Palladium-Catalyzed Intermolecular Acylative Heck Reactions with Imides as Acyl Electrophiles

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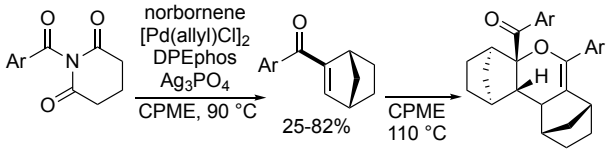
Supporting Information Placeholder

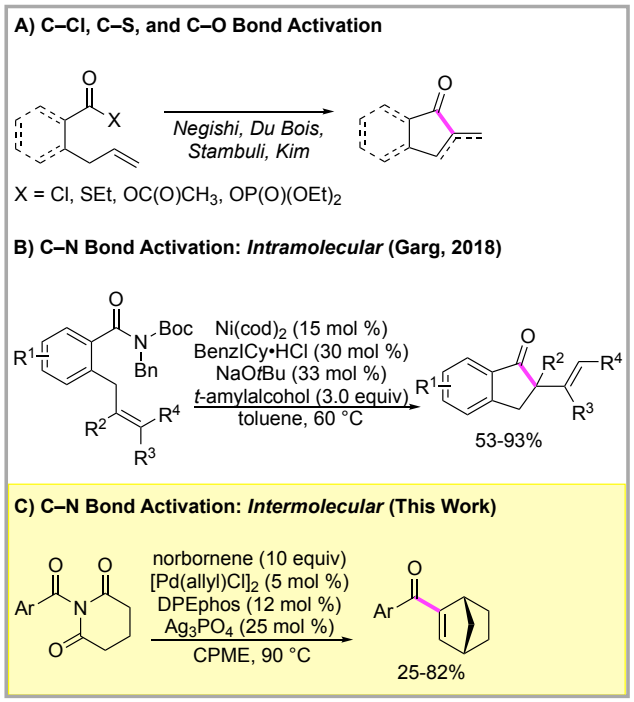


ABSTRACT: We disclose palladium-catalyzed, intermolecular acylative Heck reactions using imides as acyl electrophiles. The catalyst generated from $[Pd(allyl)Cl]_2$ and DPEphos promotes the reaction between *N*-benzoylglutarimides and norbornene in the presence of silver phosphate. The acylative Heck reaction encompasses an array of *N*-benzoylglutarimide electrophiles containing electron-donating, halogenated, and electron-withdrawing substituents to generate α,β-unsaturated ketones in moderate to high yields (25-82%). The bicylic α,β-unsaturated ketones are readily transformed into polycyclic architectures via thermal hetero-Diels-Alder reactions that occur by dimerization of the α,β-unsaturated ketones.

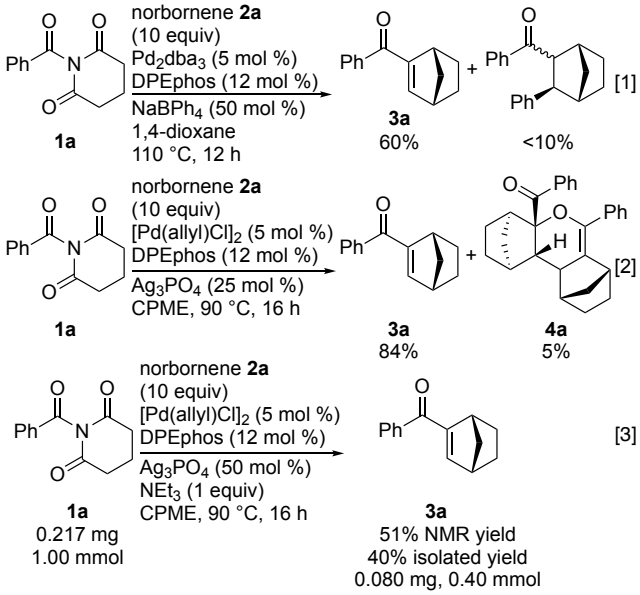
Since its discovery, the Heck reaction has been used as a key method to construct C–C bonds in a variety of molecular architectures.[1,2] Heck-type reactions now encompass a range of electrophiles that can be coupled to a variety of alkenes.[2a-c] Of particular interest to our laboratory are acylative Heck reactions that can be leveraged to rapidly generate α,β-unsaturated ketones.[3] In 1985, Negishi and co-workers reported the intramolecular acylative Heck reaction of *ortho*-allylbenzoyl chloride using stoichiometric amounts of palladium.[4] This approach to acylative Heck reactions presented an alternative to the use of toxic carbon monoxide to generate α,β-unsaturated carbonyl compounds through the Heck reaction. Further studies led to the development of intra- and intermolecular acylative Heck reactions using carboxylic acid derivatives such as acid chlorides,[3a] thioesters,[3b] carboxylic acid anhydrides,[3c,3d] and carboxylic phosphoric anhydrides[3e] via palladium-catalyzed activation of C–Cl, C–S, and C–O bonds (Scheme 1A). Recently, our group[5] and others[6] have shown amides and imides to be robust, readily accessible acyl electrophiles[7] for transition metal-catalyzed functionalization of alkenes. Garg and co-workers reported nickel-catalyzed, intramolecular acylative Heck reactions of amides via activation of C–N bonds (Scheme 1B).[6] A nickel complex generated from $Ni(cod)_2$ and an *N*-heterocyclic carbene, BenzICy, catalyzed the intramolec-

ular reactions of *ortho*-allylbenzamides to form indanone derivatives containing α-quaternary centers in good-to-excellent yields (53-93%). Currently, there are no reports of transition metal-catalyzed intermolecular acylative Heck reactions using amides or imides as acyl electrophiles.[8] Herein we report the first palladium-catalyzed, intermolecular acylative Heck reaction using imides as acyl electrophiles (Scheme 1C).

Scheme 1. Transition Metal-Catalyzed Acylative Heck Reactions



During studies to develop transition metal-catalyzed alkene carboacylation reactions, we observed that a palladium catalyst generated from Pd_2dba_3 and DPEphos catalyzed the reaction between *N*-benzoylglutarimide and norbornene in the presence of 50 mol % sodium tetraphenylborate to form the acylative Heck product, bicyclo[2.2.1]hept-2-en-2-yl(phenyl)methanone **3a**, in 60% yield and products of formal alkene carboacylation in <10% yield (eq 1; see supporting information, Table S1).[9] Intrigued by this result, we set out to identify reaction conditions for the palladium-catalyzed intermolecular acylative Heck reaction of *N*-benzoylglutarimide **1a** with norbornene in the presence of a base.



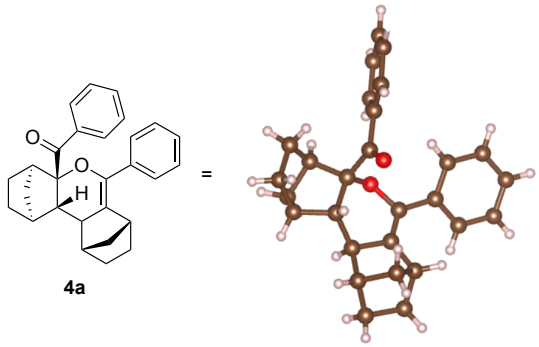
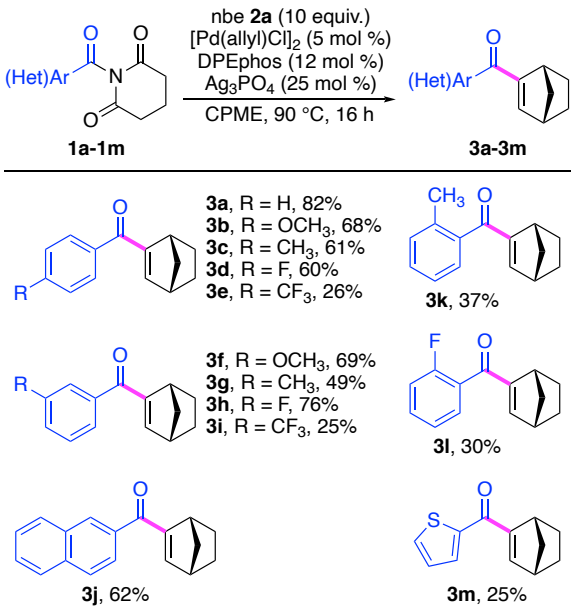


Figure 1. X-ray crystal structure of hetero-Diels-Alder adduct **4a**.

After rigorous screening of bases and precatalysts (see supporting information, Table S2), we observed that the model reaction of *N*-benzoylglutarimide **1a** with norbornene **2a** in the presence of 5 mol % $[Pd(allyl)Cl]_2$, 12 mol % DPEphos and 25 mol % silver phosphate formed **3a** in 84% yield (eq 2). In addition, the reaction also formed a hetero-Diels-Alder adduct **4a** via dimerization of **3a** in 5% yield.[10] The identity of the Diels-Alder adduct **4a** was confirmed by X-Ray crystallographic analysis (Figure 1). The parent reaction can be conducted on a 1 mmol scale with modified reaction conditions. The 1 mmol-scale reaction of **1a** with norbornene occurs to

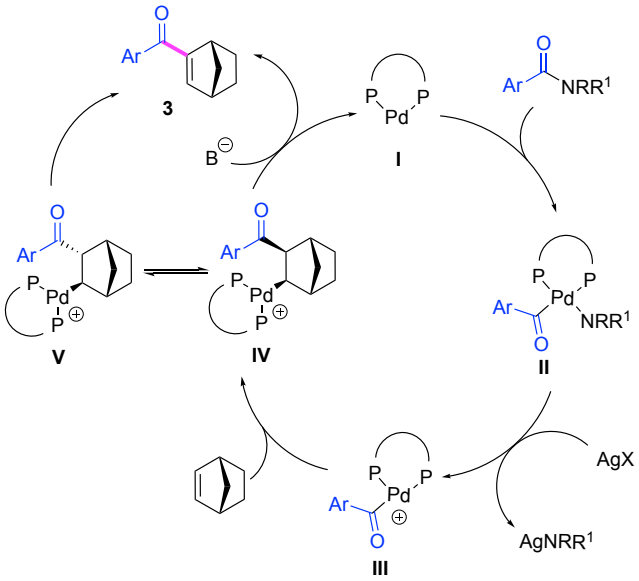
form enone **3a** in 40% yield when the reaction is run in the presence of 50 mol % Ag_3PO_4 and 1 equiv of NEt_3 to facilitate turnover of the palladium catalyst (eq 3).

Scheme 2. Scope of the Acylative Heck Reaction



The scope of the acylative Heck reaction of a variety of *N*-aroylglutarimides with norbornene is presented in Scheme 2. The Heck reactions of *para*-, *meta*-, and *ortho*-substituted *N*-benzoylglutarimide derivatives **1a-1l** and norbornene formed the corresponding Heck products **3a-3l** in 25-82% yields. Reactions of *para*-substituted *N*-benzoylglutarimides containing electron-donating, halogen, and electron-withdrawing groups formed Heck products **3b-3e** in moderate to good yields (25-68%). Reactions of *N*-benzoylglutarimides containing electron-donating, halogen, and electron-withdrawing *meta*-substituents formed the Heck products **3f-3i** in 25-76% yields. The reaction of a polyaromatic *N*-aroylglutarimide, 1-(2-naphthoyl)piperidine-2,6-dione **1j**, with norbornene formed product **3j** in 62% yield. We also found that the reaction tolerated *ortho*-substituted *N*-benzoylglutarimides. Reactions of *ortho*-methyl and *ortho*-fluoro substituted *N*-benzoylglutarimides **2k** and **2l** formed the corresponding enone products **3k** and **3l** in 37 and 30% yields, respectively. An *N*-heteroaroylglutarimide, 1-(thiophene-2-carbonyl)piperidine-2,6-dione **1m**, also proved to be a suitable electrophile and reacted to form the enone product **3m** in 25% yield. Unfortunately, reactions of *N*-benzoylglutarimides with additional bicyclic alkenes did not occur in high yields (see supporting information, Scheme S1).

Scheme 3. Proposed Catalytic Cycle

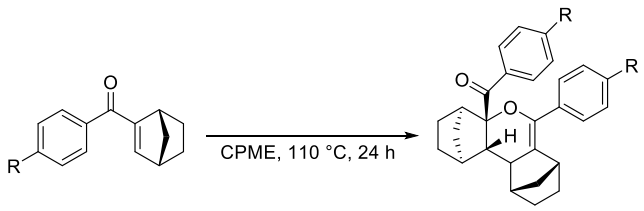


We propose a classical Pd(0)/Pd(II) cycle for Pd-catalyzed, intermolecular, acylative Heck reactions between *N*-benzoylglutarimides and norbornene (Scheme 3). The active catalyst **I** undergoes oxidative addition into the C–N bond of the imide to form acyl-palladium-amido complex **II**. Complex **II** reacts with silver phosphate to form cationic acyl-palladium complex **III**.[11] Migratory insertion of norbornene into the Pd–C(O) bond forms alkyl-palladium complex **IV**. We envision two potential pathways exist to form product **3** from alkyl-palladium complex **IV**. A base-assisted, non-classical *β*-hydride elimination of complex **IV** could generate product **3** and regenerate the Pd(0) catalyst. Alternatively, epimerization of the stereocenter alpha to the carbonyl carbon to form the diastereomeric

alkyl-palladium complex **V** and subsequent classical β-hydride elimination lead to the generation of product **3**.

After exploring the scope of the acylative Heck reaction, we sought to develop a simple method to generate the hetero-Diels-Alder adducts **4** (Scheme 4). We found that the product of the acylative Heck reaction **3a** could be dissolved in cyclopentyl methyl ether (CPME) and heated at 110 °C for 24 h to obtain hetero-Diels-Alder adduct **4a** in 48% yield. Additionally, we observed that the hetero-Diels-Alder reaction proceeded more efficiently with substrates containing electron-withdrawing groups. The reaction of fluorine-substituted α,β-unsaturated ketone **3d** formed hetero-Diels-Alder adduct **4b** in 62% yield; however, the reaction of methyl-substituted **3c** generated adduct **4c** in 35% yield. Through this hetero-Diels-Alder reaction, we have demonstrated a pathway from readily accessible α,β-unsaturated ketones to complex polycyclic heterocycles.

Scheme 4. Hetero-Diels-Alder Reaction



4a, R = H: 48%
4b, R = F: 62%
4c, R = Me: 35%

In summary, we have developed palladium-catalyzed, intermolecular, acylative Heck reactions between a wide range of *N*-benzoylglutarimides and norbornene to form α,β-unsaturated ketones in 25-82% yields. These α,β-unsaturated ketones can be transformed through a hetero-Diels-Alder reaction into complex polycyclic heterocycles.

EXPERIMENTAL SECTION

General Information. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under nitrogen unless otherwise stated. Benzene, toluene, dichloromethane (DCM), diethylether (Et_2O), and tetrahydrofuran (THF) were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous 1,4-dioxane and cyclopentyl methyl ether (CPME) were purchased from Sigma-Aldrich and used as received. Unless otherwise stated, all reagents were purchased from commercial sources and used without purification. All imides were synthesized according to literature procedures.[12] Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63μm, 60Å) or using a Teledyne Isco Combiflash® R*f* system with Redi*Sep* GoldTM columns using hexane/ethyl acetate or hexane/Et_2O or pentane/Et_2O. Reaction products were visualized on TLC under UV light or by staining with $KMnO_4$.

Instrumentation. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Elemental analysis was performed at the Iowa State University Chemical Instrumentation Facility on the Perkin Elmer 2100 Series II CHN/S Analyzer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). ^{19}F NMR shifts are reported based on indirect reference to $CDCl_3$.[13] Coupling constants are reported in hertz. Diffraction data was collected on a Bruker-AXS Venture D8 single crystal diffractometer with a Mo microsource tube.

General Procedure A for Synthesis of Heck Products 3a-3m. An oven-dried 1-dram vial was charged with [Pd(allyl)Cl]$_2$ (1.80 mg, 0.005 mmol), DPEphos (6.50 mg, 0.012 mmol), imide (0.100 mmol), silver phosphate (10.5 mg, 0.025 mmol), alkene (1.00 mmol), and cyclopentyl methyl ether (0.333 M, 0.300 mL). The reaction mixture was stirred at 90 °C in an oil bath for 16 h. Upon completion of the reaction, the reaction mixture was filtered through a short plug of silica using ethyl acetate (20 mL) and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give Heck products **3a**-**3m**.

General Procedure B for Synthesis of Hetero-Diels-Alder Products 4a-4c. α,β-Unsaturated ketones **3a**, **3c**, or **3d** were prepared according to General Procedure A. The appropriate ketone **3a**, **3c**, or **3d** was dissolved in CPME (0.333 M) and heated at 110 °C in an oil bath for 24 h. The crude reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by flash column chromatography to give hetero-Diels-Alder products **4a-4c**.

General Procedure C for 1 mmol-Scale Synthesis of Heck Product 3a. An oven-dried scintillation vial was charged with [Pd(allyl)Cl]$_2$ (18.3 mg, 0.050 mmol), DPEphos (64.6 mg, 0.120 mmol), 1-benzoylpiperidine-2,6-dione (217 mg, 1.00 mmol, 1.00 equiv), silver phosphate (209.3 mg, 0.500 mmol), triethylamine (139 µL, 1.00 mmol, 1.00 equiv), norbornene (942 mg, 10.0 mmol, 10.0 equiv), and cyclopentyl methyl ether (0.333 M, 3.00 mL). The reaction mixture was stirred at 90 °C in an oil bath for 16 h. Upon completion of the reaction, the reaction mixture was filtered through a short plug of silica using ethyl acetate (20 mL) and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give (bicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone **3a** in 40% yield (80.0 mg, 0.403 mmol).

(Bicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone **3a**: Prepared according to General Procedure A from 1-benzoylpiperidine-2,6-dione (21.7 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 93:7 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone **3a** as a white solid in 82 % yield (16.2 mg, 0.082 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.75 (d, 2H, J = 7.2 Hz), 7.51 (t, 1H, J = 7.2 Hz), 7.42 (t, 2H, J = 7.2 Hz), 6.65 (d, 1H, J = 3.0 Hz), 3.47 (s, 1H), 3.12 (s, 1H), 1.77-1.86 (m, 2H), 1.55-1.59 (m, 1H), 1.27 (d, 1H, J = 8.7 Hz), 1.18-1.24 (m, 1H), 1.05-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 192.9, 149.9, 148.7, 138.4, 132.0, 129.0, 128.3, 47.2, 44.5, 42.6, 25.5, 24.8. **HRMS** (ESI): Calcd. for $C_{14}H_{15}O^+$ ($[M+H]^+$): 199.1117, Found: 199.1119.

(Bicyclo[2.2.1]hept-2-en-2-yl)(4-methoxyphenyl)methanone ***3b***: Prepared according to General Procedure A from 1-(4-methoxybenzoyl)piperidine-2,6-dione (24.7 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 94:6 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(4-methoxyphenyl)methanone **3b** as a white solid in 68% yield (15.5 mg, 0.068 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz,): δ 7.78 (ddd, 2H, J = 8.9, 2.8, 2.1 Hz), 6.91 (ddd, 2H, J = 8.9, 2.8, 2.1 Hz), 6.60 (d, 1H, J = 3.1Hz), 3.86 (s, 3H), 3.43 (s, 1H), 3.11 (s, 1H), 1.76-1.85 (m, 2H), 1.53-1.58 (m, 1H), 1.19-1.27 (m, 2H), 1.05-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 191.8,

162.9, 148.7, 148.2, 133.23, 133.16, 113.5, 55.6, 47.2, 44.5, 43.0, 25.6, 24.9. **HRMS** (ESI): Calcd. for $C_{15}H_{17}O_2^+$ ($[M+H]^+$): 229.1223, Found: 229.1227.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(p-tolyl)methanone **3c***: Prepared according to General Procedure A from 1-(4-methylbenzoyl)piperidine-2,6-dione (23.1 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 93:7 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(*p*-tolyl)methanone **3c** as a white solid in 61% yield (12.9 mg, 0.061 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H *J* = 7.9 Hz), 7.22 (d, 2H, *J* = 7.9 Hz), 6.63 (d, 1H, *J* = 3.1 Hz), 3.45 (s, 1H), 3.11 (s, 1H), 2.40 (s, 3H), 1.76-1.85 (m, 2H), 1.54-1.58 (m, 1H), 1.24-1.28 (m, 1H), 1.18-1.23 (m, 1H), 1.04-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 192.7, 149.1, 148.7, 142.7, 135.7, 129.2, 129.0, 47.2, 44.5, 42.7, 25.5, 24.8, 21.7. **HRMS** (ESI): Calcd. for $C_{15}H_{17}O^+$ ($[M+H]^+$): 213.1274, Found: 213.1278.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(4-fluorophenyl)methanone **3d***: Prepared according to General Procedure A from 1-(4-fluorobenzoyl)piperidine-2,6-dione (23.5 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(4-fluorophenyl)methanone **3d** as a white solid in 60% yield (13.0 mg, 0.060 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78 (dd, 2H, *J* = 8.8, 5.5 Hz), 7.09 (t, 2H, *J* = 8.8 Hz), 6.63 (d, 1H, *J* = 3.2 Hz), 3.45 (s, 1H), 3.11-3.14 (m, 1H), 1.77-1.87 (m, 2H), 1.54-1.58 (m, 1H), 1.17-1.29 (m, 2H), 1.05-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 191.4, 165.3 (C–F, $^1J_{C-F}$ = 251.5 Hz, 1C), 149.6, 148.6, 134.6 (C–F, $^4J_{C-F}$ = 3.0 Hz), 131.4 (C–F, $^3J_{C-F}$ = 9.0 Hz), 115.4 (C–F, $^2J_{C-F}$ = 21.6 Hz), 47.2, 44.5, 42.8, 25.5, 24.8. **^{19}F{^{1}H} NMR** ($CDCl_3$, 376 MHz): δ -107.28 (m, 1F). **HRMS** (ESI): Calcd. for $C_{14}H_{14}FO^+$ ($[M+H]^+$): 217.1023, Found: 217.1025.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(4-(trifluoromethyl)phenyl)methanone **3e***: Prepared according to General Procedure A from 1-(4-trifluoromethylbenzoyl)piperidine-2,6-dione (28.5 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(4-(trifluoromethyl)phenyl)methanone **3e** as a white solid in 26% yield (6.9 mg, 0.026 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.83 (d, 2H, *J* = 8.1 Hz), 7.69 (d, 2H, *J* = 8.1 Hz), 6.68 (d, 1H, *J* = 3.1 Hz), 3.49 (s, 1H), 3.15 (d, 1H *J* = 1.28 Hz), 1.79-1.89 (m, 2H), 1.57-1.61 (m, 1H), 1.30 (dd, 1H, *J* = 8.8, 0.8 Hz), 1.16-1.25 (m, 1H), 1.05-1.13 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 191.6, 151.2, 148.6, 141.3 (C–F, $^4J_{C-F}$ = 1.32 Hz), 133.4 (C–F, $^2J_{C-F}$ = 32.4 Hz), 129.2, 125.3 (C–F, $^3J_{C-F}$ = 3.7 Hz), 123.9 (C–F, $^1J_{C-F}$ = 271.7 Hz), 47.3, 44.7, 42.4, 25.5, 24.7. **^{19}F{^{1}H} NMR** ($CDCl_3$, 376 MHz): δ -62.96 (s, 3F). **HRMS** (ESI): Calcd. for $C_{15}H_{14}F_3O^+$ ($[M+H]^+$): 267.0991, Found: 267.0895.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(3-methoxyphenyl)methanone **3f***: Prepared according to General Procedure A from 1-(3-methoxybenzoyl)piperidine-2,6-dione (24.7 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane:diethyl ether)

to yield (bicyclo[2.2.1]hept-2-en-2-yl)(3-methoxyphenyl)methanone **3f** as a white solid in 69% yield (15.7 mg, 0.069 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.27-7.34 (m, 3H), 7.04-7.09 (m, 1H), 6.68 (d, 1H, *J* = 3.16 Hz), 3.84 (s, 3H), 3.46 (s, 1H), 3.12 (s, 1H), 1.76-1.86 (m, 2H), 1.55-1.59 (m, 1H), 1.17-1.28 (m, 2H), 1.05-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 192.6, 159.6, 149.9, 148.7, 139.7, 129.2, 121.7, 118.3, 113.5, 55.5, 47.2, 44.5, 42.6, 25.5, 24.8. **HRMS** (ESI): Calcd. for $C_{15}H_{17}O_2^+$ ($[M+H]^+$): 229.1223, Found: 229.1228.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(m-tolyl)methanone **3g***: Prepared according to General Procedure A from 1-(3-methylbenzoyl)piperidine-2,6-dione (23.1 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(*m*-tolyl)methanone **3g** as a white solid in 49% yield (10.4 mg, 0.049 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.52-7.56 (m, 2H), 7.31-7.34 (m, 1H), 7.30 (t, 1H, *J* = 7.4 Hz), 6.64 (d, 1H, *J* = 3.1 Hz), 3.46 (s, 1H), 3.12 (s, 1H), 2.39 (s, 3H), 1.76-1.86 (m, 2H), 1.55-1.59 (m, 1H), 1.17-1.28 (m, 2H), 1.04-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 193.2, 149.8, 148.8, 138.4, 138.1, 132.8, 129.4, 128.1, 126.3, 47.2, 44.5, 42.5, 25.5, 24.8, 21.5. **HRMS** (ESI): Calcd. for $C_{15}H_{17}O^+$ ($[M+H]^+$): 213.1274, Found: 213.1280.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(3-fluorophenyl)methanone **3h***: Prepared according to General Procedure A from 1-(3-fluorobenzoyl)piperidine-2,6-dione (23.5 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(3-fluorophenyl)methanone **3h** as a white solid in 76% yield (16.4 mg, 0.076 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.53 (d, 1H, *J* = 7.7 Hz), 7.37-7.45 (m, 2H), 7.21 (td, 1H, *J* = 8.2, 2.3 Hz), 6.69 (d, 1H, *J* = 3.1 Hz), 3.46 (s, 1H), 3.14 (s, 1H), 1.77-1.87 (m, 2H), 1.55-1.59 (m, 1H), 1.15-1.29 (m, 2H), 1.05-1.12 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 191.4 (C–F, $^4J_{C-F}$ = 2.0 Hz), 162.6 (C–F, $^1J_{C-F}$ = 247.5 Hz), 150.4, 148.5, 140.4 (C–F, $^3J_{C-F}$ = 6.2 Hz), 130.0 (C–F, $^3J_{C-F}$ = 7.7 Hz), 124.7 (C–F, $^4J_{C-F}$ = 3.0 Hz), 119.0 (C–F, $^2J_{C-F}$ = 21.3 Hz), 115.8 (C–F, $^2J_{C-F}$ = 22.3 Hz), 47.2, 44.6, 42.6, 25.5, 24.7. **^{19}F{^{1}H} NMR** ($CDCl_3$, 376 MHz): δ -112.49 (m, 1F). **HRMS** (ESI): Calcd. for $C_{14}H_{14}FO^+$ ($[M+H]^+$): 217.1023, Found: 217.1023.

*(Bicyclo[2.2.1]hept-2-en-2-yl)(3-(trifluoromethyl)phenyl)methanone **3i***: Prepared according to General Procedure A from 1-(3-trifluoromethylbenzoyl)piperidine-2,6-dione (28.5 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(3-(trifluoromethyl)phenyl)methanone **3i** as a white solid in 25% yield (6.7 mg, 0.025 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.92 (d, 1H, *J* = 7.8 Hz), 7.77 (d, 1H, *J* = 7.8 Hz), 7.56 (t, 1H, *J* = 7.8 Hz), 6.67 (d, 1H, *J* = 2.8 Hz), 3.48 (s, 1H), 3.16 (s, 1H), 1.78-1.88 (m, 2H), 1.60 (d, 1H, *J* = 8.7 Hz), 1.30 (d, 1H, *J* = 8.8 Hz), 1.16-1.25 (m, 1H), 1.05-1.13 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 191.3, 150.9, 148.5, 138.9, 132.1 (C–F, $^4J_{C-F}$ = 1.6 Hz), 130.91 (C–F, $^2J_{C-F}$ = 32.7 Hz), 128.96, 128.5 (C–F, $^3J_{C-F}$ = 3.7 Hz), 125.8 (C–F, $^3J_{C-F}$ =

3.8 Hz, 1C), 123.9 (C–F, $^{1}J_{C–F}$ = 272.6 Hz), 47.2, 44.7, 42.5, 25.5, 24.7. **^{19}F{^{1}H} NMR** ($CDCl_3$, 376 MHz): δ -62.74 (s, 3F). **HRMS** (ESI): Calcd. for $C_{15}H_{14}F_3O^+$ ($[M+H]^+$): 267.0991, Found: 267.1004.

(Bicyclo[2.2.1]hept-2-en-2-yl)(naphthalen-2-yl)methanone ***3j***: Prepared according to General Procedure A from 1-(2-naphthoyl)piperidine-2,6-dione (26.7 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane/ethyl acetate) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(naphthalen-2-yl)methanone **3j** as a white solid in 62% yield (15.4 mg, 0.062 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.26 (s, 1H), 7.93-7.95 (m, 1H), 7.84-7.90 (m, 3H), 7.52-7.60 (m, 2H), 6.72 (d, 1H, *J* = 3.2 Hz), 3.52 (s, 1H), 3.17 (s, 1H), 1.80-1.89 (m, 2H), 1.65 (dp, 1H, *J* = 8.7, 1.9 Hz), 1.23-1.33 (m, 2H), 1.08-1.15 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 192.9, 149.8, 148.9, 135.6, 135.2, 132.5, 130.2, 129.4, 128.3, 128.0, 127.9, 126.7, 125.3, 47.2, 44.6, 42.8, 25.6, 24.8. **HRMS** (ESI): Calcd. for $C_{18}H_{17}O^+$ ($[M+H]^+$): 249.1274, Found: 249.1277.

(Bicyclo[2.2.1]hept-2-en-2-yl)(o-tolyl)methanone ***3k***: Prepared according to General Procedure A from 1-(2-methylbenzoyl)piperidine-2,6-dione (23.1 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(*o*-tolyl)methanone **3k** as a white solid in 37% yield (7.84 mg, 0.037 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30 (td, 1H, *J* = 7.5, 1.4 Hz), 7.24-7.26 (m, 1H), 7.15-7.22 (m, 2H), 6.51 (d, 1H, *J* = 3.2 Hz), 3.51 (s, 1H), 3.06 (d, 1H, *J* = 1.3 Hz), 2.30 (s, 3H), 1.78-1.86 (m, 2H), 1.57 (dp, 1H, *J* = 8.7, 2.0 Hz), 1.29 (dd, 1H, *J* = 8.7, 0.9 Hz), 1.06-1.20 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 185.3, 151.8, 150.5, 139.2, 136.1, 131.0, 129.8, 128.1, 125.0, 47.8, 44.3, 41.1, 25.3, 24 .8, 19.8. **HRMS** (ESI): Calcd. for $C_{15}H_{17}O^+$ ($[M+H]^+$): 213.1274, Found: 213.1268.

(Bicyclo[2.2.1]hept-2-en-2-yl)(2-fluorophenyl)methanone ***3l***: Prepared according to General Procedure A from 1-(2-fluorobenzoyl)piperidine-2,6-dione (23.5 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 95:5 hexane/diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(2-fluorophenyl)methanone **3l** as a white solid in 30% yield (6.48 mg, 0.030 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40-7.45 (m, 2H), 7.17 (td, 1H, *J* = 7.6, 0.7 Hz), 7.09 (t, 1H, *J* = 8.8 Hz), 6.67 (s, 1H), 3.51 (s, 1H), 3.09 (d, 1H, *J* = 1.4 Hz), 1.77-1.86 (m, 2H), 1.59 (dp, 1H, *J* = 8.7, 1.9 Hz), 1.29 (dd, 1H, *J* = 8.7, 0.7 Hz), 1.07-1.22 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 189.6, 159.82 (C–F, $^{1}J_{C–F}$ = 251.8 Hz), 151.9 (C–F, $^{4}J_{C–F}$ = 2.2 Hz), 149.9 (C–F, $^{5}J_{C–F}$ = 1.0 Hz), 132.3 (C–F, $^{3}J_{C–F}$ = 8.3 Hz), 130.2 (C–F, $^{3}J_{C–F}$ = 3.1 Hz), 127.8 (C–F, $^{2}J_{C–F}$ = 15.0 Hz), 124.0 (C–F, $^{4}J_{C–F}$ = 3.7 Hz), 116.3 (C–F, $^{2}J_{C–F}$ = 22.1 Hz), 47.8, 44.4, 41.3, 25.2, 24.7. **^{19}F{^{1}H} NMR** ($CDCl_3$, 376 MHz): δ -113.45 (m, 1F). **HRMS** (ESI): Calcd. for $C_{14}H_{14}FO^+$ ($[M+H]^+$): 217.1023, Found: 217.1018.

(Bicyclo[2.2.1]hept-2-en-2-yl)(thiophen-2-yl)methanone ***3m***: Prepared according to General Procedure A from 1-(thiophene-2-carbonyl)piperidine-2,6-dione (22.3 mg, 0.100 mmol, 1.00 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane/diethyl ether)

to yield (bicyclo[2.2.1]hept-2-en-2-yl)(thiophen-2-yl)methanone **3m** as a white solid in 25% yield (5.10 mg, 0.025 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.68 (dd, 1H, *J* = 3.8, 1.2 Hz), 7.59 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.10 (dd, 1H, *J* = 5.0, 3.8 Hz), 6.88 (d, 1H, *J* = 3.2 Hz), 3.43 (s, 1H), 3.13 (s, 1H), 1.89-1.75 (m, 2H), 1.58-1.51 (m, 1H), 1.27-1.22 (m, 2H), 1.16-1.09 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 184.2, 148.8, 147.6, 143.9, 132.7, 132.1, 127.8, 47.1, 44.4, 43.2, 25.5, 24.9. **HRMS** (ESI): Calcd. for $C_{12}H_{13}SO^+$ ($[M+H]^+$): 205.0682, Found: 205.0681.

*Hetero-Diels-Alder adduct **4a***: Prepared according to General Procedure B from (bicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone **3a** (0.142 mmol) at 110 °C for 24 h. The crude reaction mixture was purified by flash chromatography (100:0 → 90:10 hexane/ethyl acetate) to yield **4a** in 48% yield (13.5 mg, 0.034 mmol). An X-ray quality crystal was grown by dissolving 20 mg of hetero-Diels-Alder adduct **4a** in 0.5 mL ethyl acetate. The solution was transferred to a 1 dram vial and allowed to slowly evaporate until crystal formation was observed. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.22 (dd, 2H, *J* = 8.4, 1.3 Hz). 7.54 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.39-7.47 (m, 2H), 6.95-7.06 (m, 5H), 3.03 (dd, 2H, *J* = 7.7, 4.5 Hz), 2.73 (dd, 1H, *J* = 9.7, 2.1 Hz), 2.40 (d, 1H, *J* = 10.2 Hz), 2.30 (d, 1H, *J* = 2.7 Hz), 2.25 (d, 1H, 4.2 Hz), 1.68-1.83 (m, 3H), 1.58-1.68 (m, 2H), 1.24-1.55 (m, 6H), 0.92-1.00 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 198.3. 142.0, 136.5, 135.4, 132.5, 131.8, 130.2, 128.2, 127.6, 126.92, 126.90, 94.2, 52.9, 47.2, 45.8, 42.9, 41.3, 40.7, 39.3, 36.7, 29.6, 27.6, 27.3, 23.9. **HRMS** (ESI): Calcd for $C_{28}H_{29}O_2^+$ ($[M+H]^+$): 397.2162, Found: 397.2169.

*Hetero-Diels-Alder adduct **4b***: Prepared according to General Procedure B from (bicyclo[2.2.1]hept-2-en-2-yl)(4-fluorophenyl)methanone **3d** (0.118 mmol) at 110 °C for 24 h. The crude reaction mixture was purified by flash chromatography (100:0 → 90:10 hexane/ethyl acetate) to yield **4b** in 62% yield (15.6 mg, 0.036 mmol). **^{1}H NMR** (($CDCl_3$, 600 MHz): δ 8.25-8.30 (m, 2H), 7.09-7.14 (m, 2H), 6.96-6.99 (m, 2H), 6.74-6.78 (m, 2H), 2.99 (s, 2H), 2.75 (dd, 1H, *J* = 9.7, 2.0 Hz), 2.42 (d, 1H, *J* = 10.1 Hz), 2.33 (d, 1H, *J* = 2.7 Hz), 2.28 (d, 1H, *J* = 3.7 Hz), 1.71-1.83 (m, 3H), 1.65 (t, 1H, *J* = 7.9 Hz), 1.55-1.59 (m, 1H), 1.27-1.50 (m, 6H), 0.87-1.01 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 196.7, 165.3 (C–F, $^1J_{C-F}$ = 254.4 Hz), 161.7 (C–F, $^1J_{C-F}$ = 247.0 Hz), 140.9, 132.8 (C–F, $^3J_{C-F}$ = 9.1 Hz), 132. 6 (C–F, $^4J_{C-F}$ = 3.1 Hz), 131.9 (C–F, $^5J_{C-F}$ = 1.3 Hz), 131.6 (C–F, $^4J_{C-F}$ = 3.3 Hz), 128.6 (C–F, $^3J_{C-F}$ = 8.0 Hz), 115.3 (C–F, $^2J_{C-F}$ = 21.6 Hz), 114.6 (C–F, $^2J_{C-F}$ = 21.4 Hz), 94.3, 52.7, 47.2, 45.7, 42.8, 41.0, 40.6, 39.3, 36.7, 29.6, 27.6, 27.3, 23.8. **^{19}F{^{1}H} NMR** ($CDCl_3$, 565 MHz): δ -105.66 (s, 1F), -114.76 (s, 1F). **HRMS** (ESI): Calcd for $C_{28}H_{27}F_2O_2^+$ ($[M+H]^+$): 433.1974, Found: 433.1984.

*Hetero-Diels-Alder adduct **4c***: Prepared according to General Procedure B from (bicyclo[2.2.1]hept-2-en-2-yl)(*p*-tolyl)methanone **3c** (0.179 mmol) at 110 °C for 24 h. The crude reaction mixture was purified by flash chromatography (100:0 → 90:10 hexane/ethyl acetate) to yield **4c** in 35% yield (13.2 mg, 0.031 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.15 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 2H, *J* = 8.3 Hz), 6.88 (d, 2H, *J* = 8.3 Hz), 6.83 (d, 2H, *J* = 8.3 Hz), 2.95-3.06 (m, 2H), 2.73 (dd, 1H, *J* = 9.6, 1.8 Hz), 2.43 (s, 3H), 2.36-2.42 (m, 1H), 2.26-2.35 (m, 2H), 2.20 (s, 3H), 1.67-1.77 (m, 3H), 1.59-1.67 (m, 2H), 1.36-1.45 (m, 3H), 1.23-1.35 (m, 3H), 0.83-1.00 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 197.7, 143.1, 142.2,

136.6, 133.9, 132.7, 130.7, 130.4, 128.8, 128.3, 127.0, 94.0,

52.7, 47.2, 45.8, 42.9, 41.3, 40.7, 39.3, 36.6, 29.6, 27.6, 27.4,

23.9, 21.7, 21.1. **HRMS** (ESI): Calcd for $C_{30}H_{33}O_2^+$ ($[M+H]^+$):

425.2475, Found: 425.2484.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting information and NMR spectra of compounds **3a**-**3m** and **4a**-**4c** (PDF)

X-ray crystal structure of **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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