf)_3$ promoted novel *AA′B* 2:1 coupling of imidazolone or benzofuran substituted enals with morpholine. A related $Sc(OTf)_3$/morpholine promoted reaction was demonstrated for the coupling of a benzofuran substituted enal with dihydrofuran. The formation of these adducts is consistent with formal inverse electron demand Diels–Alder cycloadditions, most likely in a stepwise manner via a domino Michael–Mannich annulation process, involving iminium ion activation of the diene. A purely amine promoted formal inverse electron demand Diels–Alder cycloaddition approach was also demonstrated in the 2:1 coupling of 2,4-hexadienal with methanol. These reactions demonstrate the concepts of dual metal/amine catalysis and amine promoted formal inverse electron demand Diels–Alder cycloadditions. They differ from known examples of organocatalyzed Diels–Alder reactions, in which iminium ion activation of the dienophiles or enamine activation of the dienes occur.

1. Introduction

Diels–Alder reactions have been widely employed in the total synthesis of alkaloid natural products.[1] In certain cases synthetic strategies to these compounds are guided or inspired by knowledge of the respective biogenetic pathways. The pyrrole–imidazole family of alkaloids, for example, are exclusively isolated from marine sponges, mainly the *Agelasidae*, *Axinellidae*, and *Halichondridae* families (Fig. 1, **1**–**3**).[2] 2-Amino-4-vinylimidazoles **1**, such as the metabolites oroidin, clathrodin, and hymenidin, are believed to be the key biogenetic precursors. Various modes of dimerization of **1** and related compounds are possible. Al Mourabit and Potier have also outlined a unified proposal for the biogenesis of the pyrrole–imidazole alkaloids through the dimerization of vinylogous 2-aminoimidazole and its tautomers.[3] Ageliferin **2**[4] and sceptrin **3**[5] are formally derived through dimerization via formal [4+2] and [2+2] cycloaddition of hymenidin, respectively. Other classes of marine alkaloids are also derived through dimerization processes involving apparent formal cycloadditions. For example, it has been suggested that the bis-indole

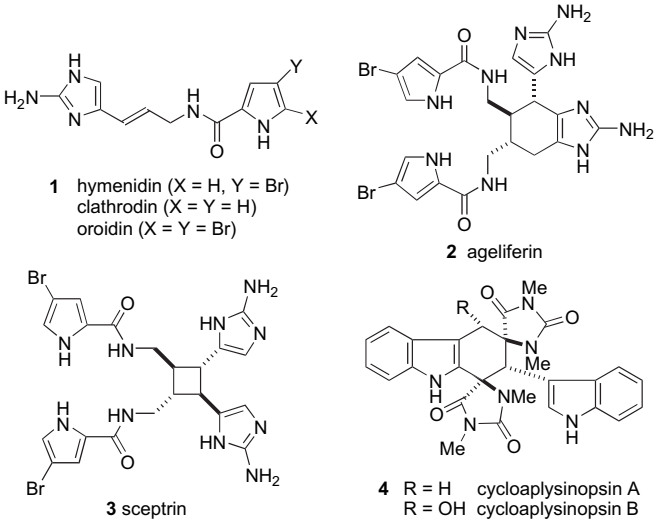

Figure 1. Marine sponge alkaloids.

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alkaloids, cycloaplysinopsin A and B **4** can be derived through formal [4+2] dimerization[6] of aplysinopsin like precursors[7] (Fig. 1). Particularly intriguing is the question of whether dimerizations to form **2** and **4** involve either concerted or stepwise formal Diels–Alder reactions, as well as the nature of the enzymes presumed to be involved in these processes.[8,9]

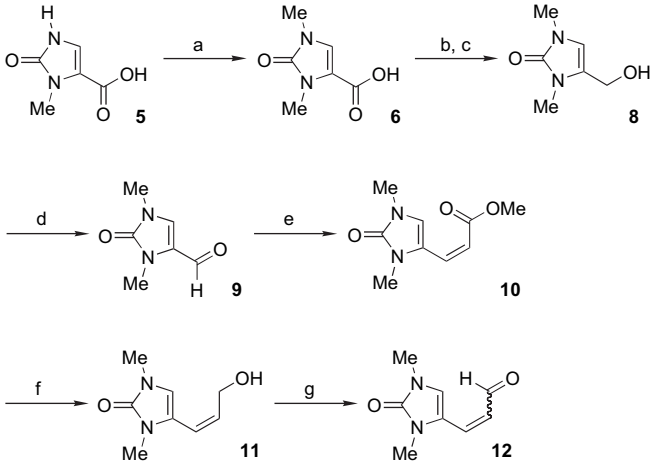
The possible occurrence of pericyclic reaction mechanisms in marine alkaloid biogenesis, raises many intriguing possibilities for potential total syntheses and analog generation. 12,12′-Dimethylageliferin, an analog of ageliferin, was synthesized by Ohta and co-workers, using a Diels–Alder cycloaddition of two vinyl imidazole units.[4a] In model studies toward a putative biomimetic synthesis of palau'amine,[10,11] the groups of both Lovely[12] and Romo[13] have used vinylimidazoles and vinyl imidazolones as dienes in Diels–Alder reactions. On the other hand, attempts by Mancini and co-workers to achieve a biomimetic Diels–Alder cycloaddition between two molecules of aplysinopsin were unsuccessful under various conditions.[6b] For each of these approaches, the Diels–Alder reactions were achieved under thermal conditions (neat in a sealed tube at 150 °C and reflux in CH_2Cl_2 or benzene). We were interested in the use of iminium ion or enamine activation strategies to achieve room temperature dimerizations of oroidin-like precursors. Activation of Diels–Alder reactions via iminium ion activation of the dienophile,[14] or diene activation through enamine intermediates are well precedented.[15–17]

As a starting point we elected to investigate the reactions of vinyl imidazolones as a model for oroidin dimerizations. As a result of these reaction prospecting studies,[18] we report herein the discovery of novel metal/amine triggered formal inverse electron demand Diels–Alder type dimerization of vinyl imidazolones in the presence of $Sc(OTf)_3$ catalyst. Related systems having similar reactivity are reported, as well as a solely amine promoted formal inverse electron demand all-carbon Diels–Alder reaction.

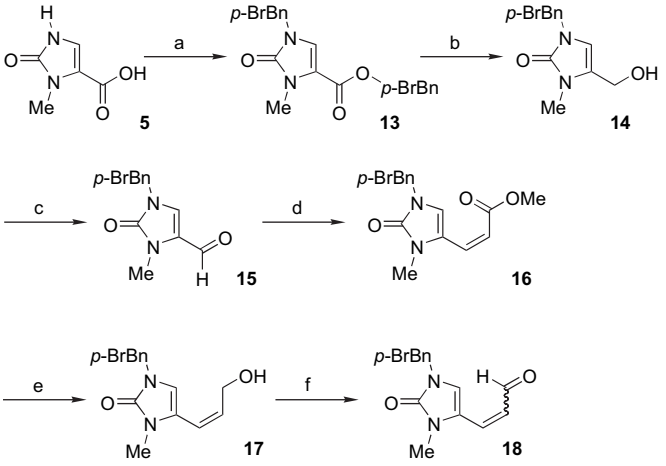
2. Results and discussion

The synthesis of imidazolone **12** was achieved from the known imidazolone **5**[19] (Scheme 1). N-Methylation of **5** using dimethylsulfate afforded the acid **6**.[19] Esterification of **6** as the benzyl ester **7**, followed by reduction with DIBAL-H afforded alcohol **8** in 43% yield after purification. The lower yield obtained for this conversion, is in part due to the high aqueous solubility of the alcohol **8**. Subsequent oxidation of **8** with MnO_2 to aldehyde **9**, followed by a Still–Gennari modified Horner–Wadsworth–Emmons olefination gave the α,β-unsaturated ester **10** (12:1 *Z*/*E*) in moderate yield.[20] Reduction of **10** with DIBAL-H to alcohol **11**, followed by oxidation with MnO_2 gave aldehyde **12** as a 3:1 mixture of *Z* and *E* stereoisomers.

The *p*-bromobenzyl substituted imidazolone **18** was prepared using an analogous approach to that used for the *N*,*N*′-dimethyl imidazolone **12** (Scheme 2). The Still–Gennari modified Horner–Wadsworth–Emmons olefination gave α,β-unsaturated methyl ester **16** (30:1 *Z*/*E*), which on subsequent DIBAL-H reduction and MnO_2 oxidation afforded α,β-



Scheme 1. Synthesis of *N*,*N*′-dimethyl imidazolone **12**. Reagents and conditions: (a) $(MeO)_2SO_2$, aq NaOH, reflux (67%); (b) BnBr, NEt_3, DMF; (c) DIBAL-H, CH_2Cl_2, −78 °C (43%, two steps); (d) MnO_2, 25:1 CH_2Cl_2/MeOH (86%); (e) $(CF_3CH_2O)_2P(O)CH_2COOMe$, K_2CO_3, 18-crown-6, 3:1 toluene/THF, −20 to 0 °C (64%; 12:1 *Z*/*E*); (f) DIBAL-H, CH_2Cl_2, −78 °C (71%; 11:1 *Z*/*E*); (g) MnO_2, CH_2Cl_2 (81%; 3:1 *Z*/*E*).

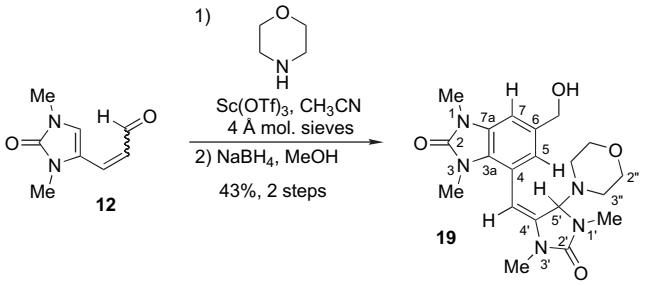


Scheme 2. Synthesis of *p*-bromobenzyl substituted imidazolone **18**. Reagents and conditions: (a) NaH, *p*-BrBnBr, DMF, 80 °C (69%); (b) DIBAL-H, CH_2Cl_2, −78 °C (94%); (c) MnO_2, CH_2Cl_2 (92%); (d) $(CF_3CH_2O)_2P(O)CH_2COOMe$, K_2CO_3, 18-crown-6, 3:1 toluene/THF, −20 to 0 °C (84%; 30:1 *Z*/*E*); (e) DIBAL-H, CH_2Cl_2, −78 °C (94%; 16:1 *Z*/*E*); (f) MnO_2, CH_2Cl_2 (quantitative; 13:1 *Z*/*E*).

unsaturated aldehyde **18** in high yield as a 13:1 mixture of *Z* and *E* stereoisomers.

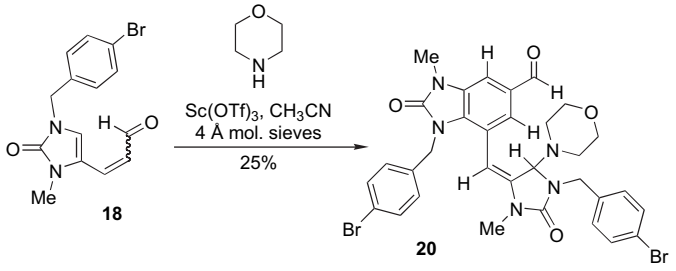
With aldehydes **12** and **18** in hand, the key iminium ion promoted dimerization could be tested. We elected to use $Sc(OTf)_3$ as the catalyst for iminium ion formation, since it is known to catalyze coupling reactions between heteroaromatic aldehydes and secondary amines,[21] and is air and water tolerant.[22] Reaction of aldehyde **12** with morpholine (1 equiv) in the presence of catalytic $Sc(OTf)_3$ at room temperature led to the formation of the aldehyde cycloadduct, the precursor to alcohol **19**, as evident by the 'downfield' singlet observed in the crude ^1H NMR spectrum. To avoid problems of aldehyde oxidation or dimethyl acetal formation during silica gel chromatography (with MeOH), the crude aldehyde mixture was

subjected to reduction with $NaBH_4$ in MeOH, affording alcohol **19** in 43% yield over two steps (Scheme 3).



Scheme 3. Morpholine and $Sc(OTf)_3$ promoted formal Diels–Alder reaction of **12**.

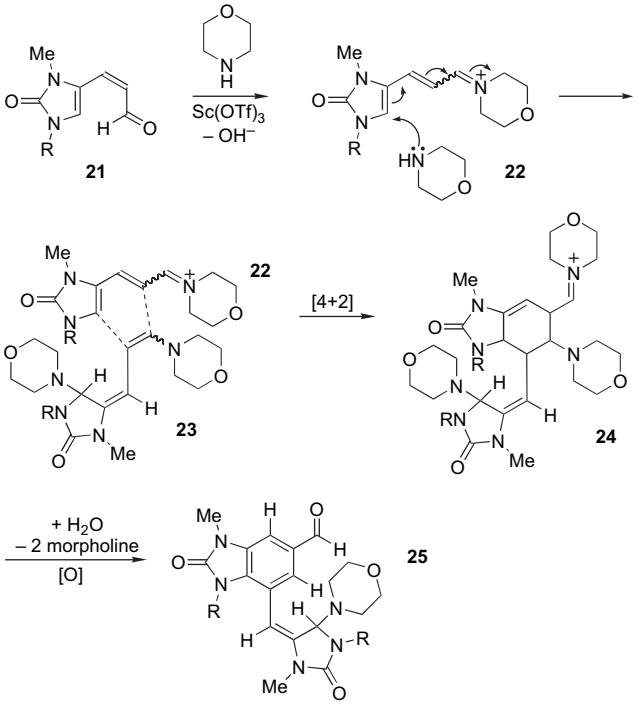
α,β-Unsaturated imidazolone aldehyde **18** underwent analogous $Sc(OTf)_3$ catalyzed dimerization in the presence of morpholine (1 equiv), to afford the corresponding 2:1 adduct **20**; albeit, in lower yield (Scheme 4). In order to determine the influence of the α,β-unsaturated aldehyde geometry, the (*E*)-isomer of **12** (isolated after slow isomerization of the (*Z*)-isomer of **12**) was subjected to the $Sc(OTf)_3$ catalyzed conditions. Comparison of the aldehyde proton resonances in the crude ^1H NMR showed a 5.5:4:1 ratio of the cycloadduct (i.e., the aldehyde precursor of dimer **19**), unreacted (*E*)-isomer of **12**, and aldehyde **9**, presumably formed via conjugate addition of morpholine to **12** followed by a retro-Mannich reaction. In contrast, reaction of the (*Z*)-isomer of aldehyde **12** resulted in a 10:0:1 ratio of **19**/(*E*)-**12**/**9** as determined in the crude ^1H NMR. The geometry of the α,β-unsaturated aldehyde thus seems to play a role in the efficiency of the reaction, with the (*Z*)-isomer **12** reacting more efficiently. Reaction of the (*Z*)-α,β-unsaturated aldehyde under general Lewis acidic conditions, but in the absence of morpholine, resulted in complete isomerization to the (*E*)-isomer, without any evidence for the formation of dimerized products or other adducts. In the absence of $Sc(OTf)_3$, the 2:1 adducts were formed, but at a slower rate, and incomplete consumption of the imidazolone aldehydes was observed.



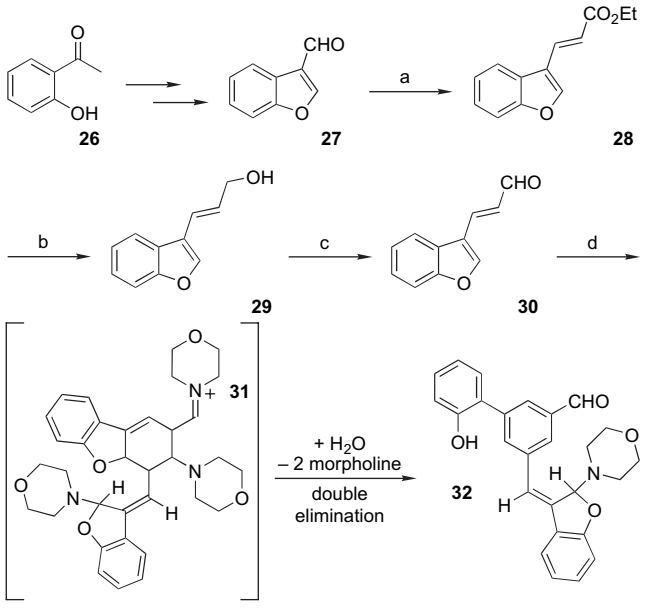
Scheme 4. Morpholine and $Sc(OTf)_3$ promoted formal Diels–Alder reaction of **18**.

The structures of adducts **19** and **20** were determined by a combination of NMR[23] and MS experiments. ^{13}C NMR, $^{13}C-^1H$ shift correlation (gHSQC), and long-range $^1H-^{15}N$ shift correlation (gHMBC) NMR experiments on **19**, confirmed the presence of 20 carbon atoms (two resonances for the four methylene carbons of morpholine) and 5 nitrogen atoms. In addition, a combination of $^{13}C-^1H$ (gHSQC) and long-range $^{13}C-^1H$ shift correlation (CIGAR) NMR experiments allowed us to define the structure of **19**.[24] In the case of dimer **19**, three-bond coupling between C-3a and 4-CH=C in the CIGAR experiment was absent, and only a weak coupling was observed between C-5 and 4-CH=C. This data is consistent with the benzimidazolone and the exocyclic imidazolone moieties being nearly orthogonal, resulting in the observation of small *J*-couplings in the CIGAR spectrum (because of a Karplus-like relationship). These two groups are presumably forced to adopt an orthogonal conformation due to steric constraints. Furthermore, a ROESY experiment of **19** revealed correlations between the alkene proton 4-CH=C and two *N*-methyl groups, Me-N3 and Me-N3′, as well as the aromatic proton H-7 with Me-N1 and 6-CH_2OH.[25] The structure of dimer **20** was also deduced through a combination of high resolution EIMS, ^{13}C and $^{13}C-^1H$ shift correlation (gHSQC), and long-range $^{13}C-^1H$ shift correlation (CIGAR) NMR experiments. Extensive 2D NMR experimentation confirmed the structural similarity with dimer **19**. Furthermore, a ROESY experiment also confirmed that this compound was formed with the same regiochemistry and (*E*)-alkene geometry. More specifically, a ROESY correlation was observed between the vinylic proton (4-CH=C) and both the methyl group (Me-N3′) of the exocyclic imidazolone group and the benzylic protons (*p*-BrPhCH_2-N3) of the benzimidazolone moiety.

The formation of **19/20** from **12/18** and morpholine are examples of *AA′B* 2:1 couplings,[26] in which **12/18** serves two distinct roles in the reaction. The most plausible mechanism for the formation of these adducts is a formal Diels–Alder cycloaddition reaction where the precursors **12/18** act as the source of the diene and dienophile components. Diels–Alder reactions involving molecules serving a dual role, as both diene and dienophile, have been proposed in the biogenesis of various alkaloids, such as the manzamines,[27] martinelline,[28] and compounds **2** and **4**. A plausible mechanism for the formation of both compounds **19** and **20** is outlined in Scheme 5. $Sc(OTf)_3$ catalyzes the formation of an iminium ion **22** from morpholine and the aldehyde **21**. The iminium ion **22** then undergoes nucleophilic attack by a second molecule of morpholine, to give the enamine **23**. The electron-rich enamine dienophile **23** then reacts either with the iminium ion activated diene **22** or with the Lewis activated electron-poor diene **21**, to give **24**. Finally, elimination of morpholine from **24**, followed by an oxidation reaction and iminium ion hydrolysis establishes the benzimidazolone unit and completes the formation of the adduct **25**. The key ring formation may occur through a concerted inverse electron demand Diels–Alder reaction[29,30] or it may be a stepwise process. In the case of a stepwise process, the reaction would occur through a Michael addition of **23** onto iminium ion activated **22** (or Lewis acid activated **21**) followed by an intramolecular Mannich reaction. Alternative reaction partners for the ring-forming step are also possible; for example, 6π-electrocyclization of aldehyde **21** could lead to an enol ether, which as an electron-rich dienophile could react with **22** in the Diels–Alder reaction.[31]



Scheme 5. Proposed formal Diels–Alder mechanism for the formation of the 2:1 adducts.



Scheme 6. Synthesis and Diels–Alder dimerization of α,β-unsaturated benzofuran **30**. Reagents and conditions: (a) Ph_3PCHCO_2Et, CH_2Cl_2 (90%); (b) DIBAL-H, CH_2Cl_2, −78 °C (99%); (c) MnO_2, $CHCl_3$, 50 °C (78%); (d) morpholine (1.0 equiv), $Sc(OTf)_3$ (10 mol %), CH_3CN, 60 °C (15%).

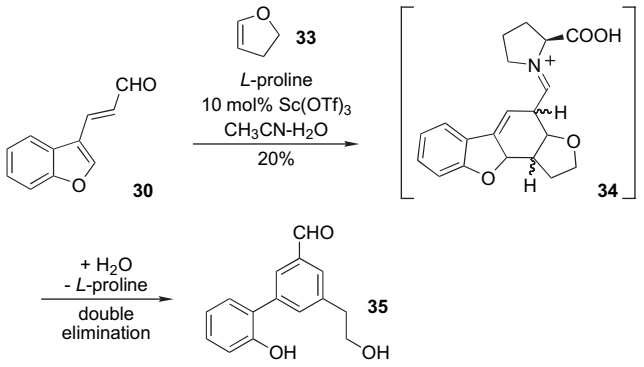
While it is recognized that the formation of these adducts **25** occurs in low yield, this mode of dual activation for an intermolecular formal inverse electron demand Diels–Alder reaction is unprecedented.[32] The low yields can be attributed to the enhanced reactivity of these iminium ion activated dienals, thus leading to several other potential reaction pathways. More specifically, several electrophilic positions along the dienal backbone can lead to undesired side reactions. For example, the major side reaction observed is a retro-Mannich process, which results in degradation of the dienal precursors to give aldehydes **9** and **15**. Moreover, intermediate **22** could undergo 1,2- and 1,4-addition reactions with enamine **23**. The ambivalent reactivity of these dienal precursors is largely responsible for the diversity in the reaction pathways thus leading to multiple products. This behavior is in accord with the ambivalent reactivity of vinylogous 2-aminoimidazoles that has been postulated in the literature.[3]

In view of the results obtained with the reactions of imidazolones **12** and **18**, we then became interested in whether other heterocycles bearing α,β-unsaturated aldehyde functionality would undergo this unique mode of dimerization, acting as electron-poor dienes in formal inverse electron demand Diels–Alder reactions. We elected to test this hypothesis with the α,β-unsaturated benzofuran aldehyde **30** (Scheme 6). The preparation of **30** involved a similar approach to the imidazolones described previously. Wittig olefination of 3-benzofuran carboxaldehyde **27**[33] provided exclusively the (*E*)-α,β-unsaturated ester **28** in 90% yield, with none of the (*Z*)-isomer detected by ^1H NMR. Finally, the two-step conversion to aldehyde **30** was accomplished in high yield by DIBAL-H reduction of **28**, followed by MnO_2 oxidation of allylic alcohol **29**. Subjection of benzofuran **30** to the $Sc(OTf)_3$ catalyzed conditions previously described resulted in no reaction at room temperature. However, heating the reaction mixture to 60 °C resulted in the formation of the *AA′B* 2:1 adduct **32**, albeit in only 15% yield (Scheme 6). The low yield obtained for compound **32** can be attributed to the complex mixture of side-products obtained, which include aldehyde **27** obtained from a retro-Mannich reaction after conjugate addition of morpholine, and the formation of several oligomeric by-products. The structure of **32** was deduced through a combination of homonuclear and heteronuclear 2D NMR experiments.[23] Formation of **32** can occur through double elimination from **31**.

The results described above can be rationalized as involving dual activation by both the Lewis acid and the secondary amine.[34] However, these examples do not distinguish between a stepwise Michael–Mannich process and a concerted Diels–Alder process. The nature of the catalysis cannot be definitively established from these examples and may be through enamine activation of the dienophile and/or iminium ion activation of the diene. Enamine activation of the dienophile component seems likely given the presence of the amine in the adducts **19**, **20**, and **32**, but iminium ion catalysis of the diene component is also possible. This type of activation is quite unusual in the context of organocatalytic Diels–Alder reactions, where the dienophile[35] is usually activated through iminium ion catalysis or the diene through enamine activation.[15–17,36] Indeed, to the best of our knowledge there are no reported examples of organocatalyzed intermolecular inverse electron demand Diels–Alder reactions that form carbocycles.[32,37]

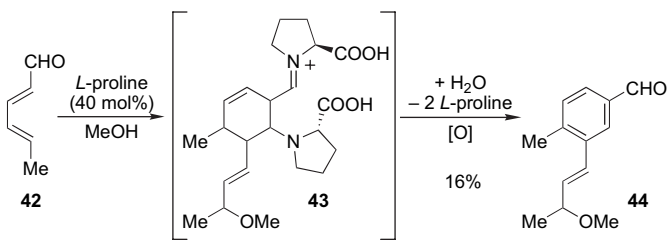
To probe for the involvement of iminium ion activation of the diene in inverse electron demand formal Diels–Alder reactions, an investigation of the possibility of coupling

electron-poor diene substrates with other electron-rich dienophiles was undertaken. Accordingly, treatment of benzofuran **30** with excess 2,3-dihydrofuran **33** (3 equiv) in the presence of L-proline (1.0 equiv) and catalytic $Sc(OTf)_3$ (10 mol %) resulted in the formation of aldehyde **35** (Scheme 7). In this case cycloaddition was *not* observed in the presence of $Sc(OTf)_3$ alone, presumably indicating iminium ion activation of diene **30** by L-proline. Cycloaddition would thus proceed via intermediate **34** followed by consecutive double elimination and hydrolysis of the iminium ion. This is similar to the mechanism proposed by Bodwell for the reaction of enamines with chromone-fused electron-deficient dienes to give 2-hydroxybenzophenones.[38] Conversely the formation of **25**, involves a domino formal inverse electron demand Diels–Alder cycloaddition/elimination/oxidation process (Scheme 5), similar to that observed by Bodwell in the reactions of enamines with coumarin-fused electron-deficient dienes.[39] It is interesting to note that attempts to achieve thermal or Lewis acid activated Diels–Alder reaction of these dienes with enol ethers were unsuccessful,[39] in contrast to the reaction of **30** with **33**.



Scheme 7. Diels–Alder cycloaddition of **30** with 2,3-dihydrofuran.

A variation of these conditions was applied to a non-heterocycle derived dienal. However, in the reaction of sorbic aldehyde **42** and 2,3-dihydrofuran **33**, the major product isolated did not incorporate the dienophile **33**.[40] Instead a 3,4-substituted benzaldehyde **44** was isolated, arising from a *AA′B* 2:1 coupling of the diene **42** and MeOH (Scheme 8). Reaction of **42** with L-proline and $Sc(OTf)_3$ also gave **44** in low yield, with a considerable amount of unidentified by-products revealed by the crude ^1H NMR analysis. Again, in the absence of catalytic proline dimerization did not occur, indicating the importance of the iminium ion/enamine activation pathway. The absence of a Lewis acid in this reaction unequivocally shows amine activation by L-proline. The most plausible mechanism involves a formal Diels–Alder cycloaddition via intermediate **43**, followed by elimination of L-proline, ring-oxidation to the aromatic ring, and iminium ion hydrolysis.



Scheme 8. Methanol and L-proline promoted Diels–Alder dimerization of **42**.

The difficulties of determining whether Diels–Alder reactions occur through concerted or stepwise processes are well known. The experiments outlined herein are similarly problematic, and the reactions may occur via stepwise Michael–Mannich, or concerted Diels–Alder mechanisms. It is perhaps more likely that the reactions occur via a stepwise mechanism, but the more inclusive term of *formal* inverse electron demand Diels–Alder reaction serves to describe both mechanisms. Stepwise mechanisms have been proposed in other organocatalyzed Diels–Alder reactions, such as for the examples described by Hong and co-workers.[41]

Finally, it is instructive to consider the various dimerization pathways that can be considered to occur through such formal Diels–Alder reactions, whether of synthetic or biogenetic origin (Fig. 2). The formal Diels–Alder dimerization pathways postulated for ageliferin **2** and cycloaplysinopsin A **4** can be considered to result from C2–C2′/C5–C3′ and C2–C3′/C5–C2′ bond constructions, via **47** and **48**, respectively. Baldwin's biogenetic proposal for manzamine involves C1–C2′/C4–C3′ bond construction through a normal electron demand Diels–Alder reaction of intermediate **49**.[27] The results of Hong and co-workers also involve a C1–C2′/C4–C3′ bond construction via **50**.[41] Conversely, the formal inverse electron demand Diels–Alder reactions postulated in the present study occur via C2–C1′/C5–C2′ bond construction,[32] i.e., through **51**. To the best of our knowledge this latter type of reactivity is quite unusual, and has not been observed in any known dimeric natural products, although related synthetic examples have been reported by Hong and Bodwell.[32,38,39]

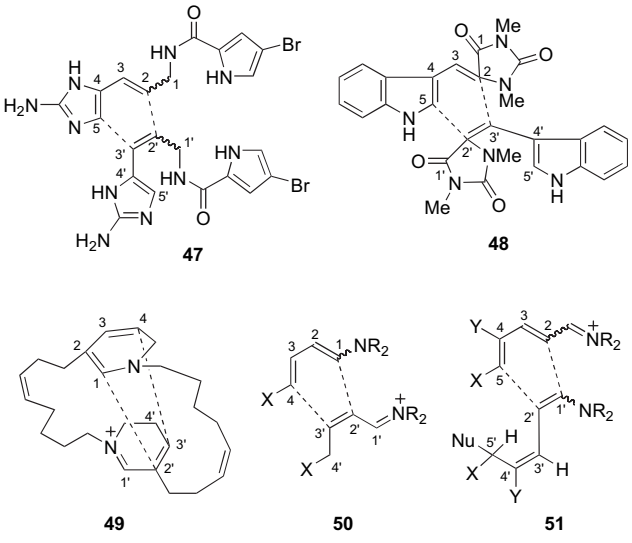


Figure 2. Overview of dimerization pathways and bond-connectivities in synthetic and biosynthetic formal Diels–Alder reactions.

3. Conclusions

As part of prospecting studies for unique reactions of vinylogous heterocycles using amine catalysis, novel *AA′B* 2:1 coupling reactions of vinylogous imidazolone aldehydes **12** and **18** with morpholine have been discovered. Product formation (**19** and **20**) can be rationalized in terms of formal inverse electron demand Diels–Alder reactions (or a domino Michael–Mannich reaction), possibly via iminium ion activation of the diene. The plausibility of such an activation pathway is supported by the formation of the 2:1 adducts **32** and **44**, and the 1:1 adduct **35**. Formation of **35** is proposed to occur via the reaction of the electron-rich dienophile dihydrofuran with an iminium ion activated electron-poor diene derived from 2,4-dienal **30**. Adducts **32** and **44** are formed via dimerization of 2,4-dienal precursors **30** and **42**, respectively, which under amine activation conditions serve as the source of both the electron-poor diene and electron-rich dienophile components. In most cases dual activation by the amine and Lewis acid catalysts was utilized. Lewis acidic catalysis alone did not promote coupling reactions. However, the formation of **44** was accomplished in the presence of L-proline alone, and is therefore an example of an amine promoted formal inverse electron Diels–Alder reaction. In combination these novel coupling reactions represent, to the best of our knowledge, the first examples of amine activated intermolecular formal inverse electron Diels–Alder reactions producing carbocyclic products. These reactions demonstrate a unique mode of reactivity, thus far unobserved in the context of amine activation or organocatalysis. The current studies also delineate problems with this approach, including the greater challenge associated with achieving carbocyclic inverse electron demand Diels–Alder reactions compared to normal electron demand Diels–Alder reactions, as well as several possible side reactions that can occur with the omniphilic dienal systems, such as retro Aldol-like reactions. Further studies are required to achieve high yielding reactions. Nevertheless these studies suggest the possibility of developing organocatalytic variants of inverse electron demand Diels–Alder reactions, a reaction class that, despite the considerable recent interest in organocatalysis, has received limited investigation.

4. Experimental section

4.1. General

Reactions were conducted under an atmosphere of nitrogen unless otherwise stated. Solvents were distilled before use and transferred via syringe using standard techniques: acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) from calcium hydride, diethyl ether (Et_2O) and tetrahydrofuran (THF) from sodium-benzophenone ketyl and toluene from sodium. All other solvents were obtained as ACS or anhydrous grade. Commercial reagents and solutions were used as received unless otherwise stated. Thin layer chromatography (TLC) was performed on aluminum-backed plates of silica precoated with Alugram SIL/G/UV_{254} (Silicycle Inc.), visualized with a UV254 lamp (Spectroline, Longlife Filter) and stained with 20% phosphomolybdic acid in ethanol, 7% (w/w) aqueous potassium permanganate, 2,4-dinitrophenylhydrazine (DNP), or ethanolic ninhydrin. Flash columns were packed with 60 Å, 230–400 mesh silica gel (Silicycle Inc.). Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. FTIR spectra were obtained on a Perkin–Elmer Spectrum 1000 with samples loaded as thin films on NaCl plates. Low resolution mass spectra (LRMS) were recorded on a Bell and Howell 21-490 spectrometer. High resolution mass spectra (HRMS) were recorded on a AEI MS3074 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz (Varian Mercury or Gemini), 400 MHz (Varian Unity), or at 500 MHz (Varian Unity). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 50 MHz (Gemini), 75 MHz (Mercury or Gemini), or at 100 MHz (Unity). Proton chemical shifts were internally referenced to TMS or to the residual proton resonance in $CDCl_3$ (δ 7.26) or DMSO-d_6 (δ 2.50). Carbon chemical shifts were internally referenced to TMS or to the deuterated solvent signals in $CDCl_3$ (δ 77.23) or DMSO-d_6 (δ 39.52). Chemical shifts are reported in parts per million (δ) and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to explain the multiplicities: s=singlet; d=doublet; dd=doublet of doublets; dt=doublet of triplets; t=triplet; q=quartet; m=multiplet. Spectral data are provided for all new compounds and for compounds that lack full characterization in the literature.

4.1.1. 4-Hydroxymethyl-1,3-dimethyl-1,3-dihydroimidazol-2-one (*8*)

To a suspension of **6**[19] (5.00 g, 32.0 mmol) in anhydrous DMF (80 mL) was added NEt_3 (8.9 mL, 64.0 mmol) followed by benzyl bromide (9.5 mL, 80.0 mmol) and the resultant mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O (40 mL) and brine (90 mL), and after vigorous stirring the mixture was further diluted with EtOAc (300 mL). The aqueous phase was separated and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (4×50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was subjected to flash chromatography on silica gel, eluting with 3:7 hexanes/EtOAc, to afford impure 1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylic acid benzyl ester (**7**) as a colorless oil. To a solution of this material (8.00 g) in CH_2Cl_2 (170 mL) at −78 °C was added a 1.0 M solution of DIBAL-H in hexanes (80.0 mL, 80.0 mmol). After 2 h an additional portion of DIBAL-H (50.0 mL, 50.0 mmol) was added, and the resultant mixture was stirred for an additional 2 h. The reaction mixture was quenched with MeOH (8 mL), the cooling bath was removed, and a saturated solution of Rochelle's salt (150 mL) was added. After stirring overnight at room temperature, the aqueous phase was separated, washed with $CHCl_3$ (2×100 mL), and concentrated in vacuo. The residual salts were extracted with $CHCl_3$ (3×100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide **8** (1.96 g, 43% over two steps) as a white solid, mp 110–112 °C. The alcohol was

used without further purification. IR (thin film) 3420, 2942, 2880, 1652, 1482, 1426, 1407, 1235, 1171, 1008, 786, 744, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (1H, s), 4.40 (2H, d, J=5.5 Hz), 3.29 (3H, s), 3.22 (3H, s), 2.64 (1H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 122.8, 109.7, 54.9, 30.4, 27.8; MS (EI) *m/e* (rel intensity) 143 (17), 142 (100), 141 (17), 126 (14), 125 (99); HRMS (EI) *m/e* calcd for $C_6H_{10}N_2O_2$ [M^+]: 142.0742; found: 142.0738.

*4.1.2. 1,3-Dimethyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbaldehyde (**9**)*

To a solution of **8** (1.96 g, 13.8 mmol) in CH_2Cl_2/MeOH (100:4 mL) at room temperature was added activated MnO_2 (10.2 g, 99.3 mmol). The resultant black suspension was stirred overnight, filtered through Celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc, afforded aldehyde **9** (1.23 g, 86% based on recovered starting material) as a white solid, mp 142–144 °C. IR (thin film) 3154, 3084, 2792, 1698, 1662, 1579, 1466, 1407, 1318, 1286, 1181, 1060, 910, 855, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (1H, s), 7.06 (1H, s), 3.56 (3H, s), 3.40 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 153.7, 128.2, 123.6, 31.3, 29.9; MS (EI) *m/e* (rel intensity) 141 (20), 140 (100), 112 (10), 111 (32); HRMS (EI) *m/e* calcd for $C_6H_8N_2O_2$ [M^+]: 140.0586; found: 140.0583.

*4.1.3. 3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-acrylic acid methyl ester (**10**)*

To a solution of 18-crown-6 (3.11 g, 11.8 mmol) in toluene (28 mL) was added oven-dried K_2CO_3 (0.828 g, 5.99 mmol) at room temperature and the resultant suspension was stirred for 2 h. After cooling to −20 °C, a solution of **9** (0.260 g, 1.86 mmol) in THF (12 mL) was added followed by bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.651 g, 2.05 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 1.5 h. The yellow reaction mixture was diluted with H_2O (20 mL) and $CHCl_3$ (110 mL), and the phases were separated. The organic phase was washed with brine (2×20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc, afforded **10** (0.235 g, 64%, 12:1 *Z*/*E*) as a yellow oil. IR (thin film) 3436, 3174, 2980, 2953, 1762, 1715, 1677, 1620, 1567, 1451, 1397, 1297, 1273, 1197, 1175, 1069, 943, 820, 747, 653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, s), 6.50 (1H, d, J=12.5 Hz), 5.75 (1H, d, J=12.5 Hz), 3.75 (3H, s), 3.34 (3H, s), 3.30 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 153.2, 128.2, 121.4, 118.8, 113.3, 51.5, 30.9, 27.6; MS (EI) *m/e* (rel intensity) 196 (55), 180 (47), 167 (14), 165 (26), 153 (37), 113 (26), 82 (56), 68 (100); HRMS (EI) *m/e* calcd for $C_9H_{12}N_2O_3$ [M^+]: 196.0848; found: 196.0855.

*4.1.4. 4-(3-Hydroxypropenyl)-1,3-dimethyl-1,3-dihydroimidazol-2-one (**11**)*

To a solution of **10** (0.122 g, 0.622 mmol) in CH_2Cl_2 (7.0 mL) at −78 °C was added a 1.0 M solution of DIBAL-H in hexanes (1.9 mL, 1.9 mmol). After 3 h, the reaction mixture was quenched with a saturated solution of Rochelle's salt (1.0 mL) and then the cooling bath was removed. After stirring for 1.5 h at room temperature, Na_2SO_4 was added and the mixture was filtered over Celite. The Celite pad was washed with CH_2Cl_2 (50 mL) and the filtrate was concentrated in vacuo to provide **11** (74.3 mg, 71%, 11:1 *Z*/*E*) as a yellow oil. The alcohol was used without further purification. IR (thin film) 3404, 3126, 2947, 2880, 1668, 1471, 1426, 1404, 1076, 1031, 802, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (1H, s), 6.09 (1H, d, J=12.0 Hz), 5.86–5.93 (1H, m), 4.32 (1H, d, J=1.5 Hz), 4.30 (1H, d, J=1.5 Hz), 3.29 (3H, s), 3.22 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 131.3, 119.6, 116.2, 111.7, 60.0, 30.7, 27.8; MS (EI) *m/e* (rel intensity) 169 (12), 168 (86), 139 (26), 125 (100), 112 (20), 110 (13), 94 (46); HRMS (EI) *m/e* calcd for $C_8H_{12}N_2O_2$ [M^+]: 168.0899; found: 168.0901.

*4.1.5. 3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-propenal (**12**)*

To a solution of **11** (0.182 g, 1.08 mmol) in CH_2Cl_2 (10 mL) at room temperature was added activated MnO_2 (0.920 g, 8.99 mmol). The resultant black suspension was stirred overnight, but incomplete consumption of the alcohol was observed. To the black suspension was added more activated MnO_2 (0.400 g, 3.91 mmol) and the reaction mixture was stirred for an additional 3 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo to afford the aldehyde **12** (0.145 g, 81%, 3:1 *Z*/*E*) as an orange oil. IR (thin film) 3443, 3276, 2935, 1660, 1615, 1575, 1465, 1398, 1287, 1161, 1131, 1064, 964, 797, 777, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (1H, d, J=5.5 Hz), 9.53 (1H, d, J=7.5 Hz), 7.48 (1H, s), 7.01 (1H, d, J=16.0 Hz), 6.81 (1H, s), 6.79 (1H, d, J=12.0 Hz), 6.43 (1H, dd, J=16.0, 7.5 Hz), 6.15 (1H, dd, J=12.0, 5.5 Hz), 3.44 (3H, s), 3.36 (3H, s), 3.35 (3H, s), 3.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 189.2, 154.0, 153.2, 137.5, 129.8, 124.8, 123.7, 120.2, 119.7, 119.1, 118.7, 31.1, 30.9, 29.2, 27.7; MS (EI) *m/e* (rel intensity) 167 (19), 166 (100), 138 (44), 137 (24), 112 (28), 109 (56); HRMS (EI) *m/e* calcd for $C_8H_{10}N_2O_2$ [M^+]: 166.0742; found: 166.0746. Slow isomerization of the 3:1 *Z*/*E* mixture to the (*E*)-isomer occurred over several days. IR (thin film) 3428, 3142, 3092, 2925, 1695, 1667, 1616, 1576, 1464, 1397, 1308, 1286, 1160, 1130, 1063, 965, 799, 778, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (1H, d, J=7.5 Hz), 7.02 (1H, d, J=16.0 Hz), 6.81 (1H, s), 6.43 (1H, dd, J=16.0, 7.5 Hz), 3.44 (3H, s), 3.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 154.1, 137.7, 123.9, 120.4, 118.9, 31.1, 29.4; MS (EI) *m/e* (rel intensity) 167 (12), 166 (100), 138 (51), 137 (27), 112 (36), 109 (86), 81 (70), 68 (63), 54 (77); HRMS (EI) *m/e* calcd for $C_8H_{10}N_2O_2$ [M^+]: 166.0742; found: 166.0742.

*4.1.6. 1-(4-Bromobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carboxylic acid 4-bromobenzyl ester (**13**)*

To a slurry of 95% NaH (0.186 g, 7.75 mmol) in anhydrous DMF (7.0 mL) at 0 °C was added **5**[19] (0.307 g, 2.16 mmol),

after which the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 30 min, 4-bromobenzyl bromide (1.85 g, 7.40 mmol) was added and the resultant mixture was heated to 80 °C and stirred overnight. The reaction mixture was diluted with water (5 mL) and brine (10 mL), and the mixture was vigorously stirred for 30 min. This mixture was further diluted with EtOAc (70 mL) and the phases were separated. The combined organic layers were washed with brine (4×15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 2:1 then with 1:1 hexanes/EtOAc, gave **13** (0.71 g, 69%) as a yellow solid, mp 128–130 °C. IR (thin film) 3447, 3106, 2942, 1719, 1690, 1588, 1489, 1460, 1395, 1351, 1240, 1169, 1089, 1069, 1012, 800, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.52 (4H, m), 7.24 (2H, d, J=8.5 Hz), 7.15 (2H, d, J=8.5 Hz), 6.97 (1H, s), 5.16 (2H, s), 4.78 (2H, s), 3.53 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 153.4, 135.0, 134.7, 132.3, 132.0, 130.3, 129.9, 122.8, 122.5, 119.9, 114.5, 65.6, 47.2, 29.9; MS (EI) *m/e* (rel intensity) 482 (27), 481 (13), 480 (44), 478 (27), 172 (12), 171 (98), 170 (13), 169 (100), 90 (35); HRMS (EI) *m/e* calcd for $C_{19}H_{16}^{79}Br_2N_2O_3$ [M^+]: 477.9528; found: 477.9532.

*4.1.7. 1-(4-Bromobenzyl)-4-hydroxymethyl-3-methyl-1,3-dihydroimidazol-2-one (**14**)*

To a solution of **13** (4.07 g, 8.48 mmol) in CH_2Cl_2 (85 mL) at −78 °C was added a 1.0 M solution of DIBAL-H in hexanes (25.4 mL, 25.4 mmol) and the resultant mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (5 mL), after which the cooling bath was removed and a saturated solution of Rochelle's salt (75 mL) was added. After stirring for 2 h at room temperature, the mixture was diluted with EtOAc (160 mL), and the aqueous phase was separated and extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 95:4:1 CH_2Cl_2/MeOH/NH_4OH, afforded **14** (2.38 g, 94%) as a white solid, mp 138–140 °C. IR (thin film) 3420, 2928, 2860, 1661, 1488, 1470, 1407, 1160, 1070, 1012, 777, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (2H, d, J=8.5 Hz), 7.15 (2H, d, J=8.5 Hz), 6.08 (1H, s), 4.72 (2H, s), 4.39 (2H, d, J=5.5 Hz), 3.34 (3H, s), 1.59 (1H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 136.0, 132.0, 129.8, 123.2, 122.0, 108.3, 55.2, 46.6, 27.9; MS (EI) *m/e* (rel intensity) 298 (60), 296 (67), 171 (100), 169 (99), 127 (21), 99 (12); HRMS (EI) *m/e* calcd for $C_{12}H_{13}^{79}BrN_2O_2$ [M^+]: 296.0160; found: 296.0153.

*4.1.8. 1-(4-Bromobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbaldehyde (**15**)*

To a solution of **14** (2.37 g, 7.99 mmol) in CH_2Cl_2 (80 mL) at room temperature was added activated MnO_2 (7.06 g, 69.0 mmol). The resultant black suspension was stirred overnight, filtered through Celite, and the filtrate was concentrated in vacuo to afford **15** (2.18 g, 92%) as a white solid, mp 105–107 °C. IR (thin film) 3419, 3095, 2942, 2819, 1702, 1659, 1577, 1489, 1467, 1422, 1405, 1339, 1163, 1070, 1012, 910, 802, 739, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, s), 7.51 (2H, d, J=8.0 Hz), 7.18 (2H, d, J=8.0 Hz), 6.93 (1H, s), 4.84 (2H, s), 3.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 153.4, 134.4, 132.4, 130.0, 126.5, 124.1, 122.8, 47.4, 30.0; MS (EI) *m/e* (rel intensity) 296 (24), 294 (25), 171 (100), 169 (99), 90 (58); HRMS (EI) *m/e* calcd for $C_{12}H_{11}^{79}BrN_2O_2$ [M^+]: 294.0004; found: 293.9996.

*4.1.9. 3-[1-(4-Bromobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl]-acrylic acid methyl ester (**16**)*

To a solution of 18-crown-6 (10.8 g, 41.0 mmol) in toluene (65 mL) was added oven-dried K_2CO_3 (2.80 g, 20.3 mmol) at room temperature and the resultant suspension was stirred for 1 h. After cooling to −20 °C, a solution of **15** (1.50 g, 5.09 mmol) in THF (20 mL) was added followed by bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (1.3 mL, 6.15 mmol). The resultant mixture was allowed to warm to room temperature and was stirred for 2 h. The yellow reaction mixture was diluted with H_2O (50 mL) and EtOAc (200 mL), and the phases were separated. The organic phase was washed with H_2O (1×50 mL) and brine (2×50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 1:1 then 1:2 hexanes/EtOAc, afforded **16** (1.51 g, 84%, 30:1 *Z*/*E*) as a yellow oil. IR (thin film) 3348, 3170, 2950, 1715, 1693, 1618, 1565, 1489, 1450, 1406, 1361, 1256, 1198, 1166, 1103, 1070, 1012, 818, 800, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, s), 7.46 (2H, d, J=8.0 Hz), 7.19 (2H, d, J=8.0 Hz), 6.49 (1H, d, J=12.5 Hz), 5.76 (1H, d, J=12.5 Hz), 4.82 (2H, s), 3.72 (3H, s), 3.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 152.8, 135.7, 132.1, 129.8, 128.0, 122.1, 119.8, 119.3, 114.0, 51.6, 47.2, 27.7; MS (EI) *m/e* (rel intensity) 352 (45), 350 (44), 181 (24), 171 (99), 169 (100), 126 (17), 90 (29); HRMS (EI) *m/e* calcd for $C_{15}H_{15}^{79}BrN_2O_3$ [M^+]: 350.0266; found: 350.0262.

*4.1.10. 1-(4-Bromobenzyl)-4-(3-hydroxypropenyl)-3-methyl-1,3-dihydroimidazol-2-one (**17**)*

To a solution of **16** (1.51 g, 4.30 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added a 1.0 M solution of DIBAL-H in hexanes (13.0 mL, 13.0 mmol) and the resultant mixture was stirred for 2 h. The reaction mixture was quenched with MeOH (4 mL), and then the cooling bath was removed and a saturated solution of Rochelle's salt (50 mL) was added. After stirring for 2.5 h at room temperature, the mixture was diluted with CH_2Cl_2 (50 mL), and the aqueous phase was separated and further extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford **17** (1.31 g, 94%, 16:1 *Z*/*E*) as a yellow solid, mp 74–76 °C. IR (thin film) 3384, 2928, 2867, 1668, 1488, 1456, 1405, 1351, 1070, 1042, 1012, 797 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (2H, d, J=8.5 Hz), 7.14 (2H, d, J=8.5 Hz), 6.09 (1H, s), 6.06 (1H, d, J=11.0 Hz), 5.84–5.93 (1H, m), 4.76 (2H, s), 4.23 (2H, d, J=6.5 Hz), 3.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 135.8, 132.1, 131.9, 129.6, 122.1, 120.4, 115.8,

110.0, 59.9, 46.8, 27.9; MS (EI) *m/e* (rel intensity) 324 (62), 322 (61), 171 (99), 169 (100), 153 (59), 110 (49), 98 (31), 97 (19), 90 (61); HRMS (EI) *m/e* calcd for $C_{14}H_{15}^{79}BrN_2O_2$ [M^+]: 322.0317; found: 322.0314.

*4.1.11. 3-[1-(4-Bromobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl]-propenal (**18**)*

To a solution of **17** (1.21 g, 3.74 mmol) in CH_2Cl_2 (40 mL) at room temperature was added activated MnO_2 (3.00 g, 29.3 mmol). The resultant black suspension was stirred overnight, filtered through Celite, and the filtrate was concentrated in vacuo to afford **18** (1.20 g, 100%, 13:1 *Z*/*E*) as an orange oil. IR (thin film) 3406, 3092, 2928, 2860, 1712, 1664, 1488, 1449, 1404, 1351, 1150, 1070, 1012, 909, 798, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, d, J=5.5 Hz), 7.48 (2H, d, J=8.5 Hz), 7.36 (1H, s), 7.19 (2H, d, J=8.5 Hz), 6.79 (1H, d, J=12.0 Hz), 6.15 (1H, dd, J=12.0, 5.5 Hz), 4.82 (2H, s), 3.33 (3H, s); ^{13}C NMR (mixture of *E* and *Z* isomers; 75 MHz, $CDCl_3$) δ 192.7, 189.2, 153.5, 152.8, 137.4, 135.1, 134.9, 132.1, 132.0, 130.0, 129.7, 129.6, 125.8, 124.1, 122.3, 122.2, 120.8, 119.4, 117.7, 117.1, 47.1, 47.0, 29.2, 27.8; MS (EI) *m/e* (rel intensity) 323 (12), 322 (26), 321 (13), 320 (24), 172 (11), 171 (96), 170 (11), 169 (100), 109 (23), 98 (12), 90 (43); HRMS (EI) *m/e* calcd for $C_{14}H_{13}^{79}BrN_2O_2$ [M^+]: 320.0160; found: 320.0150.

*4.1.12. 4-(1,3-Dimethyl-5-morpholin-4-yl-2-oxo-imidazolidin-4-ylidenemethyl)-6-hydroxymethyl-1,3-dimethyl-1,3-dihydrobenzoimidazol-2-one (**19**)*

To a solution of a 3:1 (*Z*/*E*) mixture of **12** (0.116 g, 0.697 mmol) in CH_3CN (7.0 mL) at room temperature were added sequentially 4 Å molecular sieves (72 mg), morpholine (60.0 μL, 0.697 mmol), and $Sc(OTf)_3$ (35 mg, 0.072 mmol). The resultant orange mixture was stirred overnight and filtered through Celite. The orange filtrate was treated with H_2O (10 mL), and the aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. To a solution of the crude material (0.146 g) in anhydrous MeOH (4 mL) was added $NaBH_4$ (42.3 mg, 1.12 mmol) at room temperature, and the resultant mixture was stirred for 8 h. The mixture was diluted with H_2O (10 mL) and CH_2Cl_2 (20 mL), and the aqueous phase was separated and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_4OH (20:1:1), gave the desired product that also contained several impurities. The impure material (81 mg) was subjected to a second purification by flash chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_4OH (25:1:1), to provide **19** (60 mg, 43% over two steps) as an orange foam. IR (thin film) 3422, 2942, 2854, 1702, 1684, 1670, 1458, 1415, 1394, 1284, 1252, 1114, 1089, 1012, 919, 858, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (1H, s, H-5), 6.88 (1H, s, H-7), 5.93 (1H, d, J=1.5 Hz, 4-C*H*=C), 5.05 (1H, d, J=2.0 Hz, H-5′), 4.69 (2H, d, J=4.5 Hz, 6-CH_2OH), 3.58 (3H, s, Me-N3), 3.42 (3H, s, Me-N1), 3.26–3.32 (2H, m, H-2″), 3.15–3.22 (2H, m, H-2″), 3.07 (3H, s, Me-N3′), 2.92 (3H, s, Me-N1′), 2.42–2.48 (2H, m, H-3″), 2.19–2.26 (2H, m, H-3″); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1 (C-2′), 155.4 (C-2), 140.5 (C-4′), 134.3 (C-6), 131.0 (C-7a), 127.1 (C-3a), 122.0 (C-5), 119.5 (C-4), 104.9 (C-7), 96.1 (4-*C*H=C), 77.2 (C-5′), 67.2 (C-2″), 65.5 (6-*C*H_2OH), 47.6 (C-3″), 30.3 (Me-N3), 29.8 (Me-N1′), 27.6 (Me-N1), 27.1 (Me-N3′); MS (EI) *m/e* (rel intensity) 401 (11), 316 (27), 315 (100), 313 (12), 125 (20), 100 (31); HRMS (EI) *m/e* calcd for $C_{20}H_{27}N_5O_4$ [M^+]: 401.2063; found: 401.2069.

*4.1.13. 1-(4-Bromobenzyl)-7-[1-(4-bromobenzyl)-3-methyl-5-morpholin-4-yl-2-oxo-imidazolidin-4-ylidenemethyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazole-5-carbaldehyde (**20**)*

To a solution of **18** (0.128 g, 0.399 mmol) in CH_3CN (4.0 mL) at room temperature were added sequentially 4 Å molecular sieves (49 mg), morpholine (35.0 μL, 0.401 mmol), and $Sc(OTf)_3$ (21 mg, 0.043 mmol). The resultant orange mixture was stirred for 6.5 h, diluted with CH_2Cl_2 (50 mL), and filtered through Celite. The orange filtrate was washed with H_2O (1×10 mL) and brine (2×10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc/hexanes (1:1 followed by 2:1), afforded **20** (35 mg, 25%) as an orange foam. IR (thin film) 2960, 2867, 2846, 1718, 1686, 1592, 1487, 1458, 1400, 1159, 1114, 1070, 1011, 909, 797, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (1H, s, 6-C*H*O), 7.48 (2H, d, J=8.5 Hz, *p*-Br*Ph*CH_2-N1′), 7.46 (2H, d, J=8.5 Hz, *p*-Br*Ph*CH_2-N3), 7.41 (1H, s, H-5), 7.40 (1H, s, H-7), 7.13 (2H, d, J=8.5 Hz, *p*-Br*Ph*CH_2-N1′), 6.97 (2H, d, J=8.5 Hz, *p*-Br*Ph*CH_2-N3), 5.52 (1H, d, J=1.5 Hz, 4-C*H*=C), 5.26 (2H, d, J=3.5 Hz, *p*-BrPhCH_2-N3), 4.97 (1H, d, J=2.0 Hz, H-5′), 4.72 (1H, d, J=15.5 Hz, *p*-BrPh CH_2-N1′), 4.17 (1H, d, J=15.5 Hz, *p*-BrPhCH_2-N1′), 3.54 (3H, s, Me-N1), 3.18–3.25 (2H, m, H-2″), 3.06–3.14 (2H, m, H-2″), 2.88 (3H, s, Me-N3′), 2.26–2.33 (2H, m, H-3″), 2.07–2.16 (2H, m, H-3″); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9 (6-*C*HO), 156.9 (C-2′), 155.1 (C-2), 141.3 (C-4′), 136.3 (*p*-Br*Ph*CH_2-N3), 135.9 (*p*-Br*Ph*CH_2-N1′), 132.4 (*p*-Br*Ph* CH_2-N1′), 132.2 (*p*-Br*Ph*CH_2-N3), 131.7 (C-3a), 131.6 (C-7a), 130.8 (C-6), 129.9 (*p*-Br*Ph*CH_2-N1′), 127.6 (*p*-Br*Ph*CH_2-N3), 127.5 (C-5), 122.0 (*p*-Br*Ph*CH_2-N1′), 121.9 (*p*-Br*Ph*CH_2-N3), 119.4 (C-4), 105.8 (C-7), 95.0 (4-*C*H=C), 75.3 (C-5′), 67.0 (C-2″), 47.7 (C-3″), 45.8 (*p*-BrPh *C*H_2-N1′), 45.5 (*p*-BrPh*C*H_2-N3), 28.0 (Me-N1), 27.1 (Me-N3′); MS (EI) *m/e* (rel intensity) 626 (21), 625 (55), 624 (44), 623 (100), 622 (26), 621 (52), 171 (98), 170 (99), 90 (18); HRMS (EI) *m/e* calcd for $C_{32}H_{31}^{79}Br_2N_5O_4$ [M^+]: 707.0743; found: 707.0730.

*4.1.14. 3-Benzofuran-3-yl-acrylic acid ethyl ester (**28**)*

To a stirred solution of **27**[33] (1.50 g, 10.3 mmol) in CH_2Cl_2 (50 mL) at room temperature was added 95% (carboethoxyethylene)-triphenylphosphorane (4.14 g, 11.3 mmol). The resultant yellow reaction mixture was stirred for 15 h and concentrated in vacuo. Purification by flash chromatography

on silica gel (40+M), eluting with 100:1 then with 95:5 hexanes/EtOAc, afforded the title compound (1.99 g, 90%) as a yellow solid, mp 71–72 °C. IR (thin film) 3126, 2976, 1704, 1640, 1449, 1364, 1313, 1249, 1191, 1116, 967, 831, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, s), 7.85 (1H, dd, J=7.0, 1.5 Hz), 7.79 (1H, d, J=16.0 Hz), 7.52 (1H, m), 7.36 (2H, m), 6.56 (1H, dd, J=16.0, 0.5 Hz), 4.28 (2H, q, J=7.0 Hz), 1.36 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 156.3, 147.9, 134.6, 125.6, 125.0, 123.9, 121.2, 118.7, 118.1, 112.2, 60.7, 14.6; MS (EI) *m/e* (rel intensity) 216 (100), 171 (78), 146 (37), 131 (25), 115 (85), 89 (22), 63 (28); HRMS (EI) *m/e* calcd for $C_{13}H_{12}O_3$ [M^+]: 216.0786; found: 216.0791.

*4.1.15. 3-Benzofuran-3-yl-prop-2-en-1-ol (**29**)*

To a solution of **28** (1.91 g, 8.84 mmol) in CH_2Cl_2 (70 mL) at −78 °C was added dropwise a 1.0 M solution of DIBAL-H in hexanes (22 mL). After 3 h, the reaction mixture was warmed to room temperature and quenched with 1 N HCl (40 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2×40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (40+M), eluting with EtOAc/hexanes (1:4), afforded the title compound (1.50 g, 99%) as a pale yellow oil. IR (thin film) 3358, 3044, 2915, 2853, 1450, 1186, 1108, 1013, 963, 856, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, dd, J=7.5, 1.5 Hz), 7.66 (1H, s), 7.49 (1H, dd, J=8.5, 1.5 Hz), 7.27–7.35 (2H, m), 6.70 (1H, d, J=16.0 Hz), 6.49 (1H, dt, J=10.0, 5.5 Hz), 4.37 (2H, dd, J=5.5, 4.0 Hz), 1.47 (1H, t, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 143.6, 129.6, 126.0, 124.9, 123.2, 121.0, 120.9, 118.8, 111.9, 64.2; MS (EI) *m/e* (rel intensity) 174 (100), 145 (45), 131 (79), 118 (23), 115 (32); HRMS (EI) *m/e* calcd for $C_{11}H_{10}O_2$ [M^+]: 174.0681; found: 174.0678.

*4.1.16. 3-Benzofuran-3-yl-propenal (**30**)*

To a solution of **29** (1.50 g, 8.62 mmol) in $CHCl_3$ (60 mL) at room temperature was added in two portions activated MnO_2 (9.05 g, 88.5 mmol). The resultant black suspension was stirred at room temperature for 4 h and heated to 50 °C for 2 h, cooled to room temperature, filtered through Celite, and the filtrate was concentrated in vacuo to afford the title compound (1.18 g, 78%) as a yellow crystalline solid, mp 88–90 °C. IR (thin film) 3098, 3051, 1667, 1633, 1538, 1449, 1133, 967, 855, 821, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (1H, d, J=7.5 Hz), 7.99 (1H, s), 7.84 (1H, dt, J=8.5, 1.0, 0.5 Hz), 7.60 (1H, d, J=16.0 Hz), 7.56 (1H, dt, J=8.5, 1.0, 0.5 Hz), 7.36–7.43 (2H, m), 6.87 (1H, dd, J=16.5, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 156.4, 148.8, 142.3, 129.1, 126.0, 124.5, 124.3, 121.1, 118.3, 112.3; MS (EI) *m/e* (rel intensity) 172 (77), 144 (33), 118 (34), 115 (100), 89 (21), 63 (22); HRMS (EI) *m/e* calcd for $C_{11}H_8O_2$ [M^+]: 172.0524; found: 172.0526.

*4.1.17. 2′-Hydroxy-5-(2-morpholin-4-yl-benzofuran-3-ylidenemethyl)-biphenyl-3-carbaldehyde (**32**)*

To a solution of **30** (51.0 mg, 0.399 mmol) in CH_3CN (3.0 mL) at room temperature were added sequentially 4 Å molecular sieves (38 mg), morpholine (30.0 μL, 0.344 mmol), and $Sc(OTf)_3$ (14.6 mg, 0.0297 mmol). The resultant orange mixture was heated to 60 °C and stirred for 22 h. The resultant mixture was filtered through a Celite pad and washed with EtOAc (30 mL). The orange filtrate was washed with H_2O (1×5 mL) and brine (2×5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (12+M), eluting with 10:1 followed by 4:1 and 2:1 hexanes/EtOAc, afforded the title compound (9.3 mg, 15%) as an orange oil. IR (thin film) 3321, 3055, 2959, 2915, 2849, 1693, 1593, 1464, 1455, 1369, 1318, 1296, 1148, 1111, 1005, 909, 864, 750, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.10 (1H, s), 8.37 (1H, t, J=1.5 Hz), 8.20 (1H, t, J=1.5 Hz), 7.91 (1H, t, J=1.5 Hz), 7.48 (1H, dd, J=7.5, 1.0 Hz), 7.23–7.34 (3H, m), 7.10 (1H, d, J=2.0 Hz), 7.05 (1H, dt, J=7.5, 1.0 Hz), 6.99 (1H, dd, J=8.0, 1.0 Hz), 6.94 (1H, dt, J=7.5, 1.0 Hz), 6.88 (1H, d, J=8.0 Hz), 6.02 (1H, d, J=2.0 Hz), 5.15 (1H, s), 3.59–3.62 (4H, m), 2.90–2.93 (2H, m), 2.74–2.79 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0 (CH), 161.3 (C), 152.4 (C), 138.6 (C), 137.72 (C), 137.71 (C), 137.2 (C), 136.1 (CH), 131.1 (CH), 130.4 (CH), 129.8 (CH), 129.7 (CH), 129.3 (CH), 126.9 (C), 126.0 (C), 121.3 (CH), 120.8 (CH), 120.7 (CH), 119.8 (CH), 116.2 (CH), 110.0 (CH), 99.7 (CH), 66.7 (CH_2), 46.9 (CH_2); MS (ESI) *m/e* (rel intensity) 415 (18), 414 (71), 375 (11), 328 (24), 327 (100); HRMS (ESI) *m/e* calcd for $C_{26}H_{24}NO_4$ [M+H]: 414.1692; found: 414.1699.

*4.1.18. 2′-Hydroxy-5-(2-hydroxyethyl)-biphenyl-3-carbaldehyde (**35**)*

To a stirred solution of L-proline (33.8 mg, 0.287 mmol), $Sc(OTf)_3$ (14.7 mg, 0.0290 mmol), and **30** (49.4 mg, 0.287 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 mL) at room temperature was added 2,3-dihydrofuran (76.0 μL, 1.00 mmol). After stirring for 24 h, the resultant mixture was washed with H_2O (2×10 mL) and brine (2×10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (12+M), eluting with 5:1 followed by 3:1 hexanes/EtOAc, afforded the title compound (12.9 mg, 20%) as an orange oil. IR (thin film) 3347, 2951, 2879, 2734, 1686, 1597, 1459, 1386, 1291, 1266, 1224, 1154, 1044, 755, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (1H, s), 7.85 (1H, t, J=1.5 Hz), 7.73 (1H, t, J=1.5 Hz), 7.66 (1H, t, J=1.5 Hz), 7.23–7.28 (2H, m), 7.01 (1H, td, J=7.5, 1.0 Hz), 6.93 (1H, dd, J=8.5, 1.0 Hz), 5.55 (1H, br s), 3.93 (2H, t, J=6.5 Hz), 2.98 (2H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 152.7, 140.7, 139.0, 137.4, 136.3, 130.6, 129.8, 129.3, 129.0, 127.1, 121.4, 116.5, 63.3, 38.9; MS (EI) *m/e* (rel intensity) 242 (100), 211 (47), 195 (72), 181 (37), 165 (34), 152 (20), 115 (13); HRMS (EI) *m/e* calcd for $C_{15}H_{14}O_3$ [M^+]: 242.0943; found: 242.0938.

4.1.19. 3-(3-Methoxybut-1-enyl)-4-methyl-benzaldehyde (**44**)

To a stirred solution of L-proline (0.159 g, 1.38 mmol) in anhydrous MeOH (10.0 mL) at room temperature was added **42** (0.40 mL, 3.4 mmol). The resultant yellow solution was stirred for 20 h, diluted with EtOAc (50 mL), washed with $NaHCO_3$ (2×10 mL) and brine (2×10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (12+M), eluting with 19:1 followed by 9:1 hexanes/EtOAc, afforded the title compound (58 mg, 16%) as a yellow oil. IR (thin film) 2974, 2922, 2812, 1694, 1598, 1565, 1447, 1369, 1229, 1196, 1108, 1082, 968, 820, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.98 (1H, s), 7.95 (1H, d, J=2.0 Hz), 7.67 (1H, dd, J=7.5, 1.5 Hz), 7.31 (1H, d, J=7.5 Hz), 6.75 (1H, d, J=16.0 Hz), 6.11 (1H, dd, J=16.0, 7.5 Hz), 3.95 (1H, m), 3.36 (3H, s), 2.43 (3H, s), 1.36 (3H, d, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 142.9, 137.1, 135.1, 135.0, 131.2, 128.8, 127.8, 127.4, 78.1, 56.4, 21.6, 20.5; MS (EI) *m/e* (rel intensity) 204 (24), 189 (53), 172 (100), 157 (31), 145 (38), 129 (89), 115 (31), 105 (30), 59 (68); HRMS (EI) *m/e* calcd for $C_{13}H_{16}O_2$ [M^+]: 204.1150; found: 204.1150.

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18. The term 'reaction prospecting' is inspired by the term 'prospecting library', introduced by Bartlett, see: Spaller, M. R.; Burger, M. T.; Fardis, M.; Bartlett, P. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 47–53.
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23. Reynolds, W. F.; Enríquez, R. G. *J. Nat. Prod.* **2002**, *65*, 221–244.
24. Long-range heterocoupling of H-5′ with C-3″, C-4′, and C-2′ revealed that the morpholine fragment was attached to C-5′ of one of the imidazolone units. The carbon–carbon connectivity of the benzimidazolone motif was deduced from the following three-bond heterocouplings: C-3a with H-7, H-5, and Me-N3; C-7a with Me-N1; C-5 with H-7 and 6-CH_2OH; and C-7 with H-5 and 6-CH_2OH. (Two-bond $^{13}C-^1H$ correlations involving aromatic protons are rarely observed and, if observed, are very weak).
25. A significant ROESY correlation was observed between aromatic proton H-5 and H-5′, suggesting that H-5′ is spatially oriented in the vicinity of H-5.
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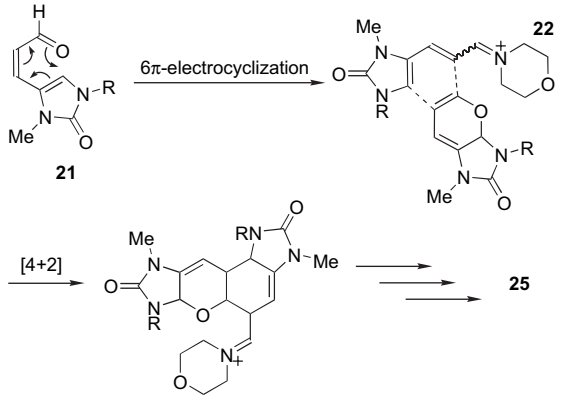
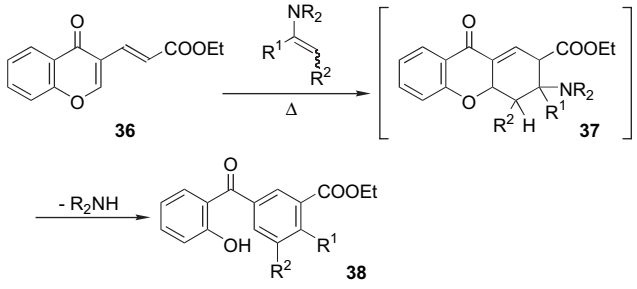
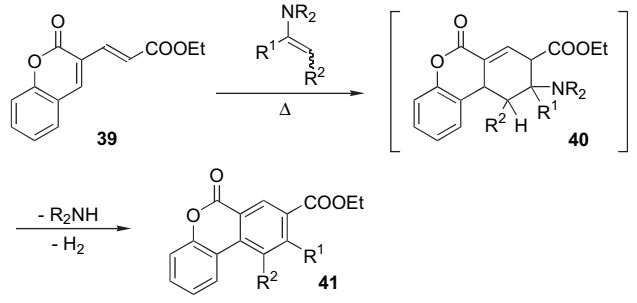
31. This mechanism cannot be excluded since the (*Z*)-isomer of **12** reacted more efficiently than the corresponding (*E*)-isomer.



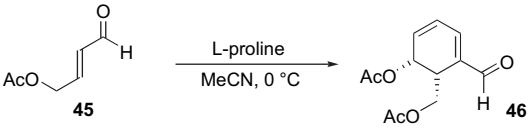
32. For an example of an organocatalyzed (50 mol % L-proline) intramolecular inverse electron demand Diels–Alder reaction of α,β,γ,δ-unsaturated aldehydes, see: Hong, B.-C.; Tseng, H.-C.; Chen, S.-H. *Tetrahedron* **2007**, *63*, 2840–2850.
33. Synthesis of **27** from **26** was achieved via a four-step literature procedure: alkylation of the phenol with ethyl chloroacetate, followed by hydrolysis of the resultant ester, cyclodehydration of the acid and SeO_2 oxidation of 3-methylbenzofuran. See: (a) Nielek, S.; Lesiak, T. *Chem. Ber*. **1982**, *115*, 1247–1251; (b) Zaidlewicz, M.; Chechlowska, A.; Prewysz-Kwinto, A.; Wojtczak, A. *Heterocycles* **2001**, *55*, 569–577.
34. For reviews of organocatalysis, see: (a) Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719–724; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138–5175; (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3726–3748.
35. There are numerous examples in the literature of organocatalyzed Diels–Alder reactions using proline and imidazolone derivatives to achieve iminium ion activation of the dienophile. See Ref. 14.
36. Jørgensen and co-workers have recently reported examples of diene activation through dienamine formation, in organocatalytic γ-aminations of α,β-unsaturated aldehydes. They also reported an example of a 1-aminodiene generated from 2-(*E*)-pentenal participating in a normal electron demand Diels-reaction with *N*-methylmaleimide in 35% yield. See: Bertelsen, S.; Marigo, M.; Brandes, S.; Binér, P.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 12973–12980.
37. Organocatalytic activation of the dienophile through enamine activation has been reported in inverse-electron demand hetero Diels–Alder reactions, see: (a) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc*. **2005**, *127*, 16028–16029; (b) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1498–1501; (c) Wabnitz, T. C.; Saaby, S.; Jørgensen, K. A. *Org. Biomol. Chem*. **2004**, *2*, 828–834.
38. The reaction of chromone-fused electron-deficient dienes **36** with enamines is proposed to occur via **37** to give 2-hydroxybenzophenones **38**. See: (a) Bodwell, G. J.; Hawco, K. M.; da Silva, R. P. *Synlett* **2003**, 179–182; (b) Bodwell, G. J.; Hawco, K. M.; Satou, T. *Synlett* **2003**, 879–881.



39. The reaction of **39** with enamines to give **41** has been proposed to occur via a domino cycloaddition/elimination/oxidation pathway. See: Bodwell, G. J.; Pi, Z.; Pottie, I. R. *Synlett* **1999**, 477–479.



40. Other solvents, such as THF, CH_3CN, DMF, DMSO, and $CHCl_3$, did not result in incorporation of **33** or in formation of any other dimerized products.
41. Reaction of **45** with proline gives the cycloadduct **46** in a formal Diels–Alder manner, proposed to occur via a stepwise enamine Michael type condensation followed by a Mannich cyclization. See: Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett*. **2006**, *8*, 2217–2220.



68% (94% e.e.)