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Palladium Catalyzed Ring-Opening of Diazabicylic Olefins with 4-Halo-1,3-Dicarbonyl Compounds: Accessing 3(2*H*)-Furanone-Appended Cyclopentenes

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Abstract: We have realized a Pd-catalyzed ring-opening of diazabicyclic olefins with 4-halo-1,3-dicarbonyl compounds. This reaction resulted in the formation of 3(2*H*)-furanone-appended hydrazino cyclopentenes. The reaction proceeds *via* the formation of a π-allylpalladium intermediate which is attacked by the active methylene species, and an intramolecular nucleophilic substitution in the 4-halo-1,3-dicarbonyl moiety furnishes the 3(2*H*)-furanone-substituted cyclopentene. We could extend this methodology to cyclopropane-appended spirotricyclic olefin for synthesizing 3(2*H*)-furanone-substituted spiro[2.4]hept-5-ene.

Keywords: 3(2*H*)-furanone; diazabicyclic olefins; 4-halo-1,3-dicarbonyl compounds

Citation: Omanakuttan, V.K.; Valsan, A.; Hopf, H.; John, J. Palladium Catalyzed Ring-Opening of Diazabicylic Olefins with 4-Halo-1,3-Dicarbonyl Compounds: Accessing 3(2*H*)-Furanone-Appended Cyclopentenes. *Organics* **2023**, *4*, 70–85. https://doi.org/10.3390/org4010006

Academic Editor: Michal Szostak

Received: 19 December 2022
Revised: 10 January 2023
Accepted: 7 February 2023
Published: 13 February 2023

1. Introduction

Among oxygen-containing heterocyclic compounds, furanones [1–4] compose an important subclass, as it constitutes the pharmacophores of many biologically active molecules (both natural and synthetic), which covers various therapeutic categories, *viz.* analgesic, anti-inflammatory, anticancer, anticonvulsant, antibacterial, antifungal, antioxidant, antiulcer, anti-tuberculosis etc. [5]. Among the different furanones, namely (i) 2(3*H*)-furanone, (ii) 2(5*H*)-furanones, and (iii) 3(2*H*)-furanone, the later occupies a salient position because of its broad range of biological activities [6–8]. In past decades, significant attention was laid on devising synthetic routes towards substituted 3(2*H*)-furanone moieties with the ultimate aim of synthesizing natural products incorporating this heterocycle [9,10]. Different synthetic protocols for the preparation of this heterocyclic compound were reported, which included acid or base mediated, Lewis acid or base catalyzed, organocatalytic and transition-metal catalyzed transformations. In 2012, the groups of Lu and Yan independently reported the organocatalytic reaction of 4-bromoacetoacetate with nitrostyrene towards the synthesis of 4,5-disubstituted-3(2*H*)-furanones, and Yu reported an asymmetric synthesis of succinimide substituted 3(2*H*)-furanones (Figure 1) [11–13]. Soon after, our group also reported the reactions of 4-halo-1,3-dicarbonyl compounds with different electrophilic species such as activated alkene, activated imine, dialkylazodicarboxylates and arynes to access various 4,5-disubstituted-3(2*H*)-furanone derivatives (Figure 1) [14–17]. There is still immense scope for exploring the reactivity of 4-halo-1,3-dicarbonyl compounds with unexplored electrophiles for generating new scaffolds.

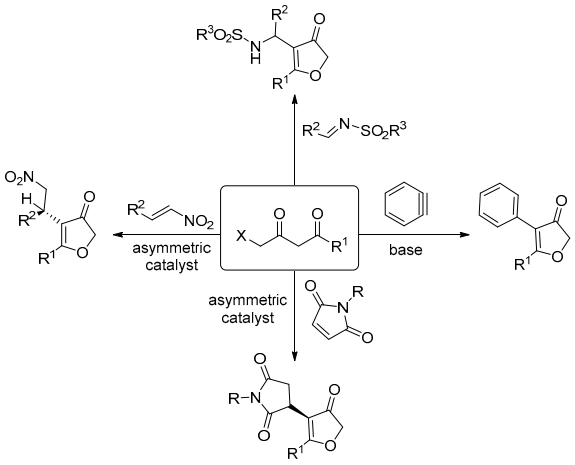


Figure 1. Synthesis of functionalized 3(2*H*)-furanones from 4-haloacetoacetate [11–16].

Diazabicyclic olefins are meso-compounds with multiple points of fracture, which upon clever ring-opening strategies can lead to highly functionalized/fused cyclopentanoids [18–21]. These heterobicyclic olefins can be easily synthesized in large quantities by the Diels Alder cycloaddition between cyclopentadiene and dialkylazodicarboxylate. The unique reactivity of these heterobicyclic olefins can be attributed to the ring strain that enables facile skeletal rearrangements under mild conditions. The initial attempts of desymmetrization involved hydroformylation, hydroboration, hydroarylation and dihydroxylation, all without ring opening of the bicyclic structure [22–27]. Mono-centered reactive species such as organometallic reagents and organic halides were later used for the ring opening of diazabicyclic olefins towards functionalized cyclopentenes [28–37]. Methodologies for cyclopentannulation with diazabicyclic olefins were then introduced by utilizing different bi-centered reactive species such as 2-iodophenol/aniline, salicylaldehyde, aryl enamides and 3-methyl 2-iodobenzoate [38–42]. In 2003, Micouin and co-workers reported the use of nucleophiles such as phenol and active methylene compounds for trapping the π-allyl palladium species generated from diazabicyclic olefin under Pd-catalysis (Figure 2a) [43]. Later, the same reactivity was extended by Radhakrishnan and co-workers to fulvene derived diazabicyclic olefins and to cyclopropane-appended spirotricyclic olefins to generate 1,4-disubstituted alkylidenecyclopentenes and *cis*-4,7-disubstituted spiro[2.4]hept-5-ene respectively [44,45]. Based on these literature reports, we hypothesized that 4-halo-1,3-dicarbonyl compounds could be used for trapping the π-allyl palladium intermediate generated from diazabicyclic olefins in the presence of Pd-catalyst for accessing 3(2*H*)-furanone-appended hydrazino cyclopentenes (Figure 2b).

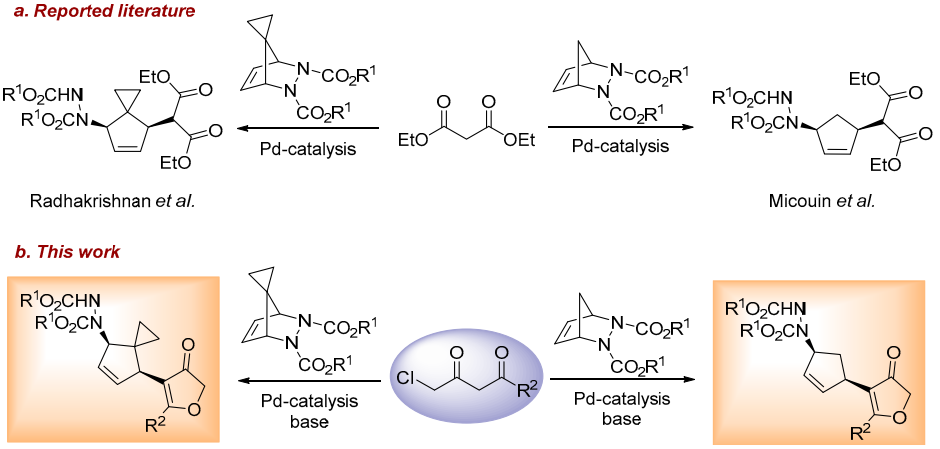


Figure 2. Pd-catalyzed ring-opening of heterobicyclic olefins with active methylene compounds. (**a**) Reported literature; (**b**) This work.

2. Results and Discussion

We planned to assess our hypothesis by taking diazabicyclic olefin **1a** and ethyl-4-chloro acetoacetate **2a** as substrates. The initial reaction was set up with 1.0 equivalent of **1a** and 1.5 equivalents of **2a** in the presence of $Pd(OAc)_2$ as the catalyst, dppf as ligand and K_2CO_3 as base in THF at 60 °C. After 12 h, we could isolate the expected 3(2*H*)-furanone-appended hydrazino cyclopentene **3a** in 10% yield from the reaction mixture (Figure 3). The structure of **3a** was assigned based on ^{1}H NMR, ^{13}C NMR, high resolution mass spectral analyses and on comparison with literature reports [43–45].

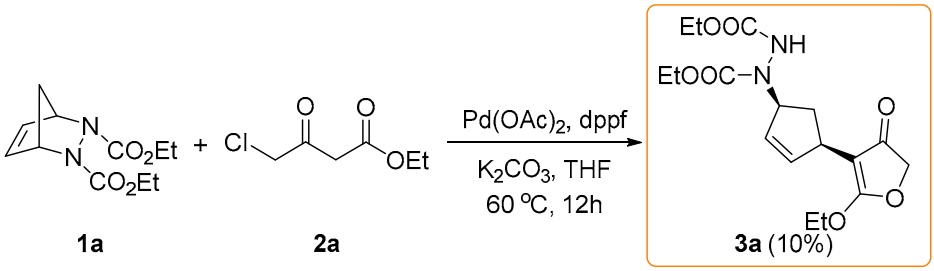


Figure 3. Pd-catalyzed ring-opening of diazabicyclic olefin **1a** with ethyl-4-chloro acetoacetate **2a**.

In the HMBC spectrum of **3a** (spectrum in SI), the proton signal at 3.40–3.42 ppm (1′) showed correlations with C5, C4 and C3 carbons (Figure 4). These relations confirmed the connectivity of cyclopentene moiety with 3(2*H*)-furanone core. The *cis* stereochemistry at the 1′ and 4′ positions was confirmed through the NOE analysis (spectrum in SI) and in comparison with the literature reports [43–45]. When we irradiated the signal at 3.40–3.42 ppm, a signal enhancement in the opposite phase was observed at 5.32 ppm. This confirmed the stereochemistry of protons at 3.40–3.42 and 5.32 ppm as in the same phase.

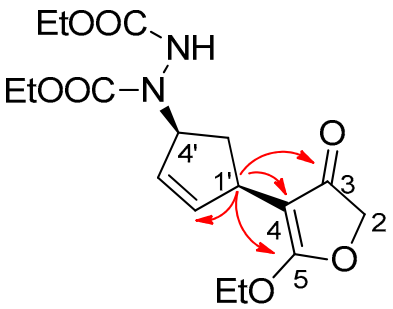


Figure 4. Selected HMBC correlations of **3a**.

The optimization of the Pd-catalyzed ring opening of diazabicyclic olefin with 4-halo-1,3-dicarbonyl compounds was carried out with **1a** and **2a** as substrates. We started with the screening of Pd-catalysts such as $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, $Pd(PPh_3)_4$, $(Pd(allyl)Cl)_2$, $PdCl_2$ and $Pd(dba)_3.CHCl_3$ among which the $(Pd(allyl)Cl)_2$ catalyzed reaction afforded the 3(2*H*)-furanone-appended hydrazino cyclopentene **3a** in 32% yield (Table 1, entries 1–6). We then checked the efficiency of different ligands like dppf, dppe, dppp, XPhos and DevPhos, from which XPhos was found to be the best option (Table 1, entries 4, 7–10). A base screen revealed that K_2CO_3 was superior to other bases like Na_2CO_3, Cs_2CO_3, NaH and NaO^{t}Bu (Table 1, entries 9, 11–14). Finally, we examined different solvents such as THF, CH_3CN, toluene, 1,4-dioxane and DCE among which **3a** was isolated in 85% yield from the reaction with DCE as the medium (Table 1, entries 9, 15–18).

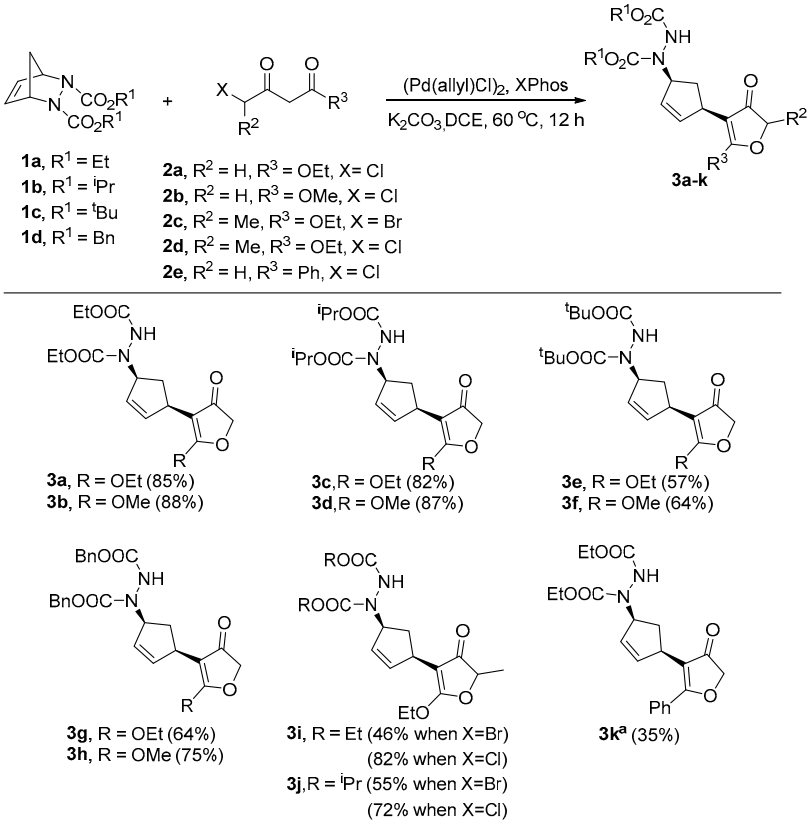
Table 1. Optimization studies.

Entry	Catalyst	Ligand	Base	Solvent	Yield
1	$Pd(OAc)_2$	dppf	K_2CO_3	THF	10
2	$Pd(OCOCF_3)_2$	dppf	K_2CO_3	THF	20
3	$Pd(PPh_3)_4$	dppf	K_2CO_3	THF	15
4	$(Pd(allyl)Cl)_2$	dppf	K_2CO_3	THF	32
5	$PdCl_2$	dppf	K_2CO_3	THF	28
6	$Pd(dba)_3.CHCl_3$	dppf	K_2CO_3	THF	23
7	$(Pd(allyl)Cl)_2$	dppe	K_2CO_3	THF	10
8	$(Pd(allyl)Cl)_2$	dppp	K_2CO_3	THF	34
9	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	THF	55
10	$(Pd(allyl)Cl)_2$	DevPhos	K_2CO_3	THF	43
11	$(Pd(allyl)Cl)_2$	XPhos	Na_2CO_3	THF	51
12	$(Pd(allyl)Cl)_2$	XPhos	Cs_2CO_3	THF	32
13	$(Pd(allyl)Cl)_2$	XPhos	NaH	THF	NR
14	$(Pd(allyl)Cl)_2$	XPhos	NaO^tBu	THF	25
15	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	CH_3CN	68
16	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	Toluene	47
17	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	1,4-Dioane	58
18	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	DCE	85

Reaction conditions: **1a** (1.0 equiv., 0.42 mmol), **2a** (1.5 equiv., 0.62 mmol), base (2.0 equiv.), catalyst (5 mol%), ligand (10 mol%), solvent (2.0 mL), 60 °C, 12 h; isolated yields.

The optimized conditions for the Pd-catalyzed synthesis of 3(2*H*)-furanone-appended hydrazino cyclopentene was found to be 1.0 equivalent of diazabicyclic olefin **1**, 1.5 equivalents of 4-halo-1,3-dicarbonyl compound **2**, 2.0 equivalents of K_2CO_3, 5 mol% of $(Pd(allyl)Cl)_2$, 10 mol% of XPhos in DCE (solvent) at 60 °C for 12 h. Under these conditions, the generality of the 3(2*H*)-furanone-appended 3,5-disubstituted cyclopentene synthesis was studied with different diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds (Figure 5). The reactions of diazabicyclic adduct **1a** with ethyl-4-chloro acetoacetate **2a** and methyl-4-chloro acetoacetate **2b** afforded the corresponding products **3a** and **3b** in 85% and 88% yields, respectively. In a similar way, the reactions of bicyclic adduct **1b** (derived from cyclopentadiene and diisopropylazodicarboxylate) with **2a** and **2b** furnished the products **3c** and **3d** in excellent yields. There was a decrease in yield for 3(2*H*)-furanone-appended hydrazino cyclopentenes **3e** (57%), **3f** (64%), **3g** (64%) and **3h** (75%) synthesized from bicyclic adducts **1c** and **1d**. The Pd-catalyzed reactions of ethyl 4-bromo-3-oxopentanoate **2c** with bicyclic adducts **1a** and **1b** were found to afford the products **3i** and **3j** in satisfactory yields (as a mixture of diastereomers) whereas the use of 4-chloro-3-oxopentanoate **2d** instead of **2c** resulted in better reactions affording **3i** and **3j** in good to excellent yields. A phenyl moiety was introduced to the fifth position of 3(2*H*)-furanone moiety of **3k** by starting from 4-chloro-1-phenylbutane-1,3-dione **2e** and bicyclic adduct **1a**.

Having established a methodology for accessing 3(2*H*)-furanone-appended hydrazino cyclopentene from diazabicyclic olefins and 4-halo-1,3-dicarbonyl compounds, we were interested in expanding the scope of olefins used. In this line we checked the reactivity of spirotricyclic olefin **4a** (derived from spiro[2.4]hepta-4,6-diene and diethylazodicarboxylate) with ethyl-4-chloro acetoacetate **2a** under the optimized conditions developed for diazabicyclic olefin. As expected the 3(2*H*)-furanone-substituted hydrazino-spiro[2.4]hept-5-ene **5a** was isolated from the reaction in 12% yield (Figure 6). A significant improvement in the yield of **5a** to 81% was observed when the solvent was changed from DCE to THF.



Reaction conditions: **1** (1.0 equiv., 1.05 mmol), **2** (1.5 equiv., 1.58 mmol), K_2CO_3 (2.0 equiv.), $(Pd(allyl)Cl)_2$ (5 mol%), XPhos (10 mol%), DCE (5.0 mL), 60 °C, 12 h, isolated yields. [**a**] rt.

Figure 5. Generality of 3(2*H*)-furanone-appended hydrazino cyclopentene synthesis from diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds.

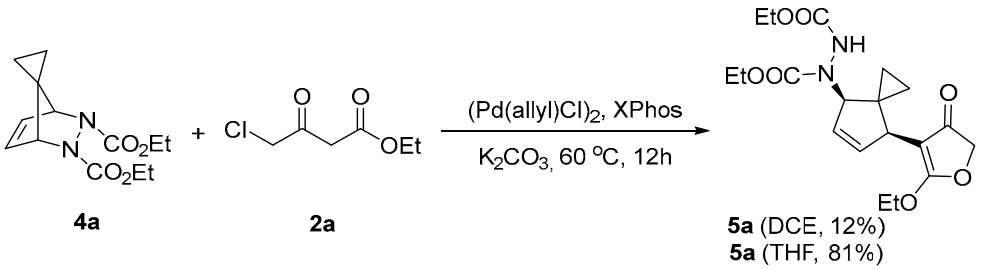
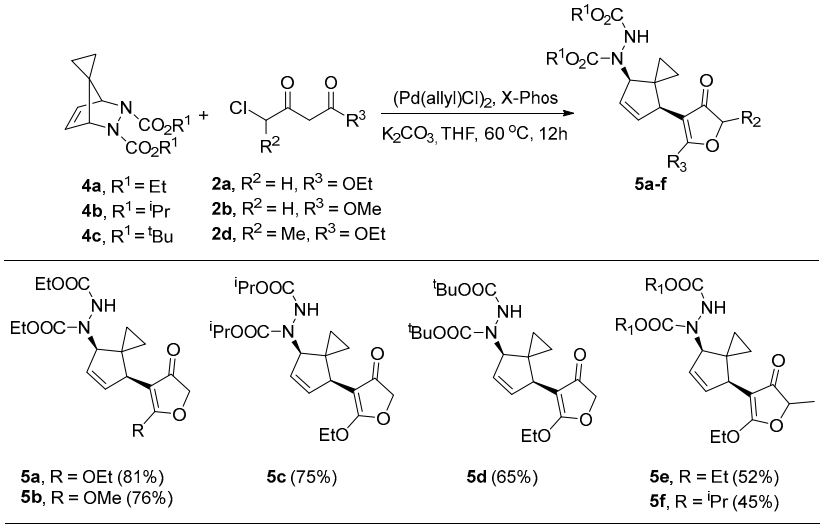


Figure 6. Pd-catalyzed ring-opening of spirotricyclic olefin (**4a**) with ethyl-4-chloro acetoacetate (**2a**).

The generality of the Pd-catalyzed ring opening of spirotricyclic olefins with 4-halo-1,3-dicarbonyl compounds were then investigated (Figure 7). The reactions of the olefins **4a**–**4c** with 4-chloro-ethyl/methyl acetoacetates **2a**–**2b** afforded the corresponding 3(2*H*)-furanone-substituted hydrazino-spiro[2.4]hept-5-enes **5a** to **5d** in good to excellent yields. The reactions of 4-chloro-3-oxopentanoate **2d** with spirotricyclic olefins **4a** & **4b** also afforded the expected products **5e** and **5f** (as a mixture of diastereomers) in 52% and 45% yields, respectively.



Reaction conditions: **4** (1.0 equiv., 1.05 mmol), **2** (1.5 equiv., 1.58 mmol), K_2CO_3 (2.0 equiv.), $(Pd(allyl)Cl)_2$ (5 mol%), XPhos (10 mol%), THF (5.0 mL), 60 °C, 12 h, Isolated yields.

Figure 7. Generality of 3(2H)-furanone-substituted hydrazino-spiro[2.4]hept-5-ene synthesis from diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds.

We propose a mechanism for the Pd-catalyzed synthesis of 3(2*H*)-furanone-appended hydrazino cyclopentene from diazabicyclic olefin and 4-halo acetoacetate based on literature precedents (Figure 8) [43–46].

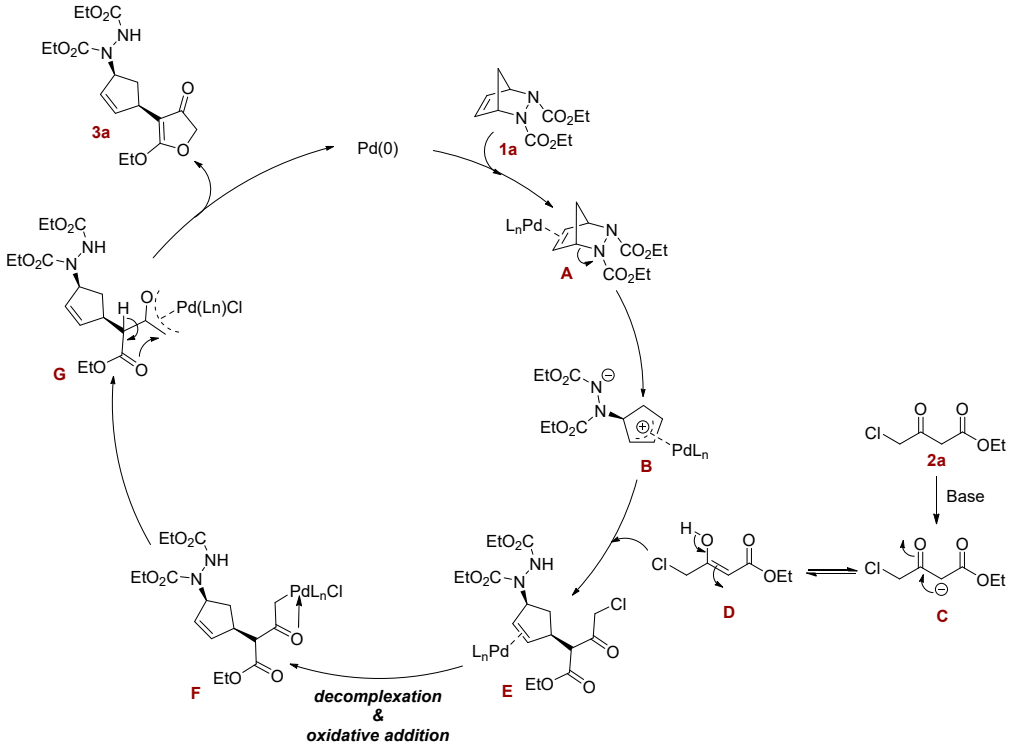
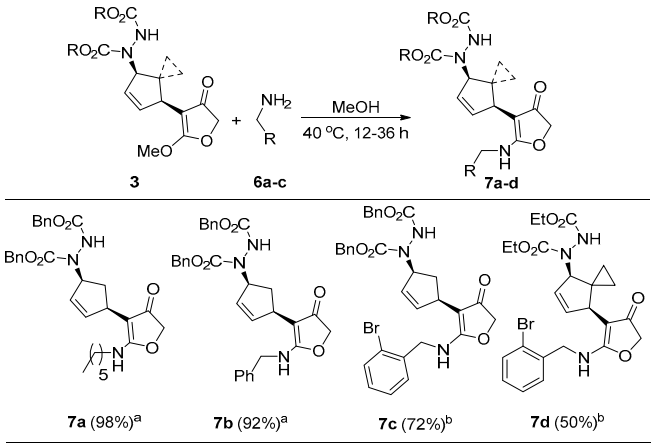


Figure 8. Proposed mechanism for the Pd-catalyzed ring-opening of azabicyclic olefin with 4-halo acetoacetate.

The reaction proceeds through three stages; the first one being the attack of Pd(0) species to the double bond (through *exo*-face) of the diazabicyclic olefin **1a** to form the π-allylpalladium intermediate **B** (via **A**) by the cleavage of one C-N bond (*endo* phase). The second stage involves the attack of the anionic species **C** or **D** (generated from **2a**) to one end of the π-allylpalladium intermediate (through the opposite side of that of Pd) **B** generating the species **E**. Then, the decomplexation of Pd-species from the cyclopentene ring occurs, followed by the oxidative addition of Pd(0)Ln to the C–Cl bond to form **F**. The intermediate **F** is easily converted into oxy-π-allylpalladium intermediate **G** and the ester enolate formed by the abstraction of the acidic proton attacks the carbon end of the oxy-π-allyl Pd-intermediate resulting in the 3(2*H*)-furanone ring. The classical double inversion mechanism is the reason for the *cis*-stereochemistry in the product.

Our next attempt was to utilize the synthesized 3(2*H*)-furanone-appended hydrazino cyclopentenes for the generation of biologically relevant furanone-analogues [47,48]. This transformation was effected by treating the 3(2*H*)-furanone-appended hydrazino cyclopentene **3** with an amine **6** in MeOH at 40 °C. These reactions were found to be completed in 12 to 24 h, from which the respective furanone-analogues **7a–d** were isolated in moderate to excellent yields (Figure 9).



Reaction conditions: [a] **3** (1.0 equiv.), **6** (1.1 equiv.), MeOH (0.2 mM), 40 °C, 12 h, Isolated yields; [b] 24 h.

Figure 9. Generality of amine-functionalized 3(2H)-furanone-appended hydrazino cyclopentene synthesis.

During the synthesis of amine-functionalized 3(2*H*)-furanone derivatives, we chose different *ortho*-bromo-benzylamines to access scaffolds that can be subjected to further transformations towards complex fused moieties. We hypothesized that, by subjecting compound **7c** to intramolecular Heck coupling conditions, a tri-ring-fused azocine moiety, namely 3(2*H*)-furanone-fused cyclopetano-benzoazocine could be synthesized. The first trial run of the intramolecular Heck coupling of **7c** was carried out with $Pd(OAc)_2$ as the catalyst, P(*o*-tol)$_3$ as the ligand, and Et_3N as the base in CH_3CN at 100 °C (Figure 10). After 12 h, to our dismay, we isolated the dehalogenated 3(2*H*)-furanone **7b**. We then changed different conditions to see if the expected 3(2*H*)-furanone-fused cyclopetano-benzoazocine could be synthesized [49]. All the attempts were in vain, furnishing the dehalogenated product. The reason for failure might be due to the fact that oxidatively added palladium species might not be in a bonding distance with that of the alkene (of cyclopentene) for insertion reaction.

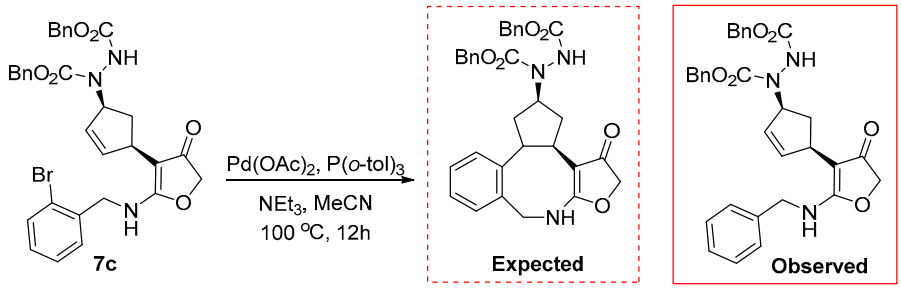


Figure 10. Attempted intramolecular Heck coupling of amine-functionalized 3(2*H*)-furanone derivatives towards 3(2*H*)-furanone-fused tetrahydroazocine derivative.

3. Materials and Methods

All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using silica, and mixtures of ethyl acetate hexanes were used for elution. Melting points were measured with a Fisher John melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) spectrophotometer instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and qdd (doublet of doublets). Mass spectra were performed with a Thermo Finnigan MAT95XL, a Thermo Fisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer.

All chemicals were purchased from TCI Chemicals (India), Sigma-Aldrich (Merck-India) or Spectrochem (India).

4-Bromoacetoacetates and 4-Chlorooacetoacetates were prepared by the reported procedures [50–52].

The synthesized 3(2*H*)-furanone-appended cyclopentenes contains hydrazide moieties, and the peaks in ^{1}H and ^{13}C NMR spectra were broadened (or doubled) by the presence of amide rotamers [53].

Experimental procedure for the synthesis of 3(2*H*)-furanone-appended hydrazino cyclopentene**:** A mixture of diazabicyclic olefin (1.0 equiv.), 4-haloacetoacetate (1.5 equiv.), $[Pd(allylCl)]_2$ (5 mol%), Xphos (10 mol%) and K_2CO_3 (2.0 equiv.) was weighed into a dry Schlenk tube and degassed for 10 min. Dry DCE (0.2 mM) was added and the reaction mixture was purged with argon and allowed to stir at 60 °C for 12 h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding 3(2*H*)-furanone-appended hydrazino cyclopentene.

Synthesis and characterization of 3(2*H*)-furanone-appended hydrazino cyclopentenes **3a** to **3k**:

Diethyl-1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3a**): The reaction was performed according to the general procedure with diazabicyclic olefin (derived from cyclopentadiene and diethylazadicarboxylate) **1a** (100 mg, 0.42 mmol), ethyl-4-chloroacetoacetate **2a** (103 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), Xphos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at 60 °C for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified over silica gel (100–200 mesh)

column chromatography (70% ethyl acetate in hexanes) to afford the product **3a** as pale-yellow viscous liquid (130 mg, 85%). Analytical data of **3a**: FTIR (ν_{max} in cm^{-1}): 3307, 2983, 2936, 1712, 1468, 1411, 1375, 1231, 1118, 1104, 1040, 953, 762, 663, 565. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65–5.57 (m, 2H), 5.32 (brs, 1H), 4.46 (s, 2H), 4.42–4.38 (m 2H), 4.11 (brs, 5H), 3.42–3.40 (m, 1H), 2.51 (brs, 1H), 1.84 (brs, 1H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.21–1.16 (m, 6H) ppm. ^{13}C NMR (125 MHz, CDCl3): δ 195.8, 181.2, 156.8, 156.1, 136.6, 129.0, 128.4, 95.2, 74.7, 66.2, 62.2, 61.5, 36.4, 32.8, 14.7, 14.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{17}H_{24}N_2NaO_7$: 391.1476; found: 391.1486

The remaining reactions were performed following this general procedure.

Diethyl-1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3b**): Pale yellow viscous liquid (131 mg, 88%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64- 5.58 (m, 2H), 5.31 (brs, 1H), 4.48 (s, 2H), 4.11 (brs, 5H), 4.00 (s, 3H), 3.42–3.38 (m, 1H), 2.51 (brs, 1H), 1.82–1.80 (m, 1H), 1.20–1.16 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.8, 181.4, 156.8, 156.0, 136.5, 128.9, 128.5, 95.3, 74.8, 66.6, 64.1, 62.1, 61.5, 56.4, 36.2, 32.7, 14.5 ppm; HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{16}H_{22}N_2NaO_7$: 377.1319; found: 377.1364

Diisopropyl-1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3c**): Yellow viscous liquid (122 mg, 82%); FTIR (ν_{max} in cm^{-1}): 3306, 2988, 2929, 1713, 1388, 1363, 1312, 1254, 1162, 1045, 1023, 964, 866, 778, 754. 1H NMR (500 MHz, $CDCl_3$, TMS): δ 5.66–5.58 (m, 2H), 5.33 (brs, 1H), 4.93–4.85 (m, 2H), 4.47–4.37 (m, 5H), 3.42–3.40 (m, 1H), 2.49–2.47 (m, 1H), 1.93 (brs, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.19–1.17 (m, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 181.2, 156.3, 155.6, 136.9, 136.3, 129.2, 128.6, 95.2, 74.6, 69.5, 69.0, 66.3, 66.1, 63.8, 36.2, 29.2, 22.1, 22.0, 14.8 ppm; HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{19}H_{28}N_2NaO_7$ 419.1789; found: 419.1782.

Diisopropyl-1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3d**): Yellow viscous liquid (130 mg, 87%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65- 5.58 (m, 2H), 5.32 (brs, 1H), 4.86–4.85 (m, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 3.41 (brs, 1H), 2.46 (brs, 1H), 1.80 (brs, 1H), 1.18–1.17 (m, 12H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.6, 181.4, 156.3, 155.6, 155.5, 136.1, 129.2, 128.7, 95.9, 95.2, 74.7, 69.5, 69.1, 63.7, 56.5, 56.3, 36.1, 35.9, 32.7, 32.1, 22.1, 21.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{18}H_{26}N_2NaO_7$: 405.1632; found: 405.1640.

Di-*tert*-butyl 1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3e**): Yellow viscous liquid (82 mg, 57%); FTIR (ν_{max} in cm^{-1}): 3308, 2971, 2922, 1721, 1396, 1372, 1323, 1249, 1164, 1054, 1018, 862, 763. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.66–5.61 (m, 2H), 5.28–5.14 (m, 1H), 4.52–4.37 (m, 5H), 3.40 (m, 1H), 2.44 (s, 1H), 1.78 (brs, 3H), 1.38–1.37 (m, 18H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.7, 181.3, 155.1, 154.8, 135.4, 129.7, 95.4, 80.6, 74.7, 66.0, 36.1, 31.9, 28.2, 28.0, 14.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{32}N_2NaO_7$: 447.2102; found: 447.2089.

Di-*tert*-butyl 1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3f**): Yellow viscous liquid (89 mg, 64%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64 (brs, 2H), 5.28 (brs, 1H), 4.46 (s, 2H), 3.98 (s, 3H), 3.40 (s, 1H), 2.44 (brs, 1H), 1.83 (brs, 1H), 1.39–1.38 (m, 18H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.7, 181.3, 155.5, 155.0, 135.7, 129.7, 95.7, 81.0, 80.6, 74.7, 56.4, 56.2, 36.1, 33.1, 32.0, 29.7, 28.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{30}N_2NaO_7$: 433.1945; found: 433.1961.

Dibenzyl 1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3g**): Brown viscous liquid (90 mg, 64%); FTIR (ν_{max} in cm^{-1}): 3278, 3069, 3040, 2965, 1712, 1567, 1498, 1417, 1306, 1254, 1219, 1244, 1080, 1045, 750, 704, 599. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24–7.19 (m, 10H), 5.62–5.32 (m, 3H), 5.08–4.99 (m, 4H), 4.48–4.36 (m, 4H), 3.39 (s, 1H), 2.51 (brs, 1H), 1.91 (brs, 1H), 1.35–1.32 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.9, 181.3, 156.8, 156.5, 155.8, 137.1, 136.3, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 95.0, 74.7, 67.5, 67.1, 66.8, 66.4, 64.3, 36.6, 32.3, 14.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{27}H_{28}N_2NaO_7$: 515.1782; found: 515.1789.

Dibenzyl 1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3h**): brown viscous liquid (98 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24–7.21 (m, 10H), 5.62–5.38 (m, 3H), 5.08–4.99 (m, 4H), 4.50–4.39 (m, 2H), 3.96 (brs, 3H), 3.39 (s, 1H), 2.50 (brs, 1H), 1.84 (brs, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.8, 181.4, 156.7, 155.8, 136.9, 136.3, 128.8, 128.4, 128.4, 128.0, 127.9, 95.1, 74.8, 67.6, 67.1, 64.3, 56.3, 36.4, 32.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{26}N_2NaO_7$: 501.1632; found: 501.1625

Diethyl 1-((1*S*,4*R*)-4-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3i**): Yellow viscous liquid (130 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64–5.56 (m, 2H), 5.32 (brs, 1H), 4.57–4.54 (m, 1H), 4.38–4.36 (m, 2H), 4.14–4.11 (m, 4H), 3.41–3.39 (m, 1H), 2.50 (brs, 1H), 1.90 (m, 1H), 1.41–1.40 (m, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.18–1.15 (m, 6H) ppm;^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.6, 180.0, 156.9, 156.1, 137.0, 128.8, 93.7, 82.9, 75.5, 66.1, 62.1, 36.5, 30.9, 29.7, 16.5, 14.7, 14.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{18}H_{26}N_2NaO_7$: 405.1632; found: 405.1629.

Diisopropyl 1-((1*S*,4*R*)-4-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3j**): yellow viscous liquid (115 mg, 72%); FTIR (ν_{max} in cm^{-1}): 3301, 2975, 2936, 1712, 1696, 1527, 1486, 1405, 1299, 1263, 1179, 1115, 1056, 941, 761, 611. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65–5.56 (m, 2H), 5.34 (brs, 1H), 4.91–4.85 (m, 2H), 4.52–4.51 (m, 1H), 4.38–4.37 (m, 2H), 3.40 (brs, 1H), 2.46 (brs, 1H), 1.92 (brs, 1H), 1.41–1.34 (m, 6H), 1.18 (brs, 12H) ppm;^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.4, 179.9, 156.4, 155.7, 136.6, 129.0, 128.4, 93.5, 82.9, 69.5, 66.0, 36.5, 32.3, 22.1, 22.0, 16.6, 14.8 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{30}N_2NaO_7$: 433.1945; found: 433.1956.

Diethyl 1-((1*S*,4*R*)-4-(4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3k**): (This reaction was performed at rt) pale yellow viscous liquid (90 mg, 35%); FTIR (ν_{max} in cm^{-1}): 3331, 2976, 2936, 1701, 1596, 1410, 1381, 1266, 1231, 1167, 1144, 1069. 947. 821, 761, 704, 651, 501, 431. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.77–7.73 (m, 2H), 7.45 (brs, 1H), 7.43–7.20 (m, 2H), 5.99 (s, 1H), 5.79–5.73 (m, 2H), 4.22–4.17 (m, 2H), 4.11–4.10 (m, 5H), 3.15 (brs, 1H), 2.52 (brs, 1H), 1.94 (brs, 1H), 1.25–1.13 (m, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 203.3, 185.9, 155.8, 154.4, 152.2, 132.8, 128., 127.1, 101.5, 87.3, 62.9,62.5, 62.0, 46.5, 30.9, 2.7, 14.5,14.1,14.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{24}N_2NaO_6$: 423.1527; found: 423.1532.

Experimental procedure for the synthesis of 3(2*H*)-furanone-appended hydrazino-spiro[2.4]hept-5-enes from spirotricyclic olefin and 4-halo-1,3-dicarbonyl compounds: A mixture of spirotricyclic olefin (1.0 equiv.), 4-haloacetoacetate (1.5 equiv.), $[Pd(allylCl)]_2$ (5 mol%), Xphos (10 mol%) and K_2CO_3 (2.0 equiv.) was weighed in a Schlenk tube and degassed for 10 min. Dry THF (0.2 mM) was added and the reaction mixture was purged with argon and allowed to stir at 60 °C for 12h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography yielded 3(2*H*)-furanone-appended hydrazino-spiro[2.4]hept-5-enes.

Synthesis and characterization of 3(2*H*)-furanone-appended hydrazino-spiro[2.4]hept-5-enes:

Diethyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl) hydrazine-1,2-dicarboxylate (**5a**): Following the general experimental procedure, spirotricyclic olefin **4a** (derived from spiro[2.4]hepta-4,6-diene and diethylazodicarboxylate) (100 mg, 0.3755 mmol), ethyl-4-chloroacetoacetate **2a** (92.7 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), Xphos (18 mg, 0.04 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in dry THF (1.9 mL) was stirred at 60 °C for 12h. The crude product was purified over silica gel (100–200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **5a** as pale brown viscous liquid (120 mg, 81%). Analytical data of **5a:** FTIR (ν_{max} in cm^{-1}): 3289, 2959, 222, 2861, 1697, 1412, 1309, 1263, 1118, 1024, 966, 798. ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.28 (brs, 0.48H) 5.73–5.57 (m, 2H), 5.00–4.91 (m, 1H), 4.51–4.49 (m, 2H), 4.37 (q, *J* = 7 Hz, 1H), 4.01–3881 (m, 4H), 3.19 (brs, 1H), 1.28–1.24 (m, 3H), 1.10–1.03 (m, 6H), 0.82–0.75 (m, 1H), 0.52–0.47 (m, 1H), 0.42–0.37 (m, 1H), 0.28–0.23 (m, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6): δ 195.6, 182.0, 156.9, 156.4, 137.6, 127.9, 92.4, 74.7,

69.7, 69.5, 66.4, 61.3, 60.4, 45.1, 27.1, 17.0, 14.1, 14.0, 13.9, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{19}H_{26}N_2NaO_7$: 417.1632; found: 417.1639.

The remaining reactions were performed following this general procedure.

Diethyl 1-((4*R*,7*S*)-7-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl) hydrazine-1,2-dicarboxylate (**5b**): Pale brown viscous liquid (107 mg, 76%); ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.21 (brs, 0.47H), 5.75–5.57 (m, 2H), 5.00–4.90 (m, 1H), 4.52–4.50(m, 2H), 3.99–3.90 (m, 7H), 3.19–3.18 (m, 1H), 1.10–1.03 (m, 6H), 0.81–0.77 (m, 1H), 0.54–0.47 (m, 1H), 0.41–0.36 (m, 1H), 0.30–0.22 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 195.5, 182.2, 156.9, 156.5, 137.5, 127.9, 92.3, 74.7, 69.7, 61.2, 60.5, 56.3, 45.0, 27.1, 17.0, 14.1, 14.0, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{18}H_{24}N_2NaO_7$: 403.1476; found: 403.1472.

Diisopropyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5c**): pale yellow viscous liquid (111 mg, 75%); FTIR (ν_{max} in cm^{-1}): 3336, 2976, 2930, 1718, 1457, 1393, 1379, 1318, 1248, 1156, 1050, 1026, 849, 773. ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.04 (brs, 0.50H), 5.75–5.68 (m, 1H), 5.58–5.57 (m, 1H), 5.00–4.88 (m, 1H), 4.78–4.64 (m, 3H), 4.50–4.80 (m, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.19 (brs, 1H), 1.27–1.25 (m, 3H), 1.12–1.03 (m, 12H), 0.81–0.73 (m, 1H), 0.51–0.46 (m, 1H), 0.42–0.38 (m, 1H), 0.27–0.22 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 186.1, 172.4, 157.0, 128.4, 128.3, 128.1, 126.7, 100.7, 70.8, 65.9, 60.8, 31.7, 30.8, 27.2, 24.8, 22.4, 21.3, 13.9, 13.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{30}N_2NaO_7$: 445.1945; found: 445.1951.

Di-*tert*-butyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5d**): pale yellow viscous liquid (111 mg, 65%); FTIR (ν_{max} in cm^{-1}): 3296, 2983, 2941, 1712, 1573, 1446, 1382, 1301, 1242, 1179, 1115, 1045, 70, 866, 790, 766. ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 8.80 (brs, 0.33H), 5.73–5.53 (m, 2H), 4.98–4.83 (m, 1H), 4.54–4.45 (m, 2H), 4.37 (m, 2H), 3.19 (brs, 1H), 1.34–1.24(m, 18H), 1.05 (brs, 3H), 0.79–0.76 (m, 1H), 0.50–0.40 (m, 2H), 0.30–0.18 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 178.8, 174.5, 174.1, 156.1, 155.8, 136.0, 131.0, 100.1, 79.7, 66.2, 61.2, 57.0, 45.7, 38.2, 27.6, 27.4, 26.6, 17.7, 13.6, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{23}H_{34}N_2NaO_7$: 473.2258; found: 473.2269.

Diethyl 1-((4*R*,7*S*)-7-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5e**): pale yellow viscous liquid (80 mg, 52%); ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.22–9.18 (m, 0.66H), 5.75–5.53 (m, 2H), 4.99–4.87 (m, 1H), 4.60 (m, 1H), 3.99–3.91 (m, 7H), 3.17 (brs, 1H), 1.31–1.28 (m, 3H), 1.17–1.16 (m, 3H), 1.10–1.03 (m, 6H), 0.79–0.74 (m, 1H), 0.52–0.49 (m, 1H), 0.42–0.36 (m, 1H), 0.29–0.15 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 197.9, 181.0, 156.8, 156.4, 137.7, 127.9, 127.8, 91.0, 83.0, 82.9, 69.7, 61.2, 60.4, 56.4, 45.0, 27.1, 17.2, 16.0, 15.9, 14.1, 14.0, 13.9, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{28}N_2NaO_7$: 431.1789; found: 431.1784.

Diisopropyl 1-((4*R*,7*S*)-7-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5f**): pale yellow viscous liquid (70 mg, 45%); ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.15–9.10 (m, 0.54H), 5.72–5.57 (m, 2H), 5.00–4.87 (m, 1H), 4.71–4.66 (m, 2H), 4.59–4.57 (m, 1H), 4.36 (m, 2H), 3.18 (brs, 1H), 1.30–1.23 (m, 6H), 1.12–1.01 (m, 12H), 0.79–0.70 (m, 1H), 0.50–0.46 (m, 1H), 0.44–0.34 (m, 1H), 0.30–0.14 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 198.0, 180.6, 156.3, 156.0, 137.5, 128.0, 91.0, 82.8, 82.7, 69.6, 68.5, 67.8, 66.2, 44.8, 36.4, 27.2, 21.4, 21.3, 16.9, 16.1, 14.0, 9.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{22}H_{32}N_2NaO_7$: 459.2102; found: 459.2109

Experimental procedure for the synthesis of amine-functionalized 3-(2*H*)-furanone-appended hydrazino cyclopentenes: A mixture of 3-(2*H*)-furanone-appended hydrazino cyclopentene (1.0 equiv.,) and amine (1.1 equiv) was weighed into a dry Schlenk tube. Dry methanol (0.2 mM) was added, and the reaction mixture was stirred at 40 °C. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the amine-functionalized 3-(2*H*)-furanone appended hydrazino cyclopentene.

Synthesis and characterization of amine-functionalized 3-(2*H*)-furanone-appended hydrazino cyclopentenes:

Dibenzyl 1-((1*S*,4*R*)-4-(2-(hexylamino)-4-oxo-4,5-dihydrofuran-3-yl) cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**7a**): Following the general experimental procedure, 3-(2*H*)-furanone-appended hydrazino cyclopentene **3h** (50 mg, 0.10 mmol) and n-hexyl amine **6a** (11.3 mg, 0.11 mmol) was weighed into a dry Schlenk tube. Dry methanol (0.5 mL) was added, and the reaction mixture was stirred at 40 °C for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (60% ethyl acetate in hexanes) to afford the desired product **7a** as pale-yellow viscous liquid (54 mg, 98%). Analytical data of **7a**: FTIR (ν_{max} in cm^{-1}): 3463, 3284, 2983, 2948, 1712, 1545, 1510, 1452, 1400, 1254, 1214, 1109, 1045, 744, 692, 587, 506. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24–7.19 (m, 10H), 5.81 (brs, 1H), 5.59 (brs, 1H), 5.06–5.04 (m, 4H), 4.87 (brs, 1H), 4.36 (s, 2H), 3.65 (brs, 1H), 3.20–3.12 (m, 2H), 2.58 (brs, 1H), 1.77 (brs, 1H), 1.45–1.53 (m, 2H), 1.21–1.18 (m, 6H), 0.80 (t, *J* = 6.5Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 191.4, 177.5, 156.7, 155.4, 135.8, 130.9, 128.6, 128.4, 128.2, 128.1, 127.7, 93.4, 74.1, 67.9, 67.7, 41.5, 35.8, 31.3, 29.9, 26.9, 26.3, 22.5, 14.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{31}H_{37}N_3NaO_6$: 570.2575; found: 570.2579.

The remaining reactions were performed following this general procedure:

Dibenzyl 1-((1*S*,4*R*)-4-(2-(benzylamino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**7b**): Pale yellow viscous liquid (52 mg, 92%); FTIR (ν_{max} in cm^{-1}): 3463, 3259, 3069, 3040, 2948, 1706, 1556, 1499, 1463, 1417, 1208, 1057, 1005, 750, 611, 576, 495. ^{1}H NMR (500 MHz, CD_3CN, TMS): δ 7.25–7.20 (m, 15H), 5.61–5.53 (m, 2H), 5.14–4.95 (m, 5H), 4.39–4.38 (m, 2H), 4.21 (brs, 2H), 3.35 (brs, 1H), 2.46–2.43 (m, 1H), 1.84 (brs, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN): δ 192.6, 178.1, 157.5, 156.1, 137.3, 129.2, 129.0, 128.5, 128.1, 128.0, 127.8, 93.0, 74.6, 67.8, 66.9, 65.6, 45.0, 37.4, 33.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{31}N_3NaO_6$: 576.2105; found: 576.2118.

Dibenzyl-1-((1*S*,4*R*)-4-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**7c**): Pale yellow viscous liquid (46 mg, 72%); FTIR (ν_{max} in cm^{-1}): 3492, 3267, 2983, 2924, 2885, 1719, 1596, 1336, 1242, 1057, 1028, 756, 675, 582. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.49 (d, *J* = 8Hz, 1H), 7.25–7.11 (m, 13H), 5.66–5.58 (m, 2H), 5.14–4.94 (m, 5H), 4.45 (s, 2H), 4.21 (s, 2H), 3.41 (brs, 1H), 2.52–2.45 (m, 1H), 1.85 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.1, 177.4, 156.6, 155.4, 136.8, 135.8, 135.7, 132.9, 131.1, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 122.9, 94.2, 74.2, 67.9, 67.7, 45.3, 35.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{30}N_3NaO_6Br$: 654.1210; found: 654.1195.

Diethyl-1-((4*R*,7*S*)-7-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**7d**): Pale yellow viscous liquid (35 mg, 50%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 2H), 7.11 (t, *J* = 7Hz, 1H), 5.94–5.82 (m, 2H), 4.58–4.50 (m, 2H), 4.45–4.35 (m, 3H), 4.17–4.00 (m, 4H), 3.73 (brs, 1H), 1.18–1.12 (m, 7H), 0.81–0.79 (m, 2H), 0.44–0.37 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.2, 177.8, 177.5, 157.3, 136.9, 133.5, 131.0, 129.4, 128.4, 127.8, 123.1, 74.3, 62.4, 45.4, 43.2, 29.7, 14.3, 10.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{24}H_{28}N_3NaO_6Br$:556.1054; found: 556.1059.

Experimental procedure for the intramolecular Heck reaction of amine-functionalized 3-(2*H*)-furanone-appended hydrazino cyclopentenes: A mixture of amine-functionalized 3-(2H)-furanone-appended hydrazino cyclopentenes (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%) and Et_3N (1.0 equiv.) was weighed in a Schlenk tube and degassed for 10 min. Dry ACN (0.025 mM) was added and the reaction mixture was purged with argon and allowed to stir at 100 °C for 12h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography yielded compound 8.

Following the general experimental procedure, Dibenzyl-1-((1*S*,4*R*)-4-(2-((2-bromobenzyl) amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate **7c** (32 mg, 0.0506 mmol) $Pd(OAc)_2$ (0.51 mg, 0.0025 mmol), P(*o*-tol)$_3$ (1.6 mg, 0.0051 mmol) and Et_3N (5.1 mg, 0.0506 mmol) was weighed in a Schlenk tube and degassed for 10 min. Dry ACN (2 mL) was added and the reaction mixture was purged with argon and allowed

to stir at 100 °C for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on silica gel (100–200 mesh) using hexanes/ethyl acetate mixture as eluent (70% ethyl acetate in hexanes) to afford the **8c** as pale-yellow viscous liquid (18 mg, 65%). Analytical data was the same as **7b**.

4. Conclusions

We have developed a methodology for the ring-opening of diazabicyclic olefins via a Pd-catalyzed reaction with 4-halo-1,3-dicarbonyl compounds. This reaction has resulted in the generation of a new class of 3(2*H*)-furanone-appended hydrazino cyclopentenes. This ring opening reaction of diazabicyclic olefins was found to be general with different 4-halo-1,3-dicarbonyl compounds and we could also synthesize another interesting scaffold, namely, 3(2*H*)-furanone-substituted spiro[2.4]hept-5-ene from cyclopropane-appended spirotricyclic olefin. We have proposed a mechanism which proceeds via the formation of a π-allylpalladium intermediate, which is quenched by the active methylene moiety generated from 4-halo1,3-dicarbonyl moiety, and an intramolecular cyclization in the intermediate then generates the product. We then utilized the synthesized 3(2*H*)-furanone-appended hydrazino cyclopentenes for the generation of amine-functionalized 3-(2H)-furanone-appended hydrazino cyclopentenes. Finally, we tried to generate a new family of 3(2*H*)-furanone-fused tetrahydroazocine derivatives which did not result in the expected outcome.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org4010006/s1, Table S1: Optimization studies for intramolecular Heck coupling; Figure S1: 1H NMR and 13C NMR Spectra of 3a; Figure S2: 1H-1H COSY Spectrum of 3a; Figure S3: HMQC Spectrum of 3a; Figure S4: HMBC Spectrum of 3a; Figure S5: 1D-NOE Spectrum of 3a; Figure S6: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3b; Figure S7: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3c; Figure S8: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3d; Figure S9: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3e; Figure S10: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3f; Figure S11: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3g; Figure S12: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3h; Figure S13: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3i; Figure S14: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3j; Figure S15: 1H NMR (500 MHz) & 13C (125 MHz) spectra of 3k; Figure S16: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5a; Figure S17: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5b; Figure S18: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5c; Figure S19: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5d; Figure S20: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5e; Figure S21: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5f; Figure S22: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7a; Figure S23: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7b; Figure S24: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7c; Figure S25: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7d.

Author Contributions: Conceptualization, J.J.; methodology, J.J., V.K.O. and A.V.; validation, J.J. and V.K.O.; formal analysis, J.J. and V.K.O. investigation J.J., V.K.O. and A.V. writing—original draft preparation, J.J. and V.K.O. writing—review and editing, J.J. and H.H. supervision, J.J.; project administration, J.J.; funding acquisition, J.J. All authors have read and agreed to the published version of the manuscript.

Funding: V.K.O. and A.V. thank UGC and CSIR for research fellowship. J.J. thanks CSIR (HCP-029 & OLP-162539), AICTE (GAP-161939) and Alexander von Humboldt Foundation for financial assistance.

Data Availability Statement: All data supporting the reported results can be found in the Supporting Information file.

Acknowledgments: The authors thank Saumini Mathew and Viji S. of CSIR-NIIST for recording NMR and mass spectra respectively.

Conflicts of Interest: The authors declare no conflict of interest.

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