

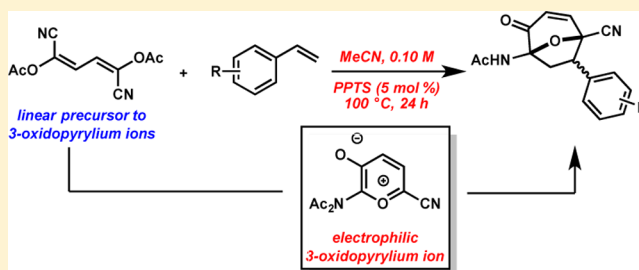
Bis(1-cyanovinyl acetate) Is a Linear Precursor to 3-Oxidopyrylium Ions

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S Supporting Information

ABSTRACT: Herein we describe the first approach to 3-oxidopyrylium ions from a linear precursor. Heating bis(1-cyanovinyl acetate) in the presence of a trace amount of pyridinium *p*-toluenesulfonate results in a series of acyl group transfers and an intramolecular cyclization event to form a 3-oxidopyrylium ion that can be trapped by reaction with several dipolarophiles. When treated with dienes, the result is a sequential [5 + 2]/[4 + 2] cycloaddition reaction that provides sp³-rich products of high molecular complexity.



INTRODUCTION

The rapid generation of molecular complexity (RGMC) from readily accessible precursors is a long-standing goal in organic synthesis.¹ Complexity-building reactions, which introduce new rings (fused and bridging) as well as additional functional groups and stereogenic centers, are conceptually and mechanistically interesting and are therefore of academic interest. From a practical perspective (e.g., in preparing complex molecules), RGMC is especially pertinent because it can reduce the number of steps needed to access architecturally intricate and functional group dense intermediates en route to a desired target.² Furthermore, the continuing emergence of unique sp³-rich chemotypes for medicinal chemistry makes new modes for generating molecular complexity highly important.^{3,4}

Cycloaddition reactions constitute textbook examples of complexity building reactions that convert relatively simple π -systems to more complex, ring-containing, compounds bearing multiple sp³ stereogenic centers in a regio- and diastereoselective manner. The Diels–Alder cycloaddition reaction (Figure 1A) epitomizes these processes as it can construct a six-membered ring and up to four contiguous stereogenic centers from acyclic precursors.

The [5 + 2] cycloaddition reaction between 3-oxidopyrylium ions and dipolarophiles represents another well-practiced

complexity-building pericyclic reaction (Figure 1B).⁵ In this case [3.2.1]-oxabicyclooctenones, which are otherwise difficult to access, are formed in a single step. As a result, cycloaddition reactions between alkenes and 3-oxidopyrylium ions have been used extensively in natural product synthesis; most notably by Wender and co-workers to access molecules such as phorbol.^{5c,6}

Though the cycloaddition reactivity of 3-oxidopyrylium ions is well-established,⁷ methods to access functionalized precursors to these intermediates remain limited. In general, two strategies have been employed in their preparation. 3-Oxidopyrylium ions can be generated from 3-hydroxy-4-pyranones by a group transfer-type reaction from kojic acid derivatives (Scheme 1, eq 1).⁸ Alternatively, these reactive intermediates can be accessed through the base-mediated transformation of pyranyl acetates, which may be obtained from the Achmatowicz rearrangement of furanyl alcohols (Scheme 1, eq 2).⁹ Extensive work by the Padwa group has shown that [5 + 2] cycloaddition reactions can also be effected with carbonyl ylides generated from the rhodium(II)-catalyzed decomposition of linear δ -diazoketones.^{10a} Unfortunately, when attempts were made to extend this reaction to generate 3-oxidopyrylium ions using linear precursors (Scheme 1, eq 3), the reactive intermediates could not be trapped, and instead, an unidentifiable dimeric side-product was obtained.^{10b} Herein, we report our discovery of a method for generating a highly functionalized 3-oxidopyrylium ion from easily synthesized bis(1-cyanovinyl acetate) (1), and we demonstrate its ability to undergo intermolecular cycloaddition reactions with various dipolarophiles (Scheme 1, eq 4). To the best of our knowledge, 1 constitutes the first reported acyclic precursor to 3-oxidopyrylium ions.

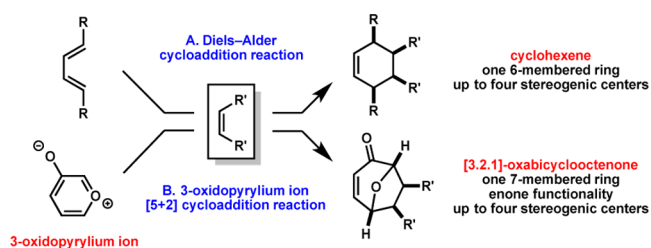
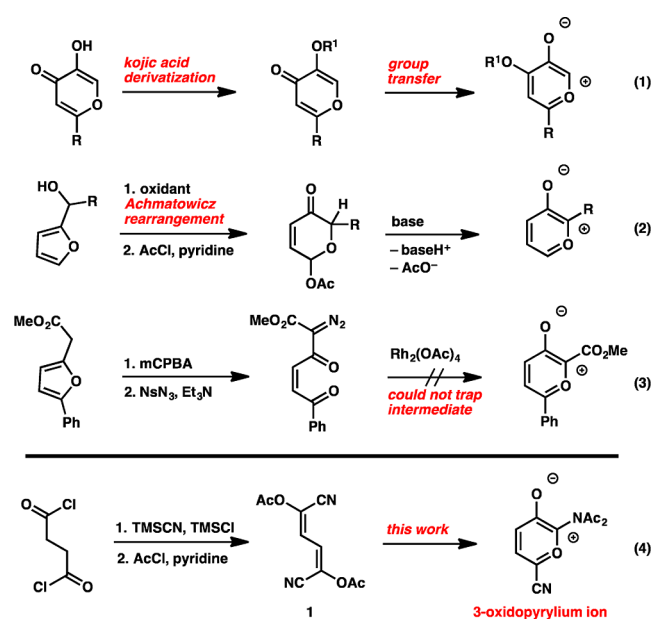


Figure 1. [4 + 2] atom and [5 + 2] atom cycloaddition reactions with alkenes and their resulting cycloadducts.

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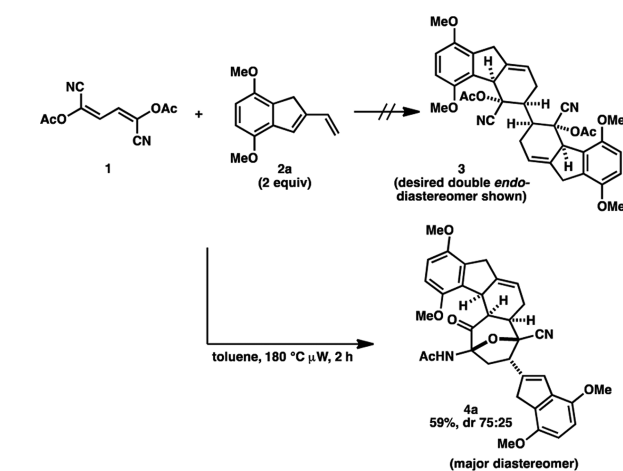
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Scheme 1. Tactics for Generating 3-Oxidopyrylium Ion Intermediates



RESULTS AND DISCUSSION

Bis(1-cyanovinyl acetate) (**1**) was first synthesized in 1992 by Oku and co-workers and was studied in the context of photochemical [2 + 2] and olefin isomerization reactions.¹¹ Since that time, diene **1** has wallowed in relative obscurity. We initially posited that **1** could serve as a masked bisketene equivalent and might undergo a double Diels–Alder cycloaddition reaction with dienes such as vinylindene **2a**¹² (Scheme 2) to give symmetrical tetrahydrofluorene dimers (e.g., **3**).^{13,14}

Scheme 2. Unexpected [5 + 2]/[4 + 2] Domino Cycloaddition Reaction between Diene **1** and Vinylindene **2a**

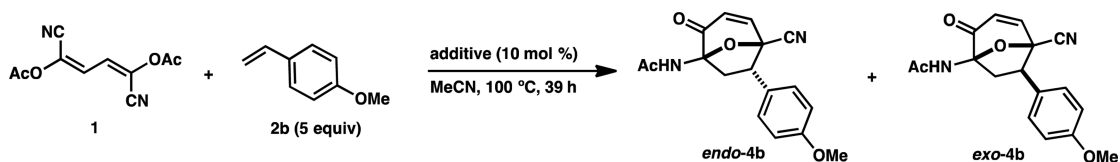
However, upon heating diene **1** with vinylindene **2a**, we found, much to our surprise, that diene **1** instead undergoes rearrangement and cycloaddition reactions (with 2 equiv of **2a**) to give a diastereomeric mixture of a bis-adduct (the connectivity of which was confirmed by X-ray crystallographic analysis of the major diastereomer, **4a**) (see the Supporting Information for details).^{15,16}

On the basis of this observation, we set out to extend this cycloaddition reaction to other dipolarophiles. We quickly identified electron-rich styrenes such as 4-methoxystyrene (4-vinylanisole; **2b**) as the most competent type of dipolarophile. Using **2b** as a model dipolarophile, we surveyed conditions to increase the yield of the corresponding [5 + 2] cycloadduct **4b** (Table 1). Heating diene **1** and **2b** (1 equiv) in toluene at 180 °C (microwave heating) gave a low yield (7% isolated) of adduct **4b**. Partly, this low yield might be attributed to the fact that **1** is only sparingly soluble in toluene (and also in 1,4-dioxane), leading to intractable polymeric tars during the course of the reaction. Using other solvents in which **1** was more soluble (e.g., acetonitrile), resulted in an increase in the isolated yield of adduct **4b** to 30% (Table 1, entry 1) with prolonged heating at lower temperatures (100 °C). Upon investigating the effect of different additives on the efficiency of the reaction, we found that the addition of acids or bases (5–10 mol %) significantly affects the efficiency of the overall process (entries 2–9).

Given that the [5 + 2] cycloadduct (e.g., **4b**) lacks one of the acetyl groups present in **1** and that the N atom in **4b** is acetylated, we tested whether carbophilic amine bases that might facilitate acyl transfers would result in higher yields (Table 1, entries 1–5). While the addition of pyridine (10 mol %) boosted the yield significantly (to 60%; Table 1, entry 2), surprisingly, the addition of 10 mol % of either 4-dimethylaminopyridine (DMAP) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), which are well-recognized “carbon bases”,¹⁷ led to diminished yields (Table 1, entries 3 and 4), whereas K₂CO₃ resulted in only nonspecific decomposition of **1**.^{18,19} From this survey of exogenous base and acid additives, pyridinium *p*-toluenesulfonate (PPTS) proved to give the highest yields (Table 1, entries 8 and 9), so these conditions have been adopted for exploring the scope of the cycloaddition process. In general, a mixture of the *endo*- and *exo*- adducts is obtained, which was easily separated to facilitate unambiguous proof of structure by X-ray crystallographic analysis (see Supporting Information). The cycloaddition reactions are readily scaled up with only a slight reduction in isolated yield. For example, *endo*-**4b** and *exo*-**4b** are formed in a combined 64% yield on 3 mmol scale.

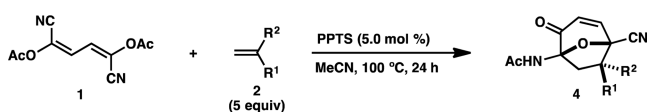
We have found that the 3-oxidopyrylium ion intermediate generated from compound **1** can be trapped with a variety of styrenes in modest to good yields (Table 2). The efficiency of the cycloaddition reaction was good using various styrene partners (see **4b**–**4h** in Table 2). Tetra-substituted centers can be generated as demonstrated by the cycloaddition with α -methylstyrene **2i** (see **4i**). Nonstyryl dipolarophiles such as electron-rich phenyl vinyl sulfide **2j** and benzyl vinyl ether **2k** also undergo cycloaddition, but proceed to give moderate isolated yields (see **4j** and **4k**). Disubstituted alkenes, albeit more strained (e.g., norbornene **2l**), are also competent dienophiles and provide the cycloadduct **4l** in good yield and excellent diastereoselectivity. Finally, compound **1** also reacts with 1-(*p*-toluenesulfonyl)-3-vinyl-indole (**2m**) to give adduct **4m** (51% isolated yield) in an aza-variant of the initial discovery described in Scheme 2. The structure of **4m** is supported by X-ray crystallographic analysis (see Supporting Information). Collectively, access to **4a** and **4m** demonstrate that additional cycloaddition reactions are possible from the [5 + 2] dipolar cycloadducts.

This newly discovered cycloaddition reaction is not without limitations. For example, thus far, attempted cycloaddition

Table 1. Optimization of Reaction Conditions with 4-Vinylanisole (2b)^a

| entry | additive | yield (%) ^b | dr (endo:exo) |
|-------|--------------------------------|------------------------|---------------|
| 1 | none | 30 | 87:13 |
| 2 | pyridine | 60 | 81:19 |
| 3 | DMAP | 28 | 86:14 |
| 4 | DBN | 43 | 84:16 |
| 5 | K ₂ CO ₃ | 0 | — |
| 6 | AcOH | 40 | 85:15 |
| 7 | PyHCl | 73 | 81:19 |
| 8 | PPTS | 83 | 74:26 |
| 9 | PPTS ^c | 83 | 74:26 |

^aBis(1-cyanovinyl acetate) (1) (0.10 mmol), 4-vinylanisole (2b) (0.50 mmol), additive (10 μmol), and MeCN (1 mL). See Supporting Information for details. ^bIsolated yields. ^c5.0 mol %. DMAP = *N,N*-dimethyl-4-aminopyridine, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, PPTS = pyridinium *p*-toluenesulfonate.

Table 2. Substrate Scope for [5 + 2] Cycloaddition Reaction with Various Dipolarophiles^a

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R = 2j SPh
2k OBn

4j 60%, dr > 95:5
4k 43%, dr > 95:5^d

4i 50%, dr > 95:5

4l 50%, dr > 95:5

4m 51%, dr > 95:5^{e,f}

4b 80%, dr 78:22
4c 64%, dr 73:27
4d 72%, dr 74:26
4e 65%, dr 72:28
4f 70%, dr 78:22
4g 66%, dr 71:29
4h 62%, dr 61:39

4i 63%, dr 83:17^{b,c}

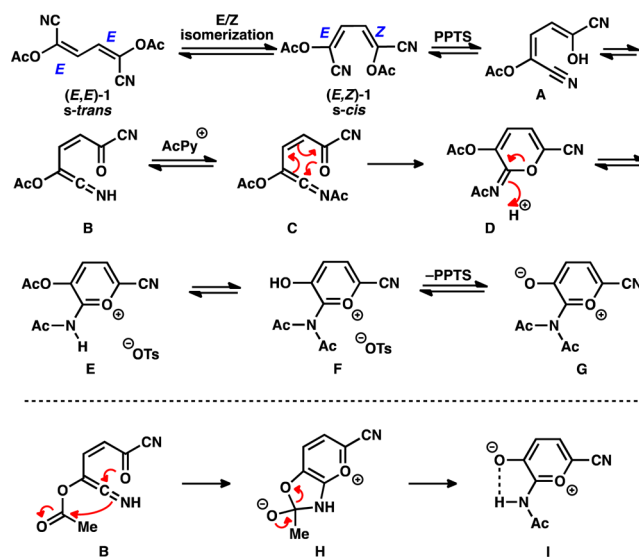
^aBis(1-cyanovinyl acetate) (1) (0.10 mmol), dipolarophile (0.50 mmol), PPTS (5.0 μmol), and MeCN (1 mL). See Supporting Information for details. ^b¹H NMR yield. 1,1,2,2-Tetrachloroethane was used as an internal standard. ^cBis(1-cyanovinyl acetate) (1) and α -methylstyrene 2i were stirred in *i*-butylmethylketone without PPTS. ^dBis(1-cyanovinyl acetate) (1) and benzyl vinyl ether 2k were stirred in THF without PPTS. ^eSecond step: Crude products were stirred with TsOH·H₂O in CH₂Cl₂ at 40 °C. ^f2 steps overall yield.

reactions with dipolarophiles such as maleic anhydride, 2-vinylnaphthalene, 4-phenylstyrene, stilbene, diphenylacetylene (Tolane), *N*-vinylphthalimide, and vinylcyclohexane have resulted in nonspecific decomposition of diene 1 upon prolonged heating. These observations may be rationalized by the steric encumbrance associated with cycloaddition to the 3-oxidopyrylium ion intermediate as well as its electron-poor

nature, and possibly suggests a stepwise [5 + 2] cycloaddition reaction. The apparent electrophilicity of the intermediate 3-oxidopyrylium ion is unusual and is likely imparted by the pendant cyano group. Other dipoles of this type not bearing cyano groups are known to undergo cycloaddition reactions with both electron-rich and electron-poor dipolarophiles.⁵

Our tentative hypothesis regarding a mechanism for the generation of the 3-oxidopyrylium ion intermediate is outlined in Scheme 3. Diene (*E,E*)-1 likely undergoes a thermally

Scheme 3. Possible Mechanism for Formation of 3-Oxidopyrylium Ion from Diene 1

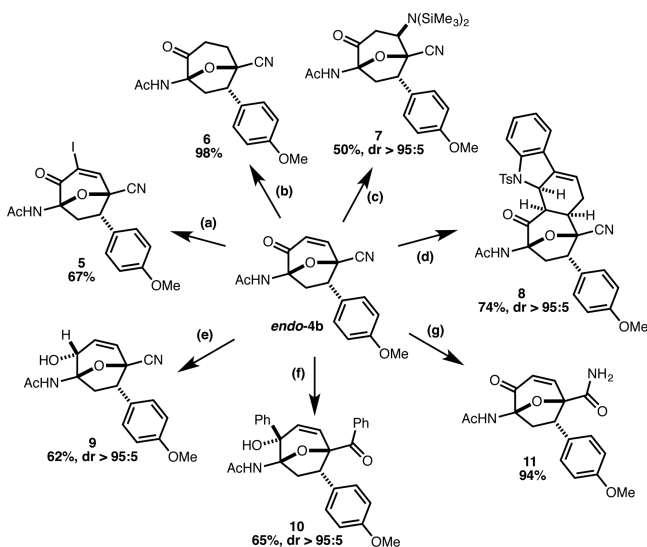


promoted *E*- to *Z*- isomerization to give diene (*E,Z*)-1 in line with the precedent of Oku and co-workers.¹¹ At this stage, a carbophilic base, which could either be acetonitrile (the solvent), the nitrile groups of 1, or pyridine (from the PPTS additive), mediates deacylation to give enol A that is in equilibrium with ketenimine-like tautomer B. A net acyl transfer to the N atom will give acyl ketenimine C, which may undergo formal 6 π -electrocyclic ring closure to provide oxidopyrylium ion precursor D. Another acyl transfer (via E)

would yield the reactive 3-oxidopyrylium ion (**G**), which undergoes [5 + 2] cycloaddition with dipolarophiles to afford cycloadducts. Alternatively, intermediate **B** could be transformed to bicyclic intermediate **H** through the formation of a C–N bond. Ring-opening of the five-membered ring would transfer the acyl group from oxygen onto nitrogen with the generation of oxidopyrylium ion **I**. At this stage, there is no direct proof to support either proposed reaction mechanism.

In a preliminary study, we have shown that the cycloadducts can be further elaborated to generate products of even higher molecular complexity. For example (Scheme 4), *endo*-**4b**

Scheme 4. Derivatization of [5 + 2]-Cycloaddition Adduct *endo*-4b**^a**



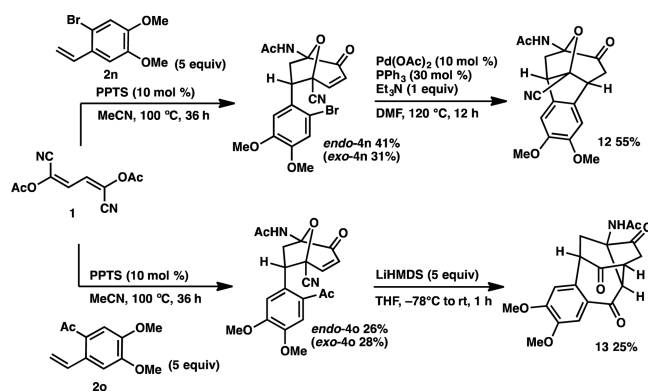
^a(a) I₂, pyridine, DCM. (b) Pd/C, H₂, THF. (c) LiHMDS, THF. (d) **2m**, MeCN, 100 °C. (e) Et₃SiH, TiCl₄, DCM. (f) PhMgBr, THF. (g) RhCl(PPh₃)₃, acetaldoxime, toluene. DCM = 1,1-dichloromethane, THF = tetrahydrofuran. See the Supporting Information for details.

undergoes Johnson iodination of the enone moiety to provide iodide **5** (67% isolated yield) in preparation for various cross-coupling reactions.²⁰ The enone double bond may also be simply removed under hydrogenation conditions (see **6**). Of note, compound **6** is formally a carbonyl ylide cycloadduct. Adduct *endo*-**4b** can also be utilized in conjugate additions (see **7**) or Diels–Alder cycloaddition reactions (see **8**). Furthermore, *endo*-**4b** undergoes highly chemo- and diastereoselective ionic reduction of the enone carbonyl group (Et₃SiH, TiCl₄) to afford allylic alcohol **9**, which may be employed in a variety of hydroxyl-directed transformations.²¹ The bridgehead cyano group of *endo*-**4b** can also be manipulated. For example, the addition of excess phenyl magnesium bromide to *endo*-**4b** yields phenyl ketone **10** whereas hydration of the nitrile group gives carboxamide **11**.²²

The rapid generation of molecular complexity afforded by these novel oxidopyrylium cycloadducts is further powerfully illustrated by the cycloadditions of styrene derivatives **2n** and **2o** to give **4n** and **4o**, respectively (Scheme 5). Subsequent intramolecular Heck and conjugate addition reactions of the *endo* adducts **4n** and **4o** into the enone moiety yields multicyclic scaffolds **12** and **13**, respectively.

In conclusion, we report the generation of a novel 3-oxidopyrylium ion intermediate (**G**) from bis(1-cyanovinyl acetate) (**1**). To our knowledge, this work represents the first

Scheme 5. Synthetic Sequences to Access Multicyclic Scaffolds



reported generation of 3-oxidopyrylium ions from a noncyclic (i.e., linear) precursor. We have demonstrated that the dipole thus generated undergoes cycloaddition reactions with various styryl dipolarophiles to give [3.1.0]-oxabicyclooctenes, which can themselves be further functionalized. In addition, a vinyl sulfide and a vinyl ether also serve as cycloaddition partners. Studies aimed at elucidating the mechanism of this unusual transformation that will shed light on the acyl transfer events, as well as the fate of the acetyl group that is lost from the final product are underway. We are also investigating the possibility of enantioselective versions of this transformation and applications to the total synthesis of natural products.

EXPERIMENTAL SECTION

General Information. All reactions were run in flame-dried round-bottomed flasks, vials, or Schlenk flasks under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography on glass-backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV irradiation and *p*-anisaldehyde (PAA), cerium molybdate (CeMo), 2,4-dinitrophenyl hydrazine (DNP), KMnO₄, or iodine (I₂) stain respectively, and the TLC visualization stains were prepared using standard procedures.²³ Dry acetonitrile (MeCN), toluene, benzene, tetrahydrofuran (THF), and methanol (MeOH) were obtained by passing these previously degassed solvents through activated alumina columns. Dichloromethane (DCM) was distilled over calcium hydride before use. Volatile solvents were removed under reduced pressure on a rotary evaporator. All flash chromatography was conducted using standard grade silica gel 60 Å, 230 × 400 mesh (40–63 μm). ¹H NMR and ¹³C NMR spectra were collected using 400, 500, and 600 MHz (100, 125, and 150 MHz for ¹³C NMR) spectrometers in CDCl₃, C₆D₆, or CD₃CN as noted. Chemical shifts were measured relative to the shift of the residual solvent (¹H NMR, CDCl₃ δ = 7.26, C₆D₆ δ = 7.16 ppm; ¹³C NMR, CDCl₃ δ = 77.2, C₆D₆ δ = 128.1 ppm, CD₃CN δ = 1.32 ppm). ¹H NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Splitting is reported with the following symbols: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, sept = septet, m = multiplet. FTIR spectra were measured using the ATR method. Spectra are reported in frequency of absorption in cm⁻¹, and only selected resonances are reported. High-resolution mass spectral data were obtained using electrospray (ESI) or electron impact (EI) ionization and using linear ion trap analyzer. Microwave-assisted reactions were performed using a Biotage Initiator 2.5 reactor on low absorbance irradiation setting with the fix-hold-time feature set to off.

(1*E*,3*E*)-1,4-Dicyanonbuta-1,3-diene-1,4-diyl diacetate (**1**) was synthesized according to literature procedures with slight modifications as described below and will be referred to as bis(1-cyanovinyl acetate).¹¹ 1-(toluene-4-sulfonyl)-3-vinyl-1*H*-indole **2m** was synthesized according to a literature procedure.²⁴ 2-Vinyl-1*H*-indene **2a**,¹² 4-

isopropylstyrene **2e**, 4-trifluoromethylstyrene **2h**, benzyl vinyl ether **2k**, 2-bromo-4,5-dimethoxystyrene **2n**, and 2-acetoxy-4,5-dibromostyrene **2o** were synthesized as described below. All other commercially available reagents were used as purchased (i.e., with stabilizers).

Modification of the Procedure to Synthesize Bis(1-cyanovinyl acetate) (1). To a flamed-dried round-bottomed flask containing a Teflon-coated stir bar and fitted with a rubber septum was added succinyl chloride (1.9 mL, 17.3 mmol, 1.0 equiv) under a positive pressure of nitrogen. Trimethylsilyl cyanide (5.2 mL, 41.6 mmol, 2.4 equiv), and trimethylsilyl chloride (270 μ L, 2.1 mmol, 0.12 equiv) were added, and the colorless homogeneous solution was stirred for 3 days at room temperature. At this time, the byproduct trimethylsilyl chloride was removed from the vessel under a slight vacuum using a Welch pump (model 2025) (~600–650 mmHg at room temperature) to give crude succinyl cyanide as a brown low melting solid, which was used immediately without further purification. To a stirred solution of the crude succinyl cyanide and acetyl chloride (3.6 mL, 50.4 mmol, 2.9 equiv) in benzene (100 mL) was added a solution of pyridine (4.1 mL, 49.6 mmol, 2.8 equiv) in benzene (120 mL) by cannula (over ~3 min). The solution turned purple and heterogeneous over time. After 1 h, the heterogeneous mixture was diluted by water, extracted with ethyl acetate ($\times 3$), washed with water and brine, dried with MgSO_4 , and evaporated to give a dark red solid containing traces of pyridine hydrochloride. SiO_2 -gel column chromatography (3:1 hexanes:ethyl acetate) gave a yellow solid which was rinsed with diethyl ether (10 mL $\times 2$) to give the desired product as a yellow solid (1.68 g, 7.6 mmol, 44%). The purified material has a melting point range of 168–171 $^\circ\text{C}$, which matches the reported literature value (165–170 $^\circ\text{C}$). Notes: The Oku procedure¹¹ (synthesis of compound **1** in their report) states that 9.06 g (6.66 mmol) of the diacid cyanide was used. For the diacid cyanide, 9.06 g actually corresponds to 66.6 mmol of substrate and not 6.66 mmol. Using 6.66 mmol, the concentration of the reaction is 0.07 M (which we used to prepare the title compound). The concentration (assuming Oku and co-workers used 9.06 g of the dicyanide) would be 0.70 M in the initial report for the preparation of compound **1**.

Synthesis of Indene 2a.¹² To a flame-dried round-bottomed flask containing a Teflon-coated stir bar and fitted with a rubber septum was added solid 2,5-dimethoxy benzaldehyde (5.00 g, 30.0 mmol, 1 equiv). The flask was evacuated and backfilled with nitrogen gas ($\times 3$). THF (300 mL) was added, and the homogeneous solution was cooled to 0 $^\circ\text{C}$. Ethynylmagnesium bromide (0.5 M in THF) (66.3 mL, 33.2 mmol, 1.1 equiv) was added dropwise over 5 min, and the solution was stirred at 0 $^\circ\text{C}$ for 1 h after which pivaloyl chloride (7.40 g, 60.1 mmol, 2.0 equiv) was added. The solution was then heated to 50 $^\circ\text{C}$ with stirring and held at this temperature for 1 h. The resulting solution was cooled to room temperature, diluted with diethyl ether (600 mL), and quenched with saturated aqueous NaHCO_3 (300 mL). The biphasic mixture was then shaken and the aqueous layer separated. The aqueous layer was extracted with diethyl ether (300 mL $\times 3$). The combined organic layers were washed with brine (300 mL $\times 3$), dried over Na_2SO_4 , concentrated, and purified by SiO_2 -gel chromatography (5:1 hexanes:diethyl ether) to afford the propargylic ester **S1**; $R_f = 0.53$ (2:1 hexanes:ethyl acetate); The product stains black with PAA; The product is isolated as a viscous yellow oil; Isolated yield 8.2 g, 99%; ^1H NMR (600 MHz, CDCl_3) δ 7.22 (s, 1H), 6.86 (dd, $J = 8.9, 3.1$ Hz, 1H), 6.82 (d, $J = 8.9$ Hz, 1H), 6.70 (d, $J = 2.2$ Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.56 (s, 1H), 1.22 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.0, 153.7, 151.0, 126.2, 114.8, 114.4, 112.1, 80.6, 74.5, 60.3, 56.3, 55.9, 38.9, 27.2; IR (ATIR) 3284, 2971, 2936, 2909, 2874, 2836, 1732 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$)⁺ m/z 299.1254 found 299.1253.

To a flame-dried Schlenk flask equipped with a Teflon-coated stir bar was added the propargylic ester **S1** (2.76 g, 10.0 mmol, 1 equiv) from the previous step. The flask was then brought into a glovebox and di- μ -chloro-dichlorobis(ethylene)-diplatinum(II) (Zeise's dimer) (294 mg, 0.50 mmol, 5 mol %) was added. The sealed flask was then brought outside of the glovebox and toluene (100 mL) was added followed by *trans*-4-octene (448 mg, 4.0 mmol, 0.4 equiv) under nitrogen atmosphere. The flask was resealed, heated to 100 $^\circ\text{C}$, and

held at this temperature for 1 h. The flask was then immediately cooled in a room temperature water bath. The solution was concentrated under reduced pressure, and the residue was purified by SiO_2 -gel chromatography (7:1 hexanes:ethyl acetate) to give the 2-indenylpivalate **S2**; $R_f = 0.35$ (10:1 hexanes:ethyl acetate); The product stains blue green with PAA; The product is isolated as a yellow solid; Isolated yield 2.07 g, 75%; ^1H NMR (500 MHz, CDCl_3) δ 6.73 (d, $J = 8.8$ Hz, 1H), 6.67 (s, 1H), 6.63 (d, $J = 8.8$ Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.53 (s, 2H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.0, 155.3, 149.7, 148.0, 133.1, 125.8, 111.4, 110.3, 107.5, 56.4, 55.8, 39.4, 36.0, 27.2; IR (ATIR) 2976, 2941, 2908, 2973, 2835, 1741, 1495 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ (M)⁺ m/z 276.1362 found 276.1366.

To a 500 mL round-bottomed flask equipped with a Teflon-coated stir bar were added the 2-indenylpivalate **S2** (2.41 g, 8.7 mmol, 1 equiv) from the previous step and potassium hydroxide (980 mg, 17.5 mmol, 2 equiv). MeOH (60 mL) was added, and the solution was stirred at room temperature for 2 h. The solution was then diluted with water (50 mL) and 1N aqueous HCl (50 mL). The reaction mixture was extracted with dichloromethane (100 mL $\times 3$), washed with water (50 mL) and brine (50 mL), dried over MgSO_4 , and concentrated to give the crude 2-indanone, which was transferred to a flame-dried 250 mL round-bottomed flask with a Teflon-coated stir bar. The flask was evacuated and backfilled with nitrogen gas ($\times 3$). THF (50 mL) was added, and the solution was cooled to 0 $^\circ\text{C}$. To the cooled solution was slowly added *t*-BuOK (10.6 mL, 1.0 M in THF) and the solution was allowed to stir at 0 $^\circ\text{C}$ for 1 h. Solid Comin's reagent²⁵ (4.10 g, 10.4 mmol, 1.2 equiv) was then added all at once at 0 $^\circ\text{C}$ by quickly removing and replacing the fitted septa. The homogeneous solution was then allowed to stir for 1 h at room temperature. The resulting solution was then diluted with water (20 mL) and ethyl acetate (20 mL), transferred to a separatory funnel and shaken. The aqueous layer was then removed, and the organic layer was washed with 1 N aqueous NaOH (10 mL) and brine (20 mL). The organic layers were dried over MgSO_4 , filtered, concentrated, and purified by SiO_2 -gel chromatography (7:1 hexanes:dichloromethane) to give the desired indenyl-2-triflate **S3**; $R_f = 0.25$ (4:1 hexanes:dichloromethane); The product is isolated as yellow oil; Isolated yield 752 mg, 27% (over two steps); ^1H NMR (500 MHz, CDCl_3) δ 6.80 (s, 1H), 6.77 (d, $J = 9.1$ Hz, 1H), 6.73 (d, $J = 8.7$ Hz, 1H), 3.84 (m, 6H), 3.62 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.1, 149.4, 148.4, 130.0, 125.9, 118.8 (q, $J_{\text{C-F}} = 319.6$ Hz), 116.6, 110.2, 109.2, 56.1, 55.8, 36.0; IR (ATIR) 3005, 2946, 2910, 2838, 1498, 1423, 1204 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{11}\text{O}_5\text{F}_3\text{S}$ (M)⁺ m/z 324.0279 found 324.0285.

To a flame-dried 100 mL round-bottomed flask equipped with a Teflon-coated stir bar was added Pd(PPh_3)₄ (76.2 mg, 66.0 μ mol, 3 mol %) inside a glovebox. The sealed flask was then brought outside of the glovebox and the indenyl-2-triflate **S3** (709 mg, 2.2 mmol, 1 equiv) from the previous step was added as a solution in dimethoxyethane (22 mL). The solution was stirred at room temperature for 20 min. At that time, a solution of K_2CO_3 (608 mg, 4.4 mmol, 2 equiv) and vinylboroxine pyridine complex²⁶ (263 mg, 1.1 mmol, 0.5 equiv) in water (7 mL) was injected into the reaction mixture. The solution was then heated to 100 $^\circ\text{C}$ and stirred at that temperature for 14 h. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (20 mL $\times 3$). The organic layers were washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , concentrated, and purified by SiO_2 -gel chromatography (100:1 hexanes:ethyl acetate) to give 2-vinyl-1H-indene **2a**; $R_f = 0.24$ (100:1 hexanes:ethyl acetate); The product is isolated as a yellow amorphous solid; Isolated yield 318 mg, 71%; ^1H NMR (500 MHz, CDCl_3) δ 6.83 (s, 1H), 6.74 (dd, $J = 17.3, 10.6$ Hz, 1H), 6.71 (d, $J = 8.5$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.42 (d, $J = 17.5$ Hz, 1H), 5.15 (d, $J = 10.6$ Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.51 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.9, 148.1, 145.7, 135.3, 133.2, 131.3, 127.1, 114.5, 109.8, 108.4, 56.2, 55.8, 35.1; IR (ATIR) 3085, 3047, 2997, 2939, 2903, 2831, 1796, 1618, 1491, 1251 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$ (M)⁺ m/z 202.0994 found 202.0998.

General Procedure for the Synthesis of 4-Isopropyl Styrene 2e and 4-Trifluoromethylstyrene 2h. To a flame-dried round-bottomed flask equipped with a Teflon-coated stir bar were added methyltriphenylphosphonium iodide (1.3 equiv) and THF (13 mL/mmole). *t*-BuOK (1.9 equiv) was added in one portion at 0 °C under nitrogen atmosphere, and the resulting yellow solution was stirred at room temperature for 1 h. The corresponding aldehyde (1 equiv) was added dropwise to the solution. After the aldehyde was consumed, the solution was filtered over a 2.54 cm pad of Celite and the residue was washed with diethyl ether. The filtrate was concentrated and purified by SiO₂-gel chromatography (hexanes only) to give the desired styrene; Spectroscopic data for these compounds were identical to that previously reported.^{27,28}

4-Isopropyl Styrene 2e. $R_f = 0.57$ (hexanes only); The product is isolated as colorless oil; The product stains purple with PAA; Isolated yield 1.13 g, 64%; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, $J = 7.9$ Hz, 2H), 7.20 (d, $J = 7.9$ Hz, 2H), 6.71 (dd, $J = 17.7, 10.9$ Hz, 1H), 5.72 (d, $J = 17.6$ Hz, 1H), 5.20 (d, $J = 10.8$ Hz, 1H), 2.91 (sept, $J = 6.5$ Hz, 1H), 1.26 (d, $J = 7.0$ Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 148.8, 136.8, 135.4, 126.7, 126.3, 113.0, 34.0, 24.1; IR (ATR) 2959, 1612, 1511, 1407, 988, 900, 836 cm⁻¹; HRMS (EI) calcd for C₁₁H₁₄ (M)⁺ m/z 146.1096 found 146.1095.

4-Trifluoromethylstyrene 2h. $R_f = 0.62$ (hexanes only); The product is isolated as colorless oil; The product stains yellow with KMnO₄; Isolated yield 861 mg, 33%; ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, $J = 8.1$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 6.75 (dd, $J = 17.7, 10.9$ Hz, 1H), 5.85 (d, $J = 17.6$ Hz, 1H), 5.39 (d, $J = 10.9$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 141.1, 135.8, 129.8 (q, $J_{C-F} = 32.3$ Hz), 126.5, 125.5 (q, $J_{C-F} = 37.5$ Hz), 124.4 (q, $J_{C-F} = 270.4$ Hz), 116.6; IR (ATR) 3095, 1618, 1321, 1164, 1111, 1066, 844 cm⁻¹; HRMS (EI) calcd for C₉H₇F₃ (M)⁺ m/z 172.0500 found 172.0499.

Synthesis of Benzyl Vinyl Ether 2k. To a flame-dried 50 mL round-bottomed flask equipped with a Teflon-coated stir bar were added *t*-BuOK (616 mg, 5.5 mmol, 2.4 equiv) and THF (3 mL) under a nitrogen atmosphere. The solution of 1-(benzyloxy)-2-bromoethane (485 mg, 2.25 mmol, 1 equiv) in THF (2 mL) was added dropwise at 0 °C. The solution was stirred at room temperature for 2 h. At that time, the reaction mixture was diluted with water (5 mL), extracted with diethyl ether (10 mL \times 3), washed with brine (5 mL), dried over Na₂SO₄, and concentrated to afford the crude product, which was purified by SiO₂-gel column chromatography (hexanes only) to give the benzyl vinyl ether 2k (210 mg, 1.57 mmol, 70%); $R_f = 0.23$ (100% hexanes); The product is isolated as a colorless oil; The product stains black with CeMo; ¹H NMR (500 MHz, CDCl₃) δ 7.42–7.30 (m, 5H), 6.58 (dd, $J = 14.4, 6.8$ Hz, 1H), 4.77 (s, 2H), 4.32 (dd, $J = 14.4, 2.3$ Hz, 1H), 4.10 (dd, $J = 6.9, 2.3$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 151.8, 137.0, 128.7, 128.1, 127.7, 87.5, 70.2; IR (ATR) 3034, 2868, 1614, 1319, 1194, 815, 734, 695 cm⁻¹; HRMS (EI) calcd for C₉H₁₀O (M)⁺ m/z 134.0732 found 134.0730. Spectroscopic data for this compound were identical to that previously reported.²⁹

Synthesis of 2-Bromo-4,5-dimethoxystyrene 2n. To a 200 mL flame-dried round-bottomed flask equipped with a Teflon-coated stir bar were added methyltriphenylphosphonium iodide (9.70 g, 24.0 mmol, 1.2 equiv) and THF (100 mL). *t*-BuOK (2.80 g, 25.0 mmol, 1.3 equiv) was added in one portion at 0 °C under a nitrogen atmosphere, and the resulting solution was stirred at 0 °C for 20 min. A solution of 6-bromoveratraldehyde³⁰ (4.90 g, 20.0 mmol, 1 equiv) in THF (30 mL) was added slowly to the solution, and warmed to room temperature. After stirring for 30 min, the solution was filtered over a pad of Celite and the residue was washed with diethyl ether (20 mL). The filtrate was concentrated and purified by SiO₂-gel chromatography (10:1 hexanes:ethyl acetate) to give 2-bromo-4,5-dimethoxystyrene 2n; $R_f = 0.21$ (10:1 hexanes:ethyl acetate); The product is isolated as an off-white solid; The product stains purple with PAA; Isolated yield 2.70 g, 56%; ¹H NMR (600 MHz, CDCl₃) δ 7.05 (s, 1H), 7.01 (s, 1H), 6.98 (dd, $J = 17.4, 11.0$ Hz, 1H), 5.59 (dd, $J = 17.4, 0.9$ Hz, 1H), 5.28 (dd, $J = 10.9, 0.8$ Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.5, 148.7, 135.6, 129.6, 115.3, 114.7, 114.4, 108.8, 56.3, 56.1; IR (ATR) 2998, 2934, 2906, 2837, 1498, 1255,

1207, 1160, 1024, 851, 793 cm⁻¹; HRMS (EI) calcd for C₁₀H₁₁O₂⁷⁹Br (M)⁺ m/z 241.9942 found 241.9945.

Synthesis of 2-Acetoxy-4,5-dimethoxystyrene 2o. To a flame-dried 200 mL round-bottomed flask equipped with a Teflon-coated stir bar were added 1-(2-bromo-4,5-dimethoxyphenyl)ethanone³¹ (2.59 g, 10.0 mmol, 1 equiv), Pd(PPh₃)₄ (578 mg, 0.50 mmol, 5 mol %), and DME (60 mL). This solution was stirred at room temperature for 20 min under a nitrogen atmosphere. To this reaction mixture, a solution of vinylboroxine pyridine complex²⁶ (900 mg, 3.7 mmol, 0.40 equiv) and K₂CO₃ (1.38 g, 10.0 mmol, 1 equiv) in water (20 mL) was injected, and the flask was warmed to 80 °C. This solution was stirred for 11 h at that temperature. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (20 mL \times 3). The organic layers were washed with water (20 mL) and brine (20 mL), dried over MgSO₄, concentrated, and purified by SiO₂-gel chromatography (5:1 hexanes:ethyl acetate) to give 2-acetoxy-4,5-dimethoxystyrene 2o; $R_f = 0.10$ (5:1 hexanes:ethyl acetate); The product is isolated as an off-white solid; Isolated yield 1.72 g, 83%; ¹H NMR (600 MHz, CDCl₃) δ 7.24 (dd, $J = 17.3, 10.9$ Hz, 1H), 7.17 (s, 1H), 7.00 (s, 1H), 5.55 (dd, $J = 17.3, 1.2$ Hz, 1H), 5.31 (dd, $J = 10.9, 1.1$ Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 2.56 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 200.2, 151.9, 148.2, 136.4, 132.9, 130.0, 115.6, 112.1, 110.1, 56.3, 56.1, 30.0; IR (ATR) 2965, 2943, 2852, 1662, 1510, 1335, 1266, 1202, 1187, 1147, 922, 875 cm⁻¹; HRMS (EI) calcd for C₁₂H₁₄O₃ (M)⁺ m/z 206.0943 found 206.0935.

Procedure for Intermolecular [5 + 2] Cycloaddition Reaction with Indene 2a. To a flame-dried 0.2–0.5 mL Biotage microwave vial were added bis(1-cyanovinyl acetate) (1) (11.0 mg, 0.050 mmol, 1 equiv) and indene 2a (20.2 mg, 0.10 mmol, 2 equiv). The vial was sealed, evacuated and backfilled with nitrogen gas (\times 3). Toluene (1.0 mL) was added, and the heterogeneous solution was heated to 180 °C in the microwave and held at this temperature for 2 h. The resulting solution was concentrated and purified by SiO₂-gel chromatography (50:3 hexanes:ethyl acetate to 100% ethyl acetate) to afford a diastereomeric mixture of adduct 4a; Isolated yield 17.3 mg, 59% (dr 75:25); $R_f = 0.56$ (1:2 hexanes:ethyl acetate); The product stains purple with DNP; Spectral data reported *endo*-4a ¹H NMR (600 MHz, CDCl₃) δ 7.17 (s, 1H), 6.79–6.76 (m, 2H), 6.71 (d, $J = 8.6$ Hz, 1H), 6.65 (d, $J = 8.6$ Hz, 1H), 6.62 (d, $J = 8.7$ Hz, 1H), 5.57 (s, 1H), 4.55 (dd, $J = 5.6, 5.6$ Hz, 1H), 4.43 (dd, $J = 12.0, 7.1$ Hz, 1H), 3.87 (s, 3H), 3.86–3.76 (m, 11H), 3.65–3.49 (m, 4H), 2.81 (dd, $J = 15.1, 8.2$ Hz, 1H), 2.65–2.56 (m, 1H), 2.52–2.44 (m, 1H), 2.39 (dd, $J = 13.3$ Hz, 7.1 Hz, 1H), 1.97 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 199.5, 170.0, 150.6, 150.3, 150.0, 147.9, 141.2, 139.6, 133.9, 132.0, 131.9, 130.8, 126.5, 117.6, 117.1, 109.8, 109.0, 108.8, 108.4, 91.5, 79.2, 56.0, 55.8, 55.7, 55.6, 49.4, 45.1, 43.6, 40.9, 39.8, 35.0, 32.1, 25.7, 24.5; IR (ATR) 3375, 2951, 2912, 2852, 1743, 1696, 1495, 1461, 1254 cm⁻¹;³² HRMS (ESI) calcd for C₃₄H₃₅O₇N₂ (M + H)⁺ 583.2439 found 583.2440; Melting point of the amorphous solid is 237–241 °C; X-ray quality crystal of the *endo*- adduct were obtained as follows: Ethanol was added to the diastereomeric mixture to precipitate the product, and the mixture was heated to the point of reflux and allowed to slowly cool to room temperature to give a white powder. The resulting powder was then filtered over glass wool, washed with hexanes, and then collected as a solution by washing with DCM to dissolve the solids and concentrated. The resulting solid was then recrystallized by vapor diffusion (hexanes into ethyl acetate).

Experimental Procedure (Table 1). To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (1) (22.0 mg, 0.10 mmol, 1 equiv), 4-methoxystyrene 2b (0.50 mmol, 5 equiv), additive (10 μ mol, 10 mol %), and dry acetonitrile (1 mL). The vial was then capped, the reaction mixture was heated to reflux (100 °C, oil bath temperature) and stirred for 39 h. At this time, the solution was concentrated and purified by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate) to afford the desired cycloaddition products *endo*- and *exo*-4b.

General Procedure for Intermolecular [5 + 2] Cycloaddition Reaction (Table 2). To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (1) (22.0 mg, 0.10 mmol, 1 equiv), the dipolarophile 2 (0.50 mmol, 5 equiv),

PPTS (1.2 mg, 5.0 μmol , 5 mol %), and dry acetonitrile (1 mL). The vial was then capped, the reaction mixture was heated to reflux (100 $^{\circ}\text{C}$, oil bath temperature) and stirred for 24 h. At this time, the solution was concentrated and purified by SiO_2 -gel chromatography to afford the desired cycloaddition products 4.

N-(5-Cyano-6-(4-methoxyphenyl)-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4b**). Purification by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 25.1 mg, 80% (dr 78:22).

endo-diastereomer $R_f = 0.43$ (1:2 hexanes:ethyl acetate); The product stains red with PAA; The product is isolated as an orange amorphous solid; Isolated yield 19.6 mg, 63%; ^1H NMR (600 MHz, C_6D_6) δ 6.75 (d, $J = 10.4$ Hz, 2H), 6.61 (d, $J = 10.5$ Hz, 2H), 6.31 (s, 1H), 5.81 (d, $J = 11.8$ Hz, 1H), 5.57 (d, $J = 11.8$ Hz, 1H), 4.37 (dd, $J = 10.8, 10.8$ Hz, 1H), 3.49 (dd, $J = 16.1, 11.4$ Hz, 1H), 3.26 (s, 3H), 1.73 (dd, $J = 16.0, 10.4$ Hz, 1H), 1.33 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 189.9, 169.2, 160.3, 148.1, 129.7, 127.2, 125.1, 116.4, 114.5, 91.4, 77.4, 54.9, 52.2, 31.5, 23.2; IR (ATIR) 3305, 3054, 2959, 2928, 2840, 1718, 1684, 1515, 1252, 1032 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ (M^{**}) m/z 312.1110 found 312.1111; Melting point of the amorphous solid is 155–158 $^{\circ}\text{C}$; X-ray quality crystals were grown by vapor diffusion of ethyl acetate into hexanes dissolving ~ 4.3 mg of *endo*-**4b** in 0.5 mL ethyl acetate.

exo-diastereomer $R_f = 0.22$ (1:2 hexanes:ethyl acetate); The product stains faint purple/red with PAA; The product is isolated as a yellow amorphous solid; Isolated yield 5.5 mg, 18%; ^1H NMR (600 MHz, CDCl_3) δ 7.63 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 9.8$ Hz, 1H), 6.96 (d, $J = 8.2$ Hz, 2H), 6.76 (s, 1H), 6.24 (d, $J = 9.8$ Hz, 1H), 3.82 (s, 3H), 3.67 (dd, $J = 9.3, 4.0$ Hz, 1H), 3.39 (dd, $J = 14.3, 4.0$ Hz, 1H), 2.41 (dd, $J = 14.2, 9.4$ Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 190.1, 170.0, 159.9, 150.7, 130.8, 129.9, 125.3, 114.8, 114.5, 93.0, 79.1, 55.4, 52.5, 33.9, 24.4; IR (ATIR) 3302, 3040, 2957, 2923, 1717, 1679, 1513, 1251, 1052, 1032 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ (M^{**}) m/z 312.1110 found 312.1111; Melting point of the amorphous solid is 208–212 $^{\circ}\text{C}$; X-ray quality crystals of *exo*-**4b** were grown by slow evaporation from a solution of isopropyl alcohol (~ 10 mg in 500 μL solvent).

N-(5-Cyano-2-oxo-6-phenyl-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4c**). Purification by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 18.1 mg, 64% (dr 73:27).

$R_f = 0.30$ (1:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as a yellow amorphous solid; Isolated yield 13.2 mg, 47%; ^1H NMR (600 MHz, CDCl_3) δ 7.04–6.95 (m, 3H), 6.84–6.79 (m, 2H), 6.32 (s, 1H), 5.70 (d, $J = 9.8$ Hz, 1H), 5.53 (d, $J = 9.8$ Hz, 1H), 4.34 (dd, $J = 9.1, 9.1$ Hz, 1H), 3.46 (dd, $J = 12.8, 10.1$ Hz, 1H), 1.74 (dd, $J = 12.9, 8.7$ Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 190.0, 171.2, 147.5, 134.4, 130.2, 129.8, 129.6, 129.5, 117.4, 93.3, 78.2, 54.0, 34.4, 23.5; IR (ATIR) 3298, 3051, 3033, 1718, 1681, 1526, 1501, 1373, 1274, 1188 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ (M^{**}) m/z 282.1004 found 282.1004.

$R_f = 0.15$ (1:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as an orange amorphous solid; Isolated yield 4.9 mg, 17%; ^1H NMR (500 MHz, CDCl_3) δ 7.70 (d, $J = 7.5$ Hz, 2H), 7.47–7.41 (m, 3H), 7.37 (t, $J = 7.4$ Hz, 1H), 6.75 (s, 1H), 6.27 (d, $J = 9.8$ Hz, 1H), 3.70 (dd, $J = 9.2, 3.8$ Hz, 1H), 3.44 (dd, $J = 14.2, 3.9$ Hz, 1H), 2.44 (dd, $J = 14.1, 9.4$ Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.0, 170.0, 150.6, 138.7, 129.2, 128.8, 128.6, 125.5, 114.7, 93.0, 78.8, 53.1, 34.0, 24.4; IR (ATIR) 3303, 3060, 3034, 2928, 2251, 1717, 1681, 1527, 1371, 1052 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ (M^{**}) m/z 282.1004 found 282.1000.

N-(5-Cyano-2-oxo-6-(*p*-tolyl)-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4d**). Purification by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 21.2 mg, 72% (dr 74:26).

$R_f = 0.22$ (2:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as a yellow amorphous solid; Isolated yield 15.5 mg, 52%; ^1H NMR (600 MHz, CDCl_3) δ 7.21 (d, $J = 7.9$ Hz, 2H), 7.17 (d, $J = 7.9$ Hz, 2H), 6.80 (s, 1H), 6.75 (d, $J = 9.8$ Hz, 1H), 6.34 (d, $J = 9.8$ Hz, 1H), 4.39 (dd, $J = 9.1, 9.1$ Hz, 1H), 3.60

(dd, $J = 13.7, 9.5$ Hz, 1H), 2.35 (s, 3H), 2.23 (dd, $J = 13.6, 8.6$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 189.8, 170.1, 148.3, 138.9, 129.9, 129.8, 128.3, 127.5, 115.8, 91.2, 77.1, 52.4, 31.6, 24.3, 21.2; IR (ATIR) 3373, 2920, 2855, 1720, 1694, 1503, 1252, 1171, 993 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$ (M^{**}) m/z 296.1161 found 296.1165.

$R_f = 0.08$ (2:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as an orange amorphous solid; Isolated yield 5.7 mg, 19%; ^1H NMR (500 MHz, CDCl_3) δ 7.56 (d, $J = 8.6$ Hz, 2H), 7.42 (d, $J = 9.8$ Hz, 1H), 7.24 (d, $J = 7.8$ Hz, 2H), 6.73 (s, 1H), 6.26 (d, $J = 9.8$ Hz, 1H), 3.66 (dd, $J = 9.7, 4.0$ Hz, 1H), 3.36 (dd, $J = 14.2, 4.2$ Hz, 1H), 2.43 (dd, $J = 13.9, 9.1$ Hz, 1H), 2.36 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.1, 170.0, 150.6, 138.5, 135.7, 129.9, 128.5, 125.5, 114.8, 93.0, 79.0, 52.7, 34.2, 24.3, 21.4; IR (ATIR) 3290, 2956, 2922, 2853, 1719, 1672, 1515, 1455, 1373, 1053 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$ (M^{**}) m/z 296.1161 found 296.1162.

N-(5-Cyano-6-(4-isopropylphenyl)-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4e**). Purification by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 21.2 mg, 65% (dr 72:28).

$R_f = 0.22$ (2:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as a yellow amorphous solid; Isolated yield 15.2 mg, 47%; ^1H NMR (600 MHz, C_6D_6) δ 6.94 (d, $J = 8.0$ Hz, 2H), 6.85 (d, $J = 8.0$ Hz, 2H), 6.33 (s, 1H), 5.76 (d, $J = 9.8$ Hz, 1H), 5.57 (d, $J = 9.8$ Hz, 1H), 4.39 (dd, $J = 9.1, 9.1$ Hz, 1H), 3.50 (dd, $J = 13.4, 9.5$ Hz, 1H), 2.66 (sept, $J = 6.6$ Hz, 1H), 1.81 (dd, $J = 13.4, 8.6$ Hz, 1H), 1.35 (s, 3H), 1.11 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 189.9, 169.2, 149.3, 148.0, 130.8, 128.7, 127.11, 127.07, 116.4, 91.4, 77.3, 52.4, 34.1, 31.4, 24.0, 23.2; IR (ATIR) 3266, 3046, 2959, 1715, 1670, 1538, 1371, 1337, 1199, 1078 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ (M^{**}) m/z 324.1474 found 324.1471.

$R_f = 0.09$ (2:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as an orange amorphous solid; Isolated yield 6.0 mg, 18%; ^1H NMR (500 MHz, CDCl_3) δ 7.59 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 9.8$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 2H), 6.75 (s, 1H), 6.25 (d, $J = 9.8$ Hz, 1H), 3.67 (dd, $J = 9.3, 3.9$ Hz, 1H), 3.36 (dd, $J = 14.4, 4.1$ Hz, 1H), 2.92 (sept, $J = 6.9$ Hz, 1H), 2.43 (dd, $J = 14.1, 9.3$ Hz, 1H), 2.15 (s, 3H), 1.25 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.1, 170.0, 150.6, 149.3, 136.0, 128.5, 127.2, 125.5, 114.8, 93.0, 78.9, 52.7, 34.3, 33.9, 24.3, 24.1, 24.0; IR (ATIR) 3281, 3057, 2961, 1719, 1673, 1539, 1373, 1331, 1206, 1184, 1052 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ (M^{**}) m/z 324.1474 found 324.1472.

N-(6-(4-(*tert*-Butyl)phenyl)-5-cyano-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4f**). Purification by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 23.8 mg, 70% (dr 78:22).

$R_f = 0.26$ (2:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as an orange amorphous solid; Isolated yield 18.6 mg, 55%; ^1H NMR (600 MHz, C_6D_6) δ 7.13 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.3$ Hz, 2H), 6.37 (s, 1H), 5.78 (d, $J = 9.8$ Hz, 1H), 5.61 (d, $J = 9.8$ Hz, 1H), 4.41 (dd, $J = 9.1, 9.1$ Hz, 1H), 3.52 (dd, $J = 13.3, 9.8$ Hz, 1H), 1.85 (dd, $J = 13.5, 8.6$ Hz, 1H), 1.38 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 189.9, 169.3, 151.5, 148.0, 130.5, 128.4, 127.1, 126.0, 116.4, 91.5, 77.3, 52.4, 34.5, 31.4, 31.1, 23.3; IR (ATIR) 3299, 3053, 2961, 2904, 2867, 1718, 1679, 1515, 1369, 1269, 1187 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ (M^{**}) m/z 338.1630 found 338.1630.

$R_f = 0.09$ (2:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as a red amorphous solid; Isolated yield 5.6 mg, 15%; ^1H NMR (500 MHz, CDCl_3) δ 7.61 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 9.8$ Hz, 1H), 6.75 (s, 1H), 6.25 (d, $J = 9.8$ Hz, 1H), 3.68 (dd, $J = 9.4, 4.0$ Hz, 1H), 3.37 (dd, $J = 14.2, 4.1$ Hz, 1H), 2.43 (dd, $J = 14.0, 9.4$ Hz, 1H), 2.15 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.1, 170.0, 151.5, 150.6, 135.7, 128.3, 126.1, 125.4, 114.8, 92.9, 78.9, 52.6, 34.7, 34.3, 31.4, 24.3; IR (ATIR) 3300, 3053, 2963, 2867, 1718, 1514, 1370, 1269, 1052 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ (M^{**}) m/z 338.1630 found 338.1629.

4-(1-Acetamido-5-cyano-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl)phenyl acetate (**4g**). Purification by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 22.3 mg, 66% (dr 71:29).

$R_f = 0.18$ (2:1 hexanes:ethyl acetate); The product stains red/purple with PAA; The product is isolated as a red amorphous solid; Isolated yield 15.8 mg, 46%; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, $J = 6.8$ Hz, 2H), 7.11 (d, $J = 6.8$ Hz, 2H), 6.80 (d, $J = 7.9$ Hz, 2H), 6.79 (s, 1H), 6.37 (d, $J = 7.8$ Hz, 1H), 4.43 (dd, $J = 7.3, 7.3$ Hz, 1H), 3.64 (dd, $J = 10.9, 7.6$ Hz, 1H), 2.31 (s, 3H), 2.21 (dd, $J = 10.9, 6.8$ Hz, 1H), 2.13 (s, 3H); ¹³C NMR (100 MHz, CD₃CN) δ 189.9, 171.2, 170.4, 152.0, 147.3, 132.0, 130.3, 123.2, 117.3, 93.2, 78.1, 53.5, 34.6, 23.5; IR (ATIR) 3315, 3056, 2927, 1754, 1719, 1691, 1510, 1197, 1170 cm⁻¹; HRMS (EI) calcd for C₁₈H₁₆N₂O₅ (M)⁺ m/z 340.1059 found 340.1062.

$R_f = 0.09$ (2:1 hexanes:ethyl acetate); The product stains red/purple with PAA; The product is isolated as a white amorphous solid; Isolated yield 6.5 mg, 19%; ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 9.8$ Hz, 1H), 7.17 (d, $J = 8.2$ Hz, 2H), 6.76 (s, 1H), 6.26 (d, $J = 9.8$ Hz, 1H), 3.71 (dd, $J = 9.4, 3.9$ Hz, 1H), 3.41 (dd, $J = 14.1, 3.9$ Hz, 1H), 2.43 (dd, $J = 14.2, 9.3$ Hz, 1H), 2.30 (s, 3H), 2.15 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.8, 170.1, 169.5, 150.8, 150.2, 136.3, 129.8, 125.7, 122.3, 114.7, 92.9, 78.7, 52.4, 34.3, 24.3, 21.4; IR (ATIR) 3304, 3051, 2952, 2928, 1758, 1717, 1691, 1507, 1371, 1197, 1170 cm⁻¹; HRMS (EI) calcd for C₁₈H₁₆N₂O₅ (M)⁺ m/z 340.1059 found 340.1057.

N-(5-Cyano-2-oxo-6-(4-(trifluoromethyl)phenyl)-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4h**). Purification by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate); Combined isolated yield for both diastereomers is 21.6 mg, 62% (dr 61:39).

$R_f = 0.20$ (2:1 hexanes:ethyl acetate); The product stains yellow with KMnO₄; The product is isolated as an orange amorphous solid; Isolated yield 13.2 mg, 38%; ¹H NMR (600 MHz, CDCl₃) δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 6.87 (s, 1H), 6.74 (d, $J = 9.8$ Hz, 1H), 6.38 (d, $J = 9.8$ Hz, 1H), 4.48 (dd, $J = 9.1, 9.1$ Hz, 1H), 3.67 (dd, $J = 13.7, 9.5$ Hz, 1H), 2.26 (dd, $J = 13.7, 8.6$ Hz, 1H), 2.13 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 189.4, 170.3, 147.3, 137.0, 131.4 (q, $J_{C-F} = 32.7$ Hz), 128.9, 128.0, 126.3 (q, $J_{C-F} = 3.8$ Hz), 123.9 (q, $J_{C-F} = 270.5$ Hz), 115.4, 91.2, 76.7, 52.4, 31.5, 24.2; IR (ATIR) 3374, 2925, 2853, 1728, 1684, 1503, 1325, 1165, 1133, 1119 cm⁻¹; HRMS (EI) calcd for C₁₇H₁₃N₂O₃F₃ (M)⁺ m/z 350.0878 found 350.0877.

$R_f = 0.09$ (2:1 hexanes:ethyl acetate); The product stains yellow with KMnO₄; The product is isolated as a red amorphous solid; Isolated yield 8.4 mg, 24%; ¹H NMR (600 MHz, CDCl₃) δ 7.87 (d, $J = 7.9$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 9.7$ Hz, 1H), 6.80 (s, 1H), 6.29 (d, $J = 9.7$ Hz, 1H), 3.75 (dd, $J = 9.4, 3.7$ Hz, 1H), 3.50 (dd, $J = 14.2, 3.7$ Hz, 1H), 2.44 (dd, $J = 14.3, 9.4$ Hz, 1H), 2.16 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 189.8, 170.1, 150.3, 142.5, 130.9 (q, $J_{C-F} = 32.3$ Hz), 129.3, 126.2 (q, $J_{C-F} = 3.8$ Hz), 125.5, 124.2 (q, $J_{C-F} = 270.5$ Hz), 114.5, 92.8, 78.2, 52.8, 33.2, 24.5; IR (ATIR) 3272, 3047, 1726, 1671, 1535, 1324, 1168, 1113, 1070, 1053 cm⁻¹; HRMS (EI) calcd for C₁₇H₁₃N₂O₃F₃ (M)⁺ m/z 350.0878 found 350.0876.

N-(5-Cyano-6-methyl-2-oxo-6-phenyl-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4i**). Procedure: To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (**1**) (22.0 mg, 0.10 mmol, 1 equiv), α -methylstyrene **2i** (59.0 mg, 0.50 mmol, 5 equiv), and *i*-butylmethylketone (1 mL). The reaction mixture was heated (100 °C, oil bath temperature) and stirred for 24 h. At this time, the solution was cooled, concentrated, and purified by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate) to afford the desired products; $R_f = 0.32$ (1:1 hexanes:ethyl acetate); The product stains orange with DNP; The product is isolated as an orange amorphous solid; Isolated yield of *endo*-**4i** 14.7 mg, 50%; ¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, $J = 7.4$ Hz, 2H), 7.36 (dd, $J = 8.0, 8.0$ Hz, 2H), 7.29 (t, $J = 7.3$ Hz, 1H), 6.93 (d, $J = 9.9$ Hz, 1H), 6.79 (s, 1H), 6.02 (d, $J = 9.9$ Hz, 1H), 3.42 (d, $J = 13.5$ Hz, 1H), 2.57 (d, $J = 13.5$ Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 189.8, 170.0, 150.1, 142.5, 129.3, 127.8, 126.2, 125.1, 116.1, 90.5, 80.0, 55.7, 36.1, 30.8, 24.5; IR (ATIR) 3374, 3198, 3061, 2926, 1722, 1694, 1679, 1498, 1374, 1267, 1180, 1059, 961 cm⁻¹; HRMS

(EI) calcd for C₁₇H₁₆N₂O₃ (M)⁺ m/z 296.1161 found 296.1165; *exo*-**4i** is easily decomposed by SiO₂-gel column chromatography; Combined NMR yield for both diastereomers is 63% (dr 83:17).

N-(5-Cyano-2-oxo-6-(phenylthio)-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4j**). Purification by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate); The product stains yellow with KMnO₄; The product is isolated as an orange amorphous solid; Isolated yield 18.8 mg, 60% (dr >95:5); $R_f = 0.19$ (2:1 hexanes:ethyl acetate); ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.53 (m, 2H), 7.39–7.34 (m, 3H), 7.31 (d, $J = 9.9$ Hz, 1H), 6.81 (s, 1H), 6.34 (d, $J = 9.9$ Hz, 1H), 4.43 (dd, $J = 9.7, 8.0$ Hz, 1H), 3.75 (dd, $J = 13.8, 9.6$ Hz, 1H), 2.06 (s, 3H), 1.85 (dd, $J = 13.8, 8.0$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 189.1, 170.2, 148.0, 133.2, 131.9, 129.7, 129.2, 127.4, 115.0, 90.6, 75.6, 53.9, 33.7, 24.2; IR (ATIR) 3284, 3069, 1718, 1693, 1662, 1525, 1441, 1363, 1275, 1102 cm⁻¹; HRMS (EI) calcd for C₁₆H₁₄N₂O₃S (M)⁺ m/z 314.0726 found 314.0725; The stereochemistry was determined by (¹H, ¹H) NOESY analysis of hydrogenated product as described below.

N-(6-(Benzyloxy)-5-cyano-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-1-yl)acetamide (**4k**). To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (**1**) (22.0 mg, 0.10 mmol, 1 equiv), benzyl vinyl ether **2k** (67.1 mg, 0.50 mmol, 5 equiv), and dry THF (1 mL). The vial was sealed, and then heated to reflux (80 °C, oil bath temperature) for 96 h. After this time, the solution was cooled to room temperature and concentrated to afford the crude cycloaddition product; Purification by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate); $R_f = 0.26$ (1:1 hexanes:ethyl acetate); The product stains red with PAA; The product is isolated as an orange amorphous solid; Isolated yield 13.5 mg, 43% (dr >95:5); ¹H NMR (600 MHz, CDCl₃) δ 7.39–7.29 (m, 5H), 7.19 (d, $J = 10.0$ Hz, 1H), 6.72 (s, 1H), 6.34 (d, $J = 9.9$ Hz, 1H), 4.94 (dd, $J = 8.9, 5.6$ Hz, 1H), 4.74 (d, $J = 11.6$ Hz, 1H), 4.67 (d, $J = 11.7$ Hz, 1H), 3.53 (dd, $J = 13.5, 8.8$ Hz, 1H), 2.06 (s, 3H), 1.77 (dd, $J = 13.5, 5.7$ Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 189.7, 170.0, 147.8, 136.4, 128.9, 128.6, 128.0, 127.6, 116.1, 90.4, 83.2, 74.1, 73.8, 32.4, 24.2; IR (ATIR) 3286, 3047, 2922, 2872, 1719, 1670, 1536, 1306, 1267, 1178, 1122, 1060, 1035 cm⁻¹; HRMS (ESI) calcd for C₁₇H₁₇N₂O₄ (M + H)⁺ m/z 313.1188 found 313.1185; The stereochemistry was determined by (¹H, ¹H) NOESY analysis as shown; It was also assigned by analogy using the previous report describing the [5 + 2] cycloaddition reaction of oxidopyrylium ions with vinyl ethers to provide *endo*-adducts.³³

N-(9-Cyano-6-oxo-1,2,3,4,4a,6,9,9a-octahydro-5H-5,9-epoxy-1,4-methanobenzo[7]annulen-5-yl)acetamide (**4l**). Purification by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate); The product stains yellow with KMnO₄; The product is isolated as an orange amorphous solid; Isolated yield 13.7 mg, 50% (dr >95:5); $R_f = 0.22$ (1:2 hexanes:ethyl acetate); ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, $J = 9.3$ Hz, 1H), 6.33 (s, 1H), 6.27 (d, $J = 9.7$ Hz, 1H), 2.80–2.77 (m, 1H), 2.46–2.43 (m, 1H), 2.36 (d, $J = 6.8$ Hz, 1H), 2.10 (s, 3H), 2.07 (d, $J = 6.9$ Hz, 1H), 1.98–1.94 (m, 1H), 1.69–1.63 (m, 2H), 1.28–1.16 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.4, 169.9, 148.5, 129.0, 115.3, 94.5, 76.4, 56.4, 49.8, 39.9, 37.4, 34.1, 28.2, 27.9, 23.2; IR (ATIR) 3368, 2994, 2975, 2870, 1720, 1674, 1498, 1428, 1367, 1213, 1170, 1063, 999 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₇N₂O₃ (M + H)⁺ m/z 273.1234 found 273.1232; The stereochemistry was assigned by analogy using the previous report describing [5 + 2] cycloaddition reaction of oxidopyrylium ions with norbornene.³⁴

Sequential [5 + 2]/[4 + 2] Cycloaddition Reaction of 1-(p-Toluenesulfonyl)-3-vinyl-1H-indole (2m) with Bis(1-cyanovinyl acetate) (1). To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (**1**) (44.0 mg, 0.20 mmol, 1 equiv), vinylindole **2m** (297.4 mg, 1.0 mmol, 5 equiv), PPTS (2.5 mg, 0.010 mmol, 5 mol %), and dry acetonitrile (2 mL). The solution was heated to reflux (100 °C, oil bath temperature) for 36 h. At this time, the solution was concentrated and purified by SiO₂-gel chromatography (2:1 hexanes:ethyl acetate) to afford the double cycloaddition product **4m** as a mixture with its aromatized tautomer (tautomer of **4m**:**4m** 90:10). Both adducts (tautomer of **4m** and **4m**) were treated with TsOH · H₂O (57.1 mg, 0.30 mmol, 1.5 equiv) in DCM (5 mL) for 12 h at 40 °C to induce aromatization to give the sole product **4m**, which was then purified by SiO₂-gel chromatography

(2:1 hexanes:ethyl acetate); $R_f = 0.16$ (2:1 hexanes:ethyl acetate); The product stains black with CeMo; The product is an off-white amorphous solid; Isolated yield 78.7 mg, 51%; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.10 (d, $J = 8.7$ Hz, 2H), 7.90 (s, 1H), 7.80–7.75 (m, 3H), 7.69 (d, $J = 8.5$ Hz, 2H), 7.46–7.34 (m, 3H), 7.31–7.21 (m, 4H), 6.96 (s, 1H), 6.75 (d, $J = 8.0$ Hz, 2H), 5.49 (d, $J = 5.8$ Hz, 1H), 4.90 (dd, $J = 12.0$, 8.0 Hz, 1H), 4.08 (dd, $J = 13.1$, 13.1 Hz, 1H), 2.86 (dd, $J = 17.0$, 5.2 Hz, 1H), 2.70 (dd, $J = 13.8$, 7.7 Hz, 1H), 2.44–2.16 (m, 4H), 2.26–2.16 (m, 2H), 2.12 (s, 3H), 2.01–1.91 (m, 1H), 1.95 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 196.6, 170.3, 145.3, 136.5, 135.8, 135.7, 134.6, 130.1, 129.9, 129.8, 128.6, 128.5, 127.3, 126.7, 126.1, 125.3, 124.6, 124.1, 123.5, 121.4, 119.4, 119.0, 117.9, 117.7, 114.3, 114.1, 90.9, 79.1, 46.7, 44.8, 42.1, 32.3, 24.6, 22.0, 21.8, 21.4, 19.8; IR (ATR) 3394, 2948, 1744, 1702, 1509, 1451, 1352, 1175, 1135 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{36}\text{O}_7\text{N}_4\text{Na}^{32}\text{S}_2$ ($\text{M} + \text{Na}$) $^+$ m/z 795.1918 found 795.1911; Melting point of the amorphous solid is 267–270 °C.

Experimental Procedure for Large Scale Synthesis of 4b. To a flame-dried 100 mL Schlenk flask equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (**1**) (660 mg, 3.0 mmol, 1 equiv), 4-vinylanisole **2b** (2.01 g, 15.0 mmol, 5 equiv), PPTS (37.7 mg, 150 μmol , 5 mol %), and dry acetonitrile (30 mL). The reaction mixture was heated to reflux (100 °C, oil bath temperature) and stirred for 24 h. At this time, the solution was concentrated and purified by SiO_2 -gel chromatography (3:2 hexanes:ethyl acetate) to provide the desired cycloaddition products *endo-4b* (460 mg, 1.47 mmol, 49%) and *exo-4b* (138 mg, 0.44 mmol, 15%).

Functionalization of [5 + 2] Cycloaddition Reaction Product *endo-4b* (Scheme 3). **Johnson Iodination of *endo-4b*.** To a flame-dried 4 mL dram vial equipped with a Teflon-coated stir bar was added *endo-4b* (21.9 mg, 0.070 mmol, 1 equiv). The vial was then fitted with a rubber septum, carefully evacuated and backfilled with nitrogen gas ($\times 3$), and then DCM (175 μL) was added. The resulting homogeneous solution was cooled to -5 °C (brine/ice bath), and anhydrous pyridine (175 μL) was added under nitrogen gas. I_2 (35.6 mg, 0.14 mmol, 2 equiv) was added as a solid all at once by quickly removing and refitting the rubber septum under a high stream of nitrogen gas at 0 °C. The initially heterogeneous orange solution was stirred at -5 °C for 1 h after which the solution turned homogeneous and purple. The solution was then taken up in diethyl ether (5 mL) while still cold and washed with 1 N aqueous HCl (5 mL $\times 2$) while warming to room temperature. The organic layers were washed with saturated aqueous Na_2SO_3 (5 mL $\times 2$), dried over MgSO_4 , concentrated, and purified by SiO_2 -gel chromatography (1:1 hexanes:ethyl acetate) to afford iodoenone **5**; $R_f = 0.10$ (2:1 hexanes:ethyl acetate); The product stains purple with DNP; The product is isolated as an off-white amorphous solid; Isolated yield 20.8 mg, 67%; $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.39 (s, 1H), 7.19 (d, $J = 8.2$ Hz, 2H), 6.92 (d, $J = 8.4$ Hz, 2H), 6.81 (s, 1H), 4.30 (dd, $J = 9.1$, 9.1 Hz, 1H), 3.82 (s, 3H), 3.60 (dd, $J = 13.7$, 9.4 Hz, 1H), 2.16 (dd, $J = 13.6$, 8.5 Hz, 1H), 2.13 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 185.1, 170.0, 160.2, 155.5, 129.4, 124.1, 114.8, 114.7, 99.6, 90.3, 79.2, 55.5, 52.5, 32.3, 24.3; IR (ATR) 3266, 3213, 3063, 3007, 2928, 2832, 1717, 1669, 1549, 1515, 1304, 1249, 1181, 1090, 1042 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_4\text{I}$ (M) $^{+}$ m/z 438.0077 found 438.0074.

Hydrogenation of *endo-4b* under Pd/C Catalysis. To a flame-dried 25 mL round-bottomed flask equipped with a Teflon-coated stir bar were added *endo-4b* (31.2 mg, 0.10 mmol, 1 equiv), 10 wt % dried Pd/C (5.3 mg, 5 μmol , 5 mol % Pd), and THF (3 mL) under nitrogen atmosphere. The flask was evacuated and backfilled with hydrogen gas at 0 °C, fitted with a balloon of hydrogen gas and the solution was stirred at room temperature for 12 h. After this time, the reaction mixture was filtered over a pad of Celite and concentrated to afford the desired product **6**; $R_f = 0.16$ (1:1 hexanes:ethyl acetate); The product stains black with CeMo; The product is an off-white amorphous solid; Isolated yield 30.8 mg, 98%; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.38 (d, $J = 8.3$ Hz, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 6.79 (s, 1H), 4.41 (dd, $J = 11.9$, 9.0 Hz, 1H), 3.83 (s, 3H), 3.45 (dd, $J = 12.6$, 12.6 Hz, 1H), 2.72 (ddd, $J = 17.8$, 17.8, 9.3 Hz, 1H), 2.62 (ddd, $J = 17.2$, 17.2, 8.8 Hz, 1H), 2.42 (ddd, $J = 14.2$, 9.3, 9.3 Hz, 1H), 2.33 (dd, $J = 13.8$, 8.7 Hz, 1H), 2.10–2.04 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 199.3,

170.2, 159.7, 128.7, 126.0, 118.3, 114.8, 90.8, 77.5, 55.5, 50.8, 32.7, 31.7, 31.1, 24.2; IR (ATR) 3391, 2919, 2846, 1738, 1682, 1518, 1495, 1249, 1026 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ m/z 315.1339 found 315.1336.

1,4-Addition of Lithium Hexamethyldisilazide. To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added *endo-4b* (31.2 mg, 0.10 mmol, 1 equiv) and THF (1 mL) under a nitrogen atmosphere. The solution was then cooled to -78 °C. LiHMDS (0.20 mL, 0.20 mmol, 2 equiv, 1.0 M THF solution) was then added dropwise to the resulting solution at -78 °C, and the reaction mixture was warmed to room temperature. After 1 h, saturated aqueous NH_4Cl (0.5 mL) was added slowly at 0 °C, and the mixture was extracted with ethyl acetate (5 mL $\times 3$), washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , and evaporated. The crude product was purified by SiO_2 -gel column chromatography (2:1 hexanes:ethyl acetate) to give the product **7**; $R_f = 0.48$ (1:1 hexanes:ethyl acetate); The product stains purple with CeMo; The product is an off-white amorphous solid; Isolated yield 23.5 mg, 50% (dr >95:5); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.25 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 8.4$ Hz, 2H), 6.61 (s, 1H), 4.34 (dd, $J = 12.2$, 7.9 Hz, 1H), 3.80 (s, 3H), 3.61 (dd, $J = 7.8$, 7.8 Hz, 1H), 3.26 (dd, $J = 16.6$, 7.9 Hz, 1H), 2.77 (dd, $J = 13.2$, 13.2 Hz, 1H), 2.73 (dd, $J = 16.5$, 7.9 Hz, 1H), 2.30 (dd, $J = 13.8$, 7.9 Hz, 1H), 2.08 (s, 3H), 0.28 (s, 9H), 0.27 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 204.3, 170.5, 160.1, 130.1, 125.5, 118.2, 115.1, 91.1, 86.1, 55.6, 53.1, 52.3, 44.7, 35.9, 23.3, 4.9, 2.0; IR (ATR) 3314, 2956, 1743, 1666, 1515, 1253, 1033, 941, 826 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{23}\text{H}_{35}\text{N}_3\text{O}_4\text{Si}_2$ (M) $^{+}$ m/z 473.2166 found 473.2165; The stereochemistry was assigned by (^1H , ^1H) NOESY analysis.

Diels–Alder Reaction of *endo-4b* with 1-(*p*-Toluenesulfonyl)-3-vinyl-1H-indole (2m**).** To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added *endo-4b* (31.2 mg, 0.10 mmol, 1 equiv), vinylindole **2m** (89.2 mg, 0.30 mmol, 3 equiv), and dry acetonitrile (1 mL). The solution was stirred at 100 °C for 17 h. At that time, the reaction mixture was cooled to room temperature, concentrated, and purified by SiO_2 -gel column chromatography (2:1 hexanes:ethyl acetate) to give the cycloadduct **8**; $R_f = 0.20$ (2:1 hexanes:ethyl acetate); The product stains black with CeMo; The product is an off-white amorphous solid; Isolated yield 45.4 mg, 74% (dr >95:5); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.82 (d, $J = 8.2$ Hz, 1H), 7.73 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.31–7.23 (m, 2H), 7.17 (d, $J = 8.1$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.03 (dd, $J = 7.5$, 7.5 Hz, 1H), 6.90 (s, 1H), 5.83–5.78 (m, 1H), 4.69 (dd, $J = 12.5$, 7.3 Hz, 1H), 4.49 (dd, $J = 6.1$, 4.5 Hz, 1H), 3.91 (s, 3H), 3.86–3.79 (m, 1H), 3.77–3.73 (m, 1H), 2.77–2.65 (m, 2H), 2.60–2.46 (m, 2H), 2.34 (s, 3H), 2.02 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 196.6, 170.1, 159.7, 144.9, 144.0, 133.6, 132.4, 130.02, 129.99, 128.1, 127.8, 127.5, 125.8, 124.4, 120.7, 117.6, 115.3, 114.8, 114.1, 91.9, 80.6, 61.0, 55.6, 50.8, 43.1, 42.3, 29.9, 25.8, 24.5, 21.7; IR (ATR) 3396, 2923, 2836, 1748, 1693, 1594, 1513, 1352, 1252, 1168 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{O}_6^{32}\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ m/z 632.1826 found 632.1832; The stereochemistry was assigned by (^1H , ^1H) COSY, (^1H , ^1H) NOESY, (^1H , ^{13}C) HSQC, and (^1H , ^{13}C) HMBC analyses.

Diastereoselective 1,2-Reduction of Enone *endo-4b* to Allylic Alcohol **9.** To a flame-dried 4 mL dram vial equipped with a Teflon-coated stir bar was added *endo-4b* (15.6 mg, 0.050 mmol, 1 equiv). After the addition of DCM (0.5 mL) and Et_3SiH (58.1 mg, 0.50 mmol, 10 equiv), TiCl_4 (0.15 mL, 0.15 mmol, 3 equiv, 1.0 M DCM solution) was added dropwise at room temperature under nitrogen. The reaction mixture was warmed to 40 °C and stirred at that temperature for 2 h. After cooling to room temperature, water (1 mL) was added and the mixture was extracted with ethyl acetate (5 mL $\times 3$), washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , concentrated, and purified by SiO_2 -gel chromatography (1:1 hexanes:ethyl acetate) to afford allylic alcohol **9** as a single diastereomer; $R_f = 0.10$ (1:1 hexanes:ethyl acetate); The product stains faint red with DNP; The product is a white amorphous solid; Isolated yield 9.8 mg, 62% (dr >95:5); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.33 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.46 (s, 1H), 5.90 (d, $J = 11.9$ Hz, 1H), 5.71 (s, 1H), 5.49 (d, $J = 9.8$ Hz, 1H), 4.75 (s, 1H), 4.00 (dd, $J = 9.8$, 9.8 Hz, 1H), 3.80 (s, 3H), 3.31 (dd, $J = 13.7$, 9.3 Hz, 1H), 2.27 (dd, $J = 13.8$,

9.2 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.0, 159.8, 131.6, 129.8, 126.1, 124.7, 117.1, 114.2, 94.6, 77.0, 72.0, 55.9, 55.5, 35.2, 23.8; IR (ATR) 3235, 2921, 1643, 1518, 1276, 1057, 1003, 733 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_4$ ($\text{M}-\text{H}$) $^+$ m/z 313.1194 found 313.1197; The stereochemistry was assigned by (^1H , ^1H) NOESY analysis of diastereomeric mixture **8** which could be synthesized by the reduction with NaBH_4 as follows; To a flame-dried 4 mL dram vial equipped with a Teflon-coated stir bar were added *endo-4b* (31.2 mg, 0.10 mmol, 1 equiv) and THF (1 mL). This solution was cooled to 0 °C and then NaBH_4 (3.8 mg, 0.10 mmol, 1 equiv) was added slowly at that temperature. After stirring at room temperature for 15 min, saturated aqueous NH_4Cl (1 mL) was added and the mixture was extracted with DCM (5 mL \times 3), washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , concentrated, and purified by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate) to afford allylic alcohol **9** as a diastereomeric mixture; R_f = 0.10 (1:1 hexanes:ethyl acetate); The product stains faint red with DNP; The product is a white amorphous solid; Isolated yield 27.5 mg, 87% (dr 70:30); ^1H NMR (500 MHz, CDCl_3) (minor diastereomer indicated by asterisk) δ 7.32 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H*), 6.86 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H*), 6.72 (s, 1H), 6.15 (dd, J = 9.7, 4.7 Hz, 1H*), 5.89 (dd, J = 9.8, 2.2 Hz, 1H), 5.82 (d, J = 9.7 Hz, 1H), 5.66 (s, 1H), 5.48 (dd, J = 9.8, 1.8 Hz, 1H), 4.75 (s, 1H), 4.18 (dd, J = 9.4, 9.4 Hz, 1H*), 4.00 (dd, J = 9.9, 9.9 Hz, 1H), 3.792 (s, 3H), 3.788 (s, 3H*), 3.75 (d, J = 4.8 Hz, 1H*), 3.38 (dd, J = 13.1, 9.4 Hz, 1H*), 3.27 (dd, J = 13.6, 9.2 Hz, 1H), 2.31 (dd, J = 13.6, 11.0 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H*), 1.88 (dd, J = 13.0, 9.4 Hz, 1H*); ^{13}C NMR (150 MHz, CDCl_3) δ 171.2, 170.9*, 159.8, 159.7*, 131.6, 130.7*, 129.7, 129.6*, 128.5*, 126.2, 125.3*, 124.8, 117.14, 117.09*, 114.3*, 114.2, 94.4, 90.9*, 77.0, 76.9*, 72.0, 68.4*, 55.8, 55.43, 55.41*, 54.3*, 35.0, 32.7*, 24.5*, 23.8; IR (ATR) 3290, 2925, 2849, 1663, 1514, 1248, 1180, 1028 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$ m/z 337.1159 found 337.1154; The stereochemistry was determined by (^1H , ^1H) NOESY analysis.

1,2-Addition of Phenyl Magnesium Bromide to *endo-4b*. To a flame-dried 25 mL round-bottomed flask equipped with a Teflon-coated stir bar were added *endo-4b* (31.2 mg, 0.10 mmol, 1 equiv), and the flask was fitted with a rubber septum. The flask was evacuated and backfilled with nitrogen gas (\times 3), and the solids were dissolved in THF (1 mL). PhMgBr (1.7 mL, 0.51 mmol, 5 equiv, 3.0 M THF solution) was added dropwise at -78 °C. The reaction mixture was stirred for 5 min, and then warmed to room temperature. After 1 h, saturated aqueous NH_4Cl (0.5 mL) was added slowly at 0 °C, and the mixture was extracted with ethyl acetate (5 mL \times 3), washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , and evaporated. The crude product was purified by SiO_2 -gel column chromatography (2:1 hexanes:ethyl acetate) to give the product **10**; R_f = 0.22 (2:1 hexanes:ethyl acetate); The product stains purple with PAA; The product is an off-white amorphous solid; Isolated yield 30.5 mg, 65% (dr >95:5); ^1H NMR (600 MHz, CDCl_3) δ 8.14 (d, J = 9.5 Hz, 2H), 7.61–7.55 (m, 3H), 7.46 (dd, J = 7.9, 7.9 Hz, 2H), 7.34 (dd, J = 7.7, 7.7 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.38 (s, 1H), 6.25 (d, J = 9.8 Hz, 1H), 6.03 (s, 1H), 5.88 (d, J = 9.8 Hz, 1H), 4.01 (dd, J = 9.5, 9.5 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J = 13.7, 8.9 Hz, 1H), 2.68 (dd, J = 13.7, 10.1 Hz, 1H), 1.85 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 195.9, 171.5, 159.3, 142.2, 135.5, 133.2, 132.5, 130.2, 130.1, 128.5, 127.9, 127.7, 127.3, 127.2, 127.1, 113.8, 96.4, 91.2, 79.2, 55.4, 55.2, 38.7, 22.9; IR (ATR) 3225, 3064, 2923, 2837, 1673, 1513, 1294, 1239, 1179, 699 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{27}\text{O}_3\text{NNA}$ ($\text{M} + \text{Na}$) $^+$ m/z 492.1777 found 492.1781; The stereochemistry was assigned by (^1H , ^1H) NOESY analysis.

Rhodium-Catalyzed Hydration of Nitrile (*endo-4b*) to Amide **11.**²² To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added *endo-4b* (31.2 mg, 0.10 mmol, 1 equiv) and $\text{RhCl}(\text{PPh}_3)_3$ (Wilkinson's catalyst) (1.9 mg, 2.0 μmol , 2 mol %). A solution of acetaldoxime (29.5 mg, 0.50 mmol, 5 equiv) in toluene (1 mL) was added to the vial under nitrogen atmosphere, and then it was stirred at 100 °C for 14 h. At that time, the reaction mixture was diluted with water (5 mL), extracted with ethyl acetate (5 mL \times 3),

washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , and concentrated to afford the crude product which was purified by SiO_2 -gel column chromatography (1:2 hexanes:ethyl acetate) to give the desired compound **11**; R_f = 0.11 (1:2 hexanes:ethyl acetate); The product stains red with PAA; The product is an off-white amorphous solid; Isolated yield 30.9 mg, 94%; ^1H NMR (500 MHz, CDCl_3) δ 7.34 (d, J = 9.9 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.99 (s, 1H), 6.80 (d, J = 8.7 Hz, 2H), 6.60 (s, 1H), 6.31 (d, J = 9.9 Hz, 1H), 5.85 (s, 1H), 4.01 (dd, J = 9.0, 9.0 Hz, 1H), 3.76 (s, 3H), 3.52 (dd, J = 13.6, 9.6 Hz, 1H), 2.18 (dd, J = 13.6, 8.3 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 191.8, 170.4, 169.9, 159.4, 152.2, 129.6, 126.7, 126.1, 113.9, 90.3, 85.2, 55.3, 52.0, 34.2, 24.3; IR (ATR) 3445, 3362, 3303, 2937, 1684, 1612, 1598, 1366, 1267, 1248, 1022 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ m/z 353.1108 found 353.1109.

Synthetic Sequences to Access Multicyclic Scaffolds (Scheme 4). **First Step: [5 + 2] Cycloaddition Reaction with Styrene **2n**.** To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added bis(1-cyanovinyl acetate) (**1**) (44.0 mg, 0.20 mmol, 1 equiv), 2-bromo-4,5-dimethoxystyrene **2n** (243 mg, 1.0 mmol, 5 equiv), PPTS (5.0 mg, 0.020 mmol, 10 mol %), and dry acetonitrile (2 mL). The resulting reaction mixture was heated to reflux (100 °C, oil bath temperature) and stirred for 24 h. At this time, the solution was concentrated and purified by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate) to afford the desired cycloaddition products **4n**; Combined isolated yield for both diastereomers is 60.6 mg, 72% (dr 57:43).

exo-diastereomer R_f = 0.41 (1:2 hexanes:ethyl acetate); The product stains purple with DNP; The product is isolated as a light brown amorphous solid; Isolated yield 26.1 mg, 31%; ^1H NMR (600 MHz, CDCl_3) δ 8.06 (s, 1H), 7.50 (d, J = 9.7 Hz, 1H), 7.04 (s, 1H), 6.82 (s, 1H), 6.25 (d, J = 9.7 Hz, 1H), 4.36 (dd, J = 9.5, 4.2 Hz, 1H), 4.06 (s, 3H), 3.89 (s, 3H), 3.61 (dd, J = 14.3, 4.2 Hz, 1H), 2.32 (dd, J = 14.3, 9.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 190.2, 169.8, 151.2, 149.8, 149.7, 129.4, 124.8, 115.0, 114.9, 114.4, 112.6, 93.0, 57.0, 56.3, 51.6, 31.2, 24.6; IR (ATR) 3289, 3056, 2927, 2851, 2353, 1723, 1668, 1508, 1253, 1210, 1157, 1022 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_5^{79}\text{Br}$ (M) $^{+}$ m/z 420.0321 found 420.0310; The stereochemistry was determined by (^1H , ^1H) NOESY analysis of hydrogenated product as described below.

endo-diastereomer R_f = 0.35 (1:2 hexanes:ethyl acetate); The product stains purple with DNP; The product is isolated as an orange amorphous solid; Isolated yield 34.5 mg, 41%; ^1H NMR (600 MHz, CDCl_3) δ 7.11 (s, 1H), 6.94 (d, J = 9.8 Hz, 1H), 6.76 (s, 1H), 6.54 (s, 1H), 6.45 (d, J = 9.8 Hz, 1H), 5.08 (dd, J = 9.1, 9.1 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.67 (dd, J = 13.7, 9.5 Hz, 1H), 2.13 (s, 3H), 2.06 (dd, J = 13.6, 8.5 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 189.7, 170.1, 150.1, 148.6, 148.5, 127.9, 123.5, 117.7, 116.7, 115.3, 111.3, 91.0, 75.8, 56.5, 56.4, 50.0, 33.7, 24.2; IR (ATR) 3380, 2920, 2842, 1719, 1689, 1514, 1254, 1207, 1163, 802, 725 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_5^{79}\text{Br}$ (M) $^{+}$ m/z 420.0321 found 420.0319; The stereochemistry was determined by (^1H , ^1H) NOESY analysis of hydrogenated product as described below.

Second Step: Palladium-Catalyzed Reaction to Access Multicyclic Core **12.** To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar were added *endo-4n* (21.1 mg, 0.050 mmol, 1 equiv), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol , 10 mol %), and PPh_3 (3.9 mg, 0.015 mmol, 30 mol %). A solution of triethylamine (5.1 mg, 50 μmol , 1 equiv) in DMF (0.3 mL) was injected into the vial under nitrogen at room temperature. The reaction mixture was heated to 120 °C and stirred for 12 h. At this time, the mixture was cooled to room temperature and diluted with water (5 mL). The mixture was extracted with ethyl acetate (5 mL \times 3), washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , and concentrated to give the crude product purified SiO_2 -gel column chromatography (1:1 hexanes:ethyl acetate) to afford the desired product **12**; R_f = 0.10 (1:2 hexanes:ethyl acetate); The product stains orange with I_2 ; The product is isolated as an off-white amorphous solid; Isolated yield 9.4 mg, 55%; ^1H NMR (500 MHz, CDCl_3) δ 6.66 (s, 2H), 6.32 (s, 1H), 4.19 (d, J = 8.0 Hz, 1H), 4.11 (dd, J = 10.9, 1.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.71 (dd, J

= 14.1, 8.2 Hz, 1H), 2.48 (dd, J = 14.1, 1.3 Hz, 1H), 2.24 (dd, J = 12.4, 10.8 Hz, 1H), 2.04–1.98 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 204.9, 170.6, 150.6, 150.5, 133.0, 131.1, 118.8, 107.1, 107.0, 93.8, 81.7, 56.23, 56.18, 52.2, 48.5, 43.0, 41.0, 22.5; IR (ATIR) 3339, 2925, 2351, 1739, 1674, 1505, 1261, 1227, 1111, 1073, 1022 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$ (M^+) m/z 342.1216 found 342.1219.

First Step: [5 + 2] Cycloaddition Reaction with Styrene 2o. A solution of bis(1-cyanovinyl acetate) (**1**) (22.0 mg, 0.20 mmol, 1 equiv), 2-acetoxy-4,5-dimethoxystyrene **2o** (81.8 mg, 0.40 mmol, 4 equiv), and PPTS (2.5 mg, 0.010 mmol, 10 mol %) in dry acetonitrile (1 mL) was heated to reflux (100 °C, oil bath temperature) and stirred for 24 h. At this time, the solution was concentrated and purified by SiO_2 -gel chromatography (5:1 dichloromethane:ethyl acetate) to afford the cycloadducts; Combined isolated yield for both diastereomers is 20.9 mg, 54% (dr 52:48).

exo-diastereomer R_f = 0.21 (5:1 dichloromethane:ethyl acetate); The product stains purple with DNP; The product is isolated as an orange amorphous solid; Isolated yield 10.8 mg, 28%; ^1H NMR (600 MHz, CDCl_3) δ 8.26 (s, 1H), 7.83 (d, J = 9.8 Hz, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 6.22 (d, J = 9.8 Hz, 1H), 4.66 (dd, J = 9.7, 4.6 Hz, 1H), 4.16 (s, 3H), 3.96 (s, 3H), 3.77 (dd, J = 14.3, 4.5 Hz, 1H), 2.63 (s, 3H), 2.17 (dd, J = 14.3, 9.7 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.5, 190.6, 170.0, 153.2, 153.0, 147.8, 133.6, 129.8, 124.1, 114.9, 112.81, 112.76, 93.0, 79.0, 57.4, 56.2, 48.7, 30.4, 29.4, 24.7; IR (ATIR) 3355, 2962, 2913, 1690, 1667, 1523, 1274, 1207, 1152, 1047 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_6$ (M^+) m/z 384.1321 found 384.1316; The stereochemistry was determined by (^1H , ^1H) NOESY analysis of hydrogenated product as described below.

endo-diastereomer R_f = 0.14 (5:1 dichloromethane:ethyl acetate); The product stains purple with DNP; The product is isolated as a brown amorphous solid; Isolated yield 9.9 mg, 26%; ^1H NMR (600 MHz, CDCl_3) δ 7.17 (s, 1H), 6.87 (d, J = 9.8 Hz, 1H), 6.68 (s, 1H), 6.43 (d, J = 9.8 Hz, 1H), 5.60 (dd, J = 9.1, 9.1 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.56 (dd, J = 13.7, 9.6 Hz, 1H), 2.67 (s, 3H), 2.14 (dd, J = 13.7, 8.5 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 200.6, 189.8, 169.8, 151.2, 148.7, 148.6, 134.0, 128.1, 125.3, 115.6, 113.0, 111.0, 91.4, 76.9, 56.33, 56.29, 46.1, 34.2, 30.2, 24.0 IR (ATIR) 3279, 3055, 1714, 1672, 1522, 1324, 1272, 1209, 1149, 1004 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) m/z 407.1214 found 407.1210; The stereochemistry was determined by (^1H , ^1H) NOESY analysis of hydrogenated product as described below.

Second Step: Base Induced Domino Cyclization Reaction to Multicyclic Core 12. To a flame-dried 4 mL vial equipped with a Teflon-coated stir bar was added *endo*-**4n** (19.2 mg, 0.050 mmol, 1 equiv). THF (0.5 mL) was injected into the vial under nitrogen at room temperature. The solution was cooled to -78 °C, and then LiHMDS (0.25 mL, 0.25 mmol, 5 equiv, 1.0 M THF solution) was added dropwise to the reaction mixture. After warming to room temperature, the reaction was stirred for 1 h. At that time, saturated aqueous NH_4Cl (0.5 mL) was added at 0 °C. The mixture was extracted with ethyl acetate (5 mL \times 3), washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , and concentrated to give the crude product, which was then purified by SiO_2 -gel column chromatography (1:2 hexanes:ethyl acetate) to afford the desired product **13**; R_f = 0.32 (ethyl acetate only); The product stains red with I_2 ; The product is isolated as an off-white amorphous solid; Isolated yield 4.8 mg, 25%; ^1H NMR (500 MHz, CDCl_3) δ 7.71 (s, 1H), 6.71 (s, 1H), 5.87 (s, 1H), 4.07 (d, J = 3.5 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.74 (d, J = 6.0 Hz, 1H), 3.23 (dd, J = 7.2, 3.0 Hz, 1H), 2.98 (dd, J = 15.7, 7.3 Hz, 1H), 2.56 (d, J = 15.7 Hz, 1H), 2.43 (dd, J = 12.1, 6.0 Hz, 1H), 2.38 (d, J = 11.5 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 209.3, 204.9, 194.4, 170.2, 154.4, 149.4, 135.8, 127.5, 111.4, 110.9, 62.5, 58.2, 56.5, 56.3, 54.7, 42.6, 40.2, 35.1, 23.1; IR (ATIR) 3271, 2926, 2849, 1764, 1723, 1651, 1594, 1513, 1272, 1206, 1050 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_6$ (M^+) m/z 357.1212 found 357.1210.

Stereochemistry of [5 + 2]-Cycloadducts 4j, *endo*-4n**, *exo*-**4n**, *endo*-**4o**, and *exo*-**4o**.** Pd/C-Catalyzed Hydrogenation of **4j**, *exo*-**4n**, *endo*-**4o**, and *exo*-**4o**. To a flame-dried 25 mL round-

bottomed flask equipped with a Teflon-coated stir bar were added cycloadduct (0.050 mmol, 1 equiv), 10 wt % dried Pd/C (10.6 mg, 0.010 mmol, 20 mol % Pd), and THF (2 mL) under nitrogen atmosphere. The flask was evacuated and backfilled quickly at 0 °C with hydrogen gas, fitted with a balloon and the solution was stirred at room temperature for 14 h. After this time, the reaction mixture was filtered over a pad of Celite and concentrated to afford the hydrogenated product.

Hydrogenation of 4j. R_f = 0.36 (1:2 hexanes:ethyl acetate); The product stains black with CeMo; The product is an off-white amorphous solid; Isolated yield 15.2 mg, 97%; ^1H NMR (600 MHz, CDCl_3) δ 7.60–7.53 (m, 2H), 7.41–7.34 (m, 3H), 6.77 (s, 1H), 4.48 (dd, J = 11.8, 7.6 Hz, 1H), 3.82 (dd, J = 12.8, 12.8 Hz, 1H), 3.02–2.93 (m, 2H), 2.69–2.55 (m, 2H), 2.05 (s, 3H), 1.87 (dd, J = 14.1, 7.5 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.2, 170.1, 132.9, 131.9, 129.7, 129.0, 116.8, 90.5, 76.2, 52.5, 36.7, 33.5, 31.7, 24.3; IR (ATIR) 3359, 2915, 1745, 1684, 1501, 1259, 979, 943, 751 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ (M^+) m/z 316.0882 found 316.0880; The stereochemistry was determined by (^1H , ^1H) NOESY analysis.

Hydrogenation of *exo*-4n**.** Purification by SiO_2 -column chromatography (2:1 hexanes:ethyl acetate); R_f = 0.36 (1:2 hexanes:ethyl acetate); The product stains faint purple with PAA; The product is an off-white amorphous solid; Isolated yield 10.6 mg, 50%; ^1H NMR (600 MHz, CDCl_3) δ 8.00 (s, 1H), 7.02 (s, 1H), 6.91 (s, 1H), 4.45 (dd, J = 9.9, 5.9 Hz, 1H), 4.07 (s, 3H), 3.88 (s, 3H), 3.69 (dd, J = 14.6, 5.9 Hz, 1H), 2.94 (ddd, J = 16.7, 12.0, 8.8 Hz, 1H), 2.78 (dd, J = 16.8, 6.3 Hz, 1H), 2.72–2.60 (m, 1H), 2.36 (dd, J = 14.6, 9.9 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.6, 169.8, 149.9, 149.4, 131.7, 115.9, 114.8, 114.3, 112.5, 92.1, 79.5, 56.9, 56.2, 49.5, 38.4, 35.7, 31.7, 24.6; IR (ATIR) 3360, 2924, 2255, 1740, 1680, 1505, 1259, 1212, 1170, 1019, 730 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_5^{79}\text{Br}$ (M^+) m/z 422.0477 found 422.0475.

Hydrogenation of *exo*-4o**.** Purification by SiO_2 -gel chromatography (2:1 hexanes:ethyl acetate); R_f = 0.29 (2:1 hexanes:ethyl acetate); The product stains faint red with PAA; The product is an off-white amorphous solid; Isolated yield 17.2 mg, 89%; ^1H NMR (600 MHz, CDCl_3) δ 8.18 (s, 1H), 7.26 (s, 1H), 6.95 (s, 1H), 4.85 (dd, J = 10.0, 6.0 Hz, 1H), 4.16 (s, 3H), 3.95 (s, 3H), 3.75 (dd, J = 14.6, 5.9 Hz, 1H), 3.07 (dd, J = 13.1, 8.1 Hz, 1H), 2.90 (ddd, J = 16.7, 12.4, 8.4 Hz, 1H), 2.73 (dd, J = 16.7, 6.6 Hz, 1H), 2.64 (s, 3H), 2.63–2.58 (m, 1H), 2.23 (dd, J = 14.5, 10.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.5, 199.4, 169.8, 153.4, 147.6, 135.9, 129.6, 116.4, 113.2, 112.6, 92.1, 80.4, 57.3, 56.2, 45.3, 37.3, 35.6, 31.8, 29.4, 24.7; IR (ATIR) 3399, 2939, 1693, 1661, 1525, 1327, 1282, 1209, 1151, 1052, 1003 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$ (M^+) m/z 386.1478 found 386.1474; The stereochemistry was determined by (^1H , ^1H) NOESY analysis.

Hydrogenation of *endo*-4o**.** Purification by SiO_2 -gel chromatography (1:1 hexanes:ethyl acetate); R_f = 0.16 (1:2 hexanes:ethyl acetate); The product stains red with PAA; The product is an off-white amorphous solid; Isolated yield 12.1 mg, 80% (15 mg, 0.039 mmol of *endo*-**4o** was used); ^1H NMR (500 MHz, CDCl_3) δ 7.17 (s, 1H), 6.73 (s, 1H), 6.58 (s, 1H), 5.55 (dd, J = 12.1, 7.1 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.12 (ddd, J = 16.8, 11.1, 5.7 Hz, 1H), 2.96 (dd, J = 12.8, 12.8 Hz, 1H), 2.65 (s, 3H), 2.57 (ddd, J = 16.7, 8.7, 5.2 Hz, 1H), 2.48 (ddd, J = 16.5, 11.2, 5.2 Hz, 1H), 2.33 (dd, J = 13.8, 7.0 Hz, 1H), 2.08 (s, 3H), 1.92 (ddd, J = 14.5, 8.7, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 203.4, 201.3, 170.4, 151.4, 148.3, 133.5, 126.9, 118.6, 113.1, 110.9, 91.7, 76.6, 56.4, 56.3, 44.9, 37.5, 33.0, 30.2, 28.8, 23.2; IR (ATIR) 3290, 2920, 2849, 1729, 1687, 1661, 1520, 1269, 1145, 1041, 1020, 877 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$ (M^+) m/z 386.1478 found 386.1481; The stereochemistry was determined by (^1H , ^1H) NOESY analysis.

Rh-Catalyzed Hydrogenation of *endo*-4n**.** To a flame-dried 10 mL round-bottomed flask equipped with a Teflon-coated stir bar were added *endo*-**4n** (14.5 mg, 0.034 mmol, 1 equiv), $\text{RhCl}(\text{PPh}_3)_3$ (Wilkinson's catalyst) (3.3 mg, 3.5 μmol , 10 mol %). The flask was evacuated and backfilled with hydrogen gas, fitted with a balloon of hydrogen gas and toluene (1 mL) was injected into the flask at room temperature. The resulting solution was stirred at 80 °C for 15 h. After

this time, the reaction mixture was concentrated to give the crude product purified by SiO₂-gel column chromatography (1:1 hexanes:ethyl acetate); *R_f* = 0.29 (1:2 hexanes:ethyl acetate); The product stains faint purple with PAA; The product is isolated as an off-white amorphous solid; Isolated yield 7.7 mg, 54%; ¹H NMR (600 MHz, CDCl₃) δ 7.12 (s, 1H), 6.65 (s, 1H), 6.58 (s, 1H), 4.91 (dd, *J* = 11.9, 7.1 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.13–3.06 (m, 2H), 2.65 (ddd, *J* = 15.6, 8.6, 6.1 Hz, 1H), 2.57 (ddd, *J* = 14.6, 11.1, 6.0 Hz, 1H), 2.27 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.09 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 202.4, 170.4, 149.7, 148.9, 125.5, 118.3, 117.1, 116.9, 110.9, 91.2, 75.9, 56.5, 56.4, 49.6, 37.4, 32.9, 29.8, 29.3, 23.4; IR (ATR) 3324, 2922, 2851, 1726, 1668, 1508, 1213, 1194, 1026 cm⁻¹; HRMS (EI) calcd for C₁₈H₁₉N₂O₅⁺Br (M)⁺ *m/z* 422.0477 found 422.0475; The stereochemistry was determined by (¹H, ¹H) NOESY analysis.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02111.

¹H and ¹³C NMR spectra for all new compounds (PDF)

X-ray crystallographic data for compound **4a** (CCDC 1485876) (CIF)

X-ray crystallographic data for compound *endo*-**4b** (CCDC 1485877) (CIF)

X-ray crystallographic data for compound *exo*-**4b** (CCDC 1485878) (CIF)

X-ray crystallographic data for compound **4m** (CCDC 1485879) (CIF)

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Notes

The authors declare no competing financial interest.

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