Palladium-Promoted Intramolecular Addition of an Aryl Iodide to a Nitroalkene

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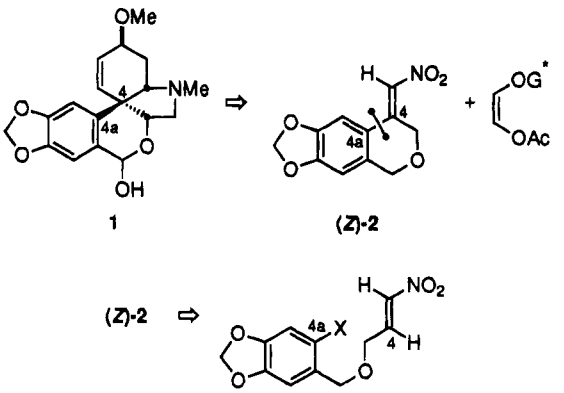
Iodoaryl nitroalkene **9** was found to undergo a palladium-promoted Heck cyclization in the presence of $Pd(OAc)_2$ (1.0 equiv), triphenylphosphine (2.0 equiv), and Ag_2CO_3 (2.0 equiv) in benzene at 25 °C to afford exocyclic 2,2-disubstituted-1-nitroalkene (*Z*)-**2** as a single geometrical isomer (43%) along with the corresponding saturated nitroalkane **10** (40%). Subsequent selenylation of the nitroalkane, oxidative elimination, and olefin isomerization afforded (*Z*)-**2** in 70% yield. The influence of Ag_2CO_3 and solvent on the cyclization and the mechanism of nitroalkane formation are proposed.

Introduction and Background

In the course of work directed toward the total synthesis of (+)-pretazettine (**1**),[1] exocyclic nitroalkene **2** was required, Scheme 1. For the synthesis of nitroalkene **2** we identified two structural challenges for which no general solutions exist: (1) the 2,2-disubstituted-1-nitroalkene is exocyclic to a six-membered ring and (2) the γ-carbon of the nitroalkene bears an oxygen. While a limited number of methods exist to access 2,2-disubstituted-1-nitroalkenes,[2] still fewer methods are available for the preparation of exocyclic nitro olefins.[3] The Henry reaction of a nitroalkene with a cyclic ketone followed by dehydration of the 2-nitro alcohol is not a viable approach to this class of nitroalkenes due to reversibility. The use of *N,N*-dimethylethylenediamine as a catalyst in the condensation has found some utility but generally the β,γ-unsaturated isomers are favored.[3b] 1-Substituted-3-hydroxy-1-nitroalkenes have been prepared by epoxidation of a 2-nitroalkene followed by removal of the α-nitro proton to afford the 1-nitroalkene with concommitant opening of the epoxide.[4] Peracid oxidation of α,β-epoxy ketoximes also affords 3-hydroxy-1-nitroalkenes;[5] however, this approach has not been extended to 2,2-disubstituted-1-nitroalkenes.

As shown in Scheme 1, the disconnection of the C(4) and C(4a) carbon atoms of nitroalkene **2** reveals a potential palladium-catalyzed olefin arylation (Heck arylation) retron.[6] The phenylation of several 2-nitrostyrene[7a] derivatives and α-nitrochalcone[7b] has been reported by

Scheme 1



Yamamura employing $Pd(OAc)_2$ in benzene. The resulting 2,2-diphenyl-1-nitroalkenes were proposed to arise from palladium(II) insersion into benzene, addition to the olefin, and elimination of the hydridopalladium species. Heating various 2-nitrostyrenes in refluxing benzene in the presence of acetic acid and a stoichiometric amount of $Pd(OAc)_2$ afforded 2,2-diphenyl-1-nitroalkenes in 14–70% yields.[7a] Similarly, α-nitrochalcone afforded the expected 2,2-diphenyl product in low yield (5%) along with a side product from a formal conjugate addition to the enone (20%).[7b] A careful search of the literature failed to unvail any examples of palladium-catalyzed aryl halide cyclizations to 1-nitroalkenes. Several potential problems could be anticipated in the proposed reaction as a result of the hyper-reactivity of the precursor including: (1) olefin isomerization, (2) polymerization, and (3) benzylic cleavage. Despite the lack of precedent for this reaction we chose to explore the potential of palladium-catalyzed aryl halide cyclizations to nitroalkenes as a route to exocyclic 2-aryl-1-nitroalkenes and specifically nitroalkene **2**. This paper addresses the synthesis of **2** by this route and the observation of a saturation pathway in Heck arylations.

Results

Preparation of Cyclization Precursors. The required aryl bromide cyclization precursor was prepared in three steps from 2-butene-1,4-diol (**3**), Scheme 2.

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(5) (a) Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1981**, *22*, 603. (b) Takamoto, T.; Ikeda, Y.; Tachimori, Y.; Seta, A.; Sudoh, R. *J. Chem. Soc., Chem. Commun.* **1978**, 350.

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(7) (a) Yamamura, K.; Watarai, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3757. (b) Yamamura, K. *J. Org. Chem.* **1978**, *43*, 724.

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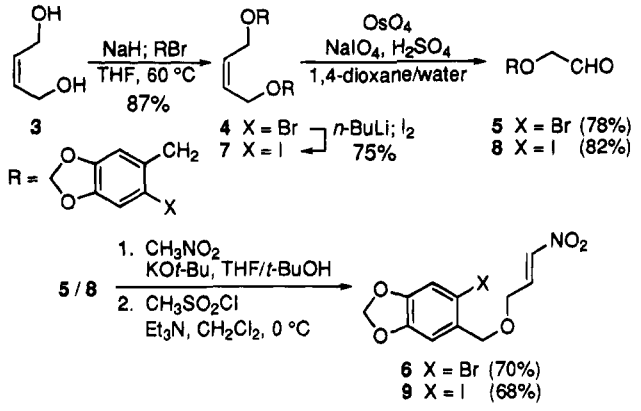
Scheme 2

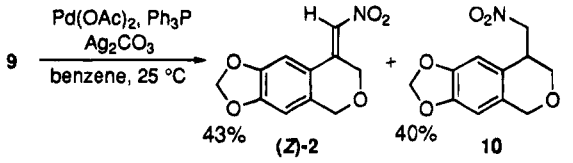


Dialkylation of the sodium alkoxide of **3** with 2-bromo-4,5-(methylenedioxy)benzyl bromide[8] in refluxing tetrahydrofuran (THF) afforded bisaryl bromide **4** in 87% yield. Initial attempts to cleave the olefin with ozone encountered competitive oxidation of the electron rich aryl rings even with the use of Congo Red indicator.[9] Successful oxidative cleavage was accomplished with osmium tetraoxide[10] (2 mol %) and $NaIO_4$ under strongly acidic conditions (H_2SO_4) to afford the desired aldehyde **5** in 78% yield. In the absence of acid, cleavage of the diol was not observed. Presumably, gauche interactions between the large aryl moieties prevents ready formation of the cyclic periodate intermediate. Nitroaldol reaction with nitromethane in a mixture of THF and *tert*-butyl alcohol catalyzed by potassium *tert*-butoxide[11] proceeded smoothly; however, tendency for retroaldol precluded isolation. Transformation of the crude nitro alcohol to the corresponding mesylate followed by elimination with triethylamine afforded nitroalkene **6** in 70% yield as solely the *E* isomer.[12] Attempts to perform the elimination through the corresponding acetate or trifluoroacetate with triethylamine resulted in low yields presumably through isomerization of the resulting nitroalkene to the enol ether.

Since preliminary results (vide post) showed difficulties with the bromoaryl nitroalkene, the corresponding iodoaryl nitroalkene was also prepared. Bis(bromoaryl) ether **4** was converted to the bis(iodoaryl) ether **7** by halogen–metal exchange followed by trapping with iodine in 75% yield. Aldehyde **8** and iodoaryl nitroalkene **9** were prepared in analogy to the corresponding bromo derivatives in 82 and 68% yields, respectively, Scheme 2.

Cyclization of Bromoaryl Nitroalkene 6. Initial attempts to perform the cyclization of bromoaryl nitroalkene **6** with $Pd(OAc)_2$ (1.0 equiv) and acetic acid in refluxing benzene following the precedent of Yamamura[7a] were encouraging. The desired nitroalkene **2** was formed, albeit in low yield (10%), along with additional phenylated products. Changing the solvent to acetonitrile failed to provide the desired product. Also, the use of common Heck arylation conditions such as $Pd(OAc)_2$ (10 mol %)/PPh_3/K_2CO_3, $Pd_2(dba)_3$ (10 mol %) /K_2CO_3/toluene, or $Pd(PPh_3)_4$ (10 mol %)/K_2CO_3/THF failed to provide any detectable product but consumed the starting material. Because an electron rich aryl system is involved, it is likely that oxidative insertion into the carbon–bromine bond may not be facile. On the basis of a precedent in a similar aryl system,[13] the iodoaryl nitroalkene was next examined with the intent of increasing the rate of oxidative insertion. In addition, the milder reaction conditions may ensure the stability of the nitroalkene.

Scheme 3



Cyclization of Iodoaryl Nitroalkene 9. In the presence of $Pd(OAc)_2$ (1.0 equiv) and acetic acid in refluxing benzene, iodoaryl nitroalkene **9** underwent the desired cyclization reaction without competitive benzene insertion; however, the isolated yields of the desired nitroalkene were still low (34%), and the reaction was capricious on larger scales. The use of acetonitrile as the solvent again resulted in lower yields. Palladium sources including $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $(CH_3CN)_2PdCl_2$ were examined either with or without added phosphine ligand (PPh_3 or dppe). Various bases (K_2CO_3, triethylamine, and Ag_2CO_3) and solvents (benzene, THF, dichloromethane, acetonitrile, DMF, and DMSO) were examined. Optimum conditions were found which employed $Pd(OAc)_2$ (1.0 equiv) as the palladium source with triphenylphosphine (2.0 equiv) as the added ligand and Ag_2CO_3 (2.0 equiv) as the base in benzene at 25 °C for 10 h. The desired nitroalkene **2** was produced as a single geometrical isomer in 43% yield along with the corresponding bicyclic nitroalkane **10** in 40% yield, Scheme 3.

In the process of optimizing the protocol several important trends were noted. Of the palladium sources examined, only $Pd(OAc)_2$ in the presence of triphenylphosphine (2 equiv/palladium) afforded the desired nitroalkene. For other sources of palladium either no reaction occurred (even at elevated temperatures) or the starting nitroalkene was consumed unproductively. The choice of base was found to be crucial with Ag_2CO_3 providing the best results. The use of $AgNO_3$ in place of Ag_2CO_3 failed to promote the reaction. The solvent was also important. Although the cyclized product **2** could be observed in benzene, THF, and to a lesser extent in dichloromethane, acetonitrile or DMF failed to promote the cyclization and DMSO resulted in decomposition of the starting nitroalkene. Attempts to perform the reaction with a catalytic amount of palladium were unsuccessful even at elevated temperatures as palladium metal precipitated from the reaction mixture. Finally, the bromoaryl nitroalkene **6** failed to react even under the optimized conditions, indicating that the aryl iodide was indeed required.

To confirm the structural identity of the side product as the saturated nitroalkane **10**, the compound was converted into the desired nitroalkene **2** through predictable synthetic steps.[2a,14] Deprotonation of nitroalkane **10** at 0 °C with *n*-butyllithium, trapping the anion with

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(9) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
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(14) (a) Sakakibara, T.; Takai, I.; Ohara, E.; Sudoh, R. *J. Chem. Soc., Chem. Commun.* **1981**, 261. (b) Sakakibara, T.; Ikuta, S.; Sudoh, R. *Synthesis* **1982**, 261.

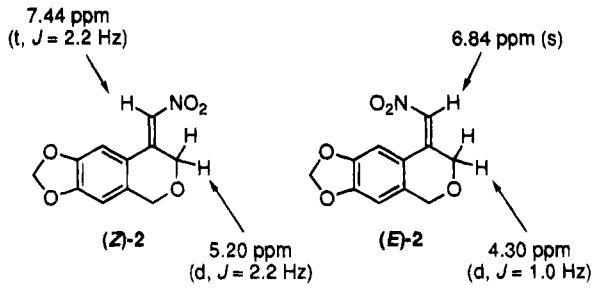
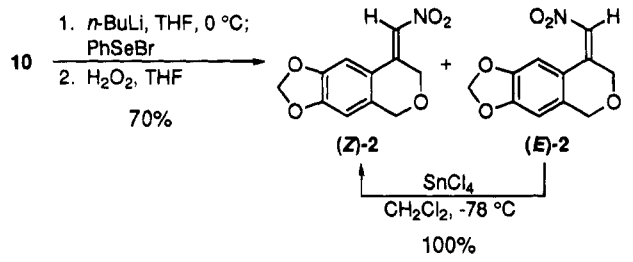


Figure 1. 400 MHz ^{1}H NMR data for (*E*)- and (*Z*)-**2**.

Scheme 4

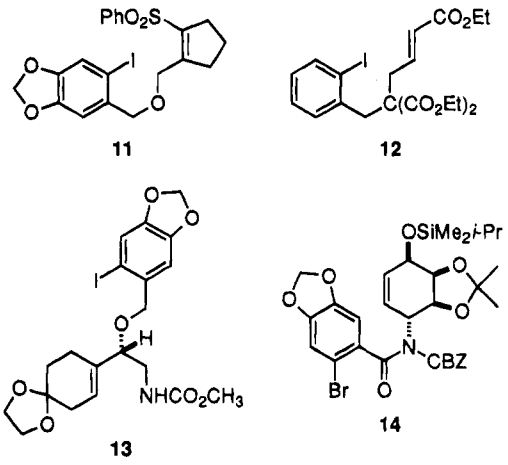


benzeneselenenyl bromide, and oxidative elimination with hydrogen peroxide afforded the (*Z*)- and (*E*)-nitroalkene isomers in a ratio of 2:1 in 70% combined yield, Scheme 4. Assignment of the olefin geometry was made possible by comparison of ^{1}H NMR chemical shifts of the allylic methylene protons as well as the α-nitro proton, Figure 1.[2a,15] In (*Z*)-**2** the allylic methylene protons are cis to the electron-poor nitro functionality and, therefore, would be expected to be deshielded by a through space interaction. As a result, the allylic methylene protons appear downfield (δ = 5.20 ppm) with respect to the corresponding allylic methylene protons of (*E*)-**2** (δ = 4.30 ppm). Likewise, the α-nitro proton in (*Z*)-**2** would be deshielded by the ring current of the aryl moiety and exhibit a chemical shift downfield (δ = 7.44 ppm) with respect to the α-nitro proton in (*E*)-**2** (δ = 6.84 ppm). On the basis of these assignments, the palladium-promoted cyclization of **9** afforded solely the (*Z*)-nitroalkene isomer.

To unambiguously confirm that the two products obtained from selenylation/oxidation were olefin geometric isomers, enriched nitroalkene (*E*)-**2** (15:1, *E*:*Z*) was dissolved in dichloromethane and treated with $SnCl_4$ (3 equiv) at −78 °C.[1a] After 30 min the mixture was quenched and the recovered nitroalkene (100%) was analyzed by high pressure liquid chromatography. A 65:1 mixture of isomers now favoring the *Z* configuration was observed. Therefore, in the presence of $SnCl_4$, a rapid isomerization of *E* and *Z* nitroalkene isomers occurred favoring the more stable *Z* configuration. As a result, through palladium-promoted cyclization of iodoaryl nitroalkene **9**, followed by selenylation, oxidative elimination, and isomerization of the nitroalkane side product, it was possible to obtain a 71% overall yield of nitroalkene (*Z*)-**2**.

Discussion

Intramolecular palladium-catalyzed cyclizations of aryl halides to olefins has become a common tool in natural product synthesis. Several examples of piperonyl-derived aryl halides as components in cyclizations with olefins have been reported including a cyclic vinyl sulfone **11**,[13] an unactivated olefin **13** in the synthesis of 6a-epipretazettine,[16] and a cyclic allylic silyl ether **14** in the synthesis of (+)-lycoricidine.[17] In each case the use of either silver or thallium salts were required for successful cyclization. In these cases as well as a report by Negishi[18] of the formation of a similar aryl, six-membered fused ring by cyclization of an aryl iodide to a tethered α,β-unsaturated ester **12**, no mention of saturated side product was reported.



A catalytic cycle for the formation of nitroalkene (*Z*)-**2** accounting for the concurrent formation of nitroalkane **10** and role of Ag_2CO_3 is depicted in Scheme 5. Zero valent palladium, formed from palladium(II) acetate and triphenylphosphine, undergoes oxidative addition into the carbon−iodine bond of the aryl iodide to form an arylpalladium(II) iodide complex (**i**).[19] The beneficial effects of silver salts have been proposed to arise from silver-mediated iodide abstraction from the arylpalladium iodide complex resulting in a highly electrophilic cationic palladium species capable of forming tight palladium−olefin complexes.[13,20] The need for a highly electrophilic arylpalladium species in our reaction stems from the low nucleophilicity of the nitro olefin and also explains the failure of highly coordinating solvents such as DMF or acetonitrile to promote the reaction even in the presence of Ag_2CO_3. Therefore, coordination of the electrophilic cationic palladium(II) species to the nitroalkene facilitates the syn addition of the palladium and aryl moieties[6] to the nitroalkene forming the (nitroalkyl)palladium intermediate **ii**. To allow for syn elimination of a hydridopalladium species,[6] σ-bond rotation must occur, Figure 2. The inability to access a syn orientation or the steric hindrance to this rotation has been proposed to influence the fate of the palladium intermediate and the outcome of the reaction.[7b,21]

(15) ^{1}H NOE experiments for *E*- and *Z*-isomers of 2-(2-methyl-4,5-(methylenedioxy)phenyl)-1-nitrobutene are consistent with the observations of proton deshielding.

(16) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.
(17) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694.
(18) O'Connor, B.; Zhang, Y.; Negishi, E.; Luo, F.-T.; Cheng, J.-W. *Tetrahedron Lett.* **1988**, *29*, 3903.
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(20) (a) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859. (b) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286. (c) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (d) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603. (e) Abelmann, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (f) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953.

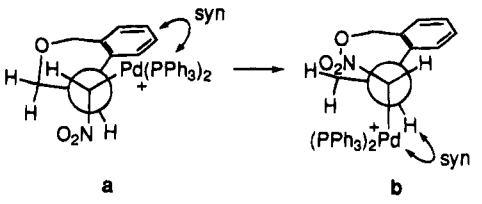
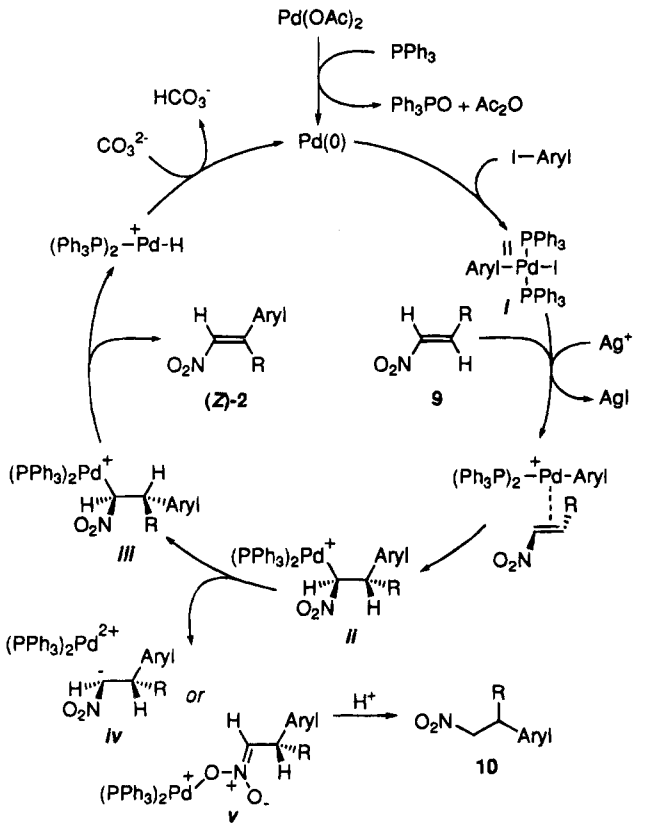


Figure 2. (Nitroalkyl)palladium conformations.

Scheme 5



Yamamura[7b] observed that with trisubstituted olefins bearing two strongly electron-withdrawing substituents at one carbon, arylation provides significant quantities of conjugate addition or olefin saturation products (12–52%). This was rationalized by a competition between syn hydridopalladium elimination and heterolytic cleavage of the palladium–carbon σ-bond to provide a stabilized carbanion and a cationic palladium species. The bifurcation of the reaction mechanism was proposed to arise from slow bond rotation of the phenyl–palladium addition product due to gauche interactions. Also, in the case of cyclic olefins where syn elimination of a hydridopalladium species is not possible, ionic mechanisms have been proposed to allow for epimerization of the palladium-bearing carbon center resulting in mixtures of alkene and saturated products.[21b,22]

The σ-bond rotation of intermediate **ii** required to provide the syn orientation of hydrogen and palladium (**iii**, Scheme 5; **b**, Figure 2) would place the nitro function in an eclipsed position to the ring methylene. The strain associated with this conformation may reduce the rate of elimination of a hydridopalladium species and allow for at least two alternative pathways to compete. First, heterolytic cleavage of the palladium–carbon bond would afford a stabilized nitronate anion (**iv**) and a cationic palladium species (Scheme 5). If it is assumed that silver sequesters the iodide ligand at the arylpalladium stage, this species must now be formally +2 charged and this route is therefore considered unlikely. Alternatively, a 1,3-shift of palladium from carbon to oxygen of the nitro group would afford a palladio nitronate (**v**). Subsequent protonation on workup would provide the nitroalkane. The lack of saturated product in the similar cyclization of the ester derivative **12**[18] supports the notion that the nitro group is uniquely required for this mechanism or otherwise accelerates the process.

The anticipated hydridopalladium elimination would afford the desired nitroalkene **2**. The exclusive formation of (*Z*)-**2** from isomerically pure (*E*)-**9** is consistent with a syn elimination process. Silver may also play an important role in the fate of the hydridopalladium species. Studies by Hallberg[20b] suggest that the hydridopalladium elimination step for Heck arylations in the presence of silver salts is irreversible thus preventing olefin isomerization to a potentially unstable cyclic enol ether.

Reductive elimination of palladium(II) by the base would in theory regenerate zero valent palladium to continue the catalytic cycle. However, the failure to observe catalysis in this case can be attributed to several factors: (1) the palladium species generated by heterolytic bond cleavage may not readily reenter the catalytic cycle, (2) formation of a palladio nitronate could sequester the palladium from the catalytic cycle until protonation, and (3) the necessity of benzene as the reaction solvent may prevent resolublization of the precipitated zero valent palladium species needed to continue the catalytic cycle.

Conclusion

1-Nitroalkenes have been found to be viable olefin acceptors for intramolecular Heck arylations with an aryl iodide. The use of Ag_2CO_3 as base is crucial for the success of the reaction presumably through formation of an electrophilic arylpalladium intermediate. Also, the influence of solvent on the reaction is atypical to classic Heck arylation conditions since the nonpolar solvent benzene provided the best results. Work is currently in progress to employ this method toward the total synthesis of (+)-pretazettine through the use of sequential nitroalkene [4 + 2]/nitronate [3 + 2] cycloadditions.

Experimental Section

General. Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures and are uncorrected. Melting points (mp) are uncorrected. Analytical high-pressure liquid chromatography (HPLC) employed a Supelco LC-Si column (250 × 4.5 mm, 5μm). All reactions were performed in oven (140 °C) or flame-dried glassware under an inert atmosphere of dry N_2. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$); dichloromethane ($CaCl_2$); *tert*-butyl methyl ether (MTBE) ($CaSO_4/FeSO_4$); ethyl acetate (K_2CO_3). Reaction solvents were distilled from the indicated drying agents: benzene (sodium), *tert*-butyl alcohol (sodium), dichloromethane (P_2O_5), 1,4-dioxane (sodium, benzophenone), and tetrahydro-

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(22) The formal conjugate addition process (hydroarylation) has been optimized by the use of formic acid as an additive: (a) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813. (b) Brunner, H.; Kramler, K. *Synthesis* **1991**, 1121. (c) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236. (d) Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713.

furan (THF) (sodium, benzophenone). Column (flash) chromatography was performed using 230–400 mesh silica gel. *n*-Butyllithium was titrated according to the method of Gilman.[23] Brine refers to a saturated aqueous solution of sodium chloride. Infrared spectra (IR) were obtained in CCl_4 unless otherwise specified. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%). ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz ^1H (100 MHz ^{13}C) with chloroform (δ 7.26 ppm for ^1H, 77.0 ppm for ^{13}C) as an internal standard in $CDCl_3$ unless otherwise specified. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants, J, are reported in hertz. Unassigned ^{13}C resonances are noted with their multiplicities from DEPT spectra. Mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Low-resolution electon impact (EI) mass spectra were obtained with an ionization voltage of 70 eV. Data are reported in the form m/z (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. $Pd(OAc)_2$ was purchased from Strem Chemicals.

(*Z*)-1,4-Bis((2-bromo-4,5-(methylenedioxy)phenyl)-methoxy)-2-butene (4). To a 250-mL, three-necked, round-bottom flask equipped with a reflux condenser, thermometer, and pressure-equalizing addition funnel was added sodium hydride (60% dispersion, 2.40 g, 60.0 mmol, 3.0 equiv) which was then suspended in THF (30 mL). A solution of 2-butene-1,4-diol (1.65 mL, 20.0 mmol) in THF (20 mL) was added dropwise maintaining an internal temperature of 25–30 °C. The suspension was allowed to stir at rt for 2 h, was cooled to 0 °C, and a solution of 2-bromo-4,5-(methylenedioxy)benzyl bromide (12.35 g, 42.0 mmol, 2.1 equiv) in THF (30 mL) was added. The mixture was then heated at 60 °C (internal temp) for 10 h, was cooled to 0 °C, and was slowly quenched with water (20 mL). The reaction mixture was diluted with MTBE (250 mL) and was washed with 0.2 N aqueous HCl (2 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with MTBE (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (4/1, 2/1)) and recrystallization (hexane (50 mL)/EtOAc (25mL)) to afford 8.98 g (87%) of dibromide **4** as a white solid. Data for **4**: mp 72–74 °C (hexane/EtOAc); ^1H NMR (400 MHz) 6.99 (s, 2 H), 6.95 (s, 2 H), 5.97 (s, 4 H), 5.82 (ddt, J_d = 1.2, 1.2, J_t = 3.8, 2 H), 4.47 (s, 4 H), 4.14 (dd, J = 3.7, 1.1, 4 H); ^{13}C NMR (100 MHz) 147.56, 147.31, 130.58, 129.37, 113.15, 112.43, 109.09, 101.62, 71.33, 66.02; IR 3010 (m), 1503 (s), 1479 (s), 1236 (s); MS (EI) 516 (M^+ + 4, 0.1), 514 (M^+ + 2, 0.3), 512 (M^+, 0.1), 213 (100); TLC R_f 0.48 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{20}H_{18}Br_2O_6$ (514.167): C, 46.72; H, 3.53; Br, 31.08. Found: C, 46.70; H, 3.50; Br, 31.11.

2-((2-Bromo-4,5-(methylenedioxy)phenyl)methoxy)-ethanal (5). Aryl bromide **4** (2.57 g, 5.0 mmol) was dissolved in a mixture of 1,4-dioxane (75 mL) and water (20 mL), and 2 N aqueous sulfuric acid (5 mL) was added. Osmium tetraoxide (4% solution in water, 635 μL, 0.10 mmol, 0.02 equiv) was added, and the solution was allowed to stir for 10 min as it turned dark brown. Solid $NaIO_4$ (4.28 g, 20.0 mmol, 4.0 equiv) was added portionwise over 20 min. An additional portion of 2 N aqueous sulfuric acid (5 mL) was added, and the mixture was allowed to stir at rt for 18 h. The reaction mixture was diluted with MTBE (250 mL) and was washed with water (5 × 25 mL) and brine (25 mL). The aqueous layers were back-extracted with MTBE (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude concentrate was purified by column chromatography (hexane/EtOAc (2/1, 1/1)) and distillation to afford 2.13 g (78%) of bromo aldehyde **5** as a white solid. Data for **5**: bp 210 °C (0.2 Torr); mp 66–68 °C; ^1H NMR (400 MHz) 9.76 (t, J = 0.7, 1 H), 7.01 (s, 1 H), 6.99 (s, 1 H), 5.99 (s, 2 H), 4.62 (s, 2 H), 4.16 (s, 2 H); ^{13}C NMR (100 MHz) 200.18, 148.07, 147.51, 129.39, 113.63, 112.59, 109.41, 101.81, 75.47, 72.65; IR 2892 (m), 1741 (s), 1504 (s); MS (EI) 274 (M^+ + 2, 13), 272 (M^+, 14), 213 (100); TLC R_f 0.19 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{10}H_9BrO_4$ (273.084): C, 43.98; H, 3.32; Br, 29.26. Found: C, 44.06; H, 3.31; Br, 29.21.

(*E*)-3-((2-Bromo-4,5-(methylenedioxy)phenyl)methoxy)-1-nitropropene (6). Bromo aldehyde **5** (1.37 g, 5.0 mmol) was dissolved in a mixture of THF (12.5 mL) and *tert*-butyl alcohol (12.5 mL) and the solution was cooled to 0 °C. Nitromethane (813 μL, 15.0 mmol, 3.0 equiv) was added followed by potassium *tert*-butoxide (56 mg, 0.5 mmol, 0.1 equiv). The mixture was allowed to warm to rt and stir for 8 h. The reaction mixture was diluted with MTBE (200 mL) and was washed with saturated aqueous NH_4Cl solution (2 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with MTBE (50 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and placed under high vacuum (0.1 Torr) for 12 h. The crude nitro alcohol was dissolved in CH_2Cl_2 (30 mL), and the solution was cooled to 0 °C. To the solution was added methanesulfonyl chloride (387 μL, 5.0 mmol, 1.0 equiv). After 5 min, triethylamine (1.40 mL, 10.0 mmol, 2.0 equiv) was slowly added, and the mixture was stirred for 15 min. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), diluted with CH_2Cl_2 (200 mL), and washed with saturated aqueous NH_4Cl solution (2 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (4/1)) to afford 1.10 g (70%) of bromo nitroalkene **6** as a yellow solid. Data for **6**: mp 67–68 °C; ^1H NMR (400 MHz) 7.29 (dt, J_d = 13.2, J_t = 3.2, 1 H), 7.23 (dt, J_d = 13.4, J_t = 1.5, 1 H), 7.03 (s, 1 H), 6.94 (s, 1 H), 6.00 (s, 2 H), 4.57 (s, 2 H), 4.32 (dd, J = 3.2, 1.7, 2 H); ^{13}C NMR (100 MHz) 148.04, 147.50, 139.61, 138.13, 129.37, 113.49, 112.62, 109.06, 72.31, 65.79; IR 1504 (m), 1480 (s), 1235 (m); MS (EI) 317 (M^+ + 2, 31), 315 (M^+, 32), 213 (100); TLC R_f 0.52 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{11}H_{10}BrNO_5$ (316.108): C, 41.80; H, 3.19; N, 4.43; Br, 25.28. Found: C, 41.81; H, 3.20; N, 4.42; Br, 25.32.

(*Z*)-1,4-Bis((2-iodo-4,5-(methylenedioxy)phenyl)-methoxy)-2-butene (7). Bromoaryl ether **4** (25.71 g, 50.0 mmol) was added to a 2-L, three-necked round-bottom flask equipped with a thermometer and a 250-mL, pressure-equalizing addition funnel and was dissolved in THF (400 mL). The solution was cooled to −78 °C, and *n*-butyllithium (2.52 M in hexane, 39.7 mL, 100 mmol, 2.0 equiv) was slowly added, not allowing the temperature to exceed −65 °C. After the solution was stirred for 15 min, a solution of iodine (31.72 g, 125 mmol, 2.5 equiv) in THF (250 mL) was slowly added, not allowing the temperature to exceed −65 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL), and after warming to 0 °C, the mixture was diluted with MTBE (600 mL) and washed with saturated aqueous NH_4Cl solution (100 mL), saturated aqueous $Na_2S_2O_3$ solution (2 × 25 mL), water (100 mL), and brine (100 mL). The aqueous layers were back-extracted with MTBE (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (6/1, 4/1, 2/1)) and crystallization (EtOAc/hexane) to afford 22.9 g (75%) of iodoaryl ether **7** as a white solid. Data for **7**: mp 75–77 °C (EtOAc/hexane); ^1H NMR (400 MHz) 7.23 (s, 2 H), 6.96 (s, 2 H), 5.97 (s, 4 H), 5.83 (ddd, J = 4.8, 3.7, 1.1, 2 H), 4.40 (s, 4 H), 4.15 (dd, J = 3.7, 1.1, 4 H); ^{13}C NMR (100 MHz) 148.42, 147.80, 133.81, 129.45, 118.42, 109.23, 101.60, 85.92, 75.89, 66.10; IR 2889 (w), 1503 (w), 1477 (m); MS (EI) 608 (M^+, 1), 261 (100); TLC R_f 0.41 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{20}H_{18}I_2O_6$ (608.168): C, 39.50; H, 2.98; I, 41.73. Found: C, 39.52; H, 2.99; I, 41.60.

2-((2-Iodo-4,5-(methylenedioxy)phenyl)methoxy)-ethanal (8). Aryl iodide **7** (12.16 g, 20.0 mmol) was dissolved in a mixture of 1,4-dioxane (320 mL) and water (85 mL) and 2 N aqueous sulfuric acid (20 mL) was added. Osmium tetraoxide (4% solution in water, 2.54 mL, 0.40 mmol, 0.02 equiv) was added, and the solution was allowed to stir for 10 min as it turned dark brown. Solid $NaIO_4$ (17.11 g, 80.0 mmol, 4.0 equiv) was added portionwise over 20 min. An additional

(23) Gilman, H.; Cartledge, F. K. *J. Organometal. Chem.* **1964**, *2*, 447.

portion of 2 N aqueous sulfuric acid (20 mL) was added, and the mixture was allowed to stir at rt for 18 h. The reaction mixture was diluted with MTBE (600 mL) and was washed with water (2 × 100 mL) and brine (100 mL). The aqueous layers were back-extracted with MTBE (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude concentrate was purified by column chromatography (hexane/EtOAc (2/1, 1/1)) to afford 10.5 g (82%) of iodo aldehyde **8** as a white solid. An analytical sample of **8** was obtained after sublimation (90 °C, 0.2 Torr). Data for **8**: mp 88–91 °C (sublimed, 90 °C, 0.2 Torr); ^{1}H NMR (400 MHz) 9.73 (t, J = 0.7, 1 H), 7.26 (s, 1 H), 6.99 (s, 1 H), 5.99 (s, 2 H), 4.53 (s, 2 H), 4.16 (d, J = 0.7, 2 H); ^{13}C NMR (100 MHz) 200.20, 148.52, 148.16, 132.60, 118.49, 109.36, 101.72, 86.24, 77.00, 75.42; IR 2893 (m), 1741 (s), 1478 (s); MS (EI) 320 (M^+, 29), 261 (100); TLC R_f 0.20 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{10}H_9IO_4$ (320.083): C, 37.52; H, 2.83; I, 39.65. Found: C, 37.54; H, 3.09; I, 39.63.

(*E*)-3-((2-Iodo-4,5-(methylenedioxy)phenyl)methoxy)-1-nitropropene (9). Iodo aldehyde **8** (8.0 g, 25.0 mmol) was dissolved in a mixture of THF (62.5 mL) and *tert*-butyl alcohol (62.5 mL), and the solution was cooled to 0 °C. Nitromethane (4.06 mL, 75.0 mmol, 3.0 equiv) was added followed by potassium *tert*-butoxide (281 mg, 2.5 mmol, 0.1 equiv). The mixture was allowed to warm to rt and stir for 10 h. The reaction mixture was diluted with MTBE (500 mL) and was washed with saturated aqueous NH_4Cl solution (2 × 100 mL) and brine (100 mL). The aqueous layers were back-extracted with MTBE (100 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and placed under high vacuum (0.1 Torr) for 12 h. The crude nitro alcohol was dissolved in CH_2Cl_2 (150 mL) and the solution was cooled to 0 °C. To the solution was added methanesulfonyl chloride (1.94 mL, 25.0 mmol, 1.0 equiv). After 5 min, triethylamine (6.99 mL, 50.0 mmol, 2.0 equiv) was slowly added, and the mixture was stirred for 15 min. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), diluted with CH_2Cl_2 (500 mL), and washed with saturated aqueous NH_4Cl solution (2 × 100 mL) and brine (100 mL). The aqueous layers were back-extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (6/1, 4/1)) and recrystallization (EtOAc (10 mL)/hexane (5 mL)) to afford 6.13 g (68%) of iodo nitroalkene **9** as a yellow solid. Data for **9**: mp 85–88 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.30 (dt, J_d = 13.2, J_t = 3.2, 1 H), 7.27 (s, 1 H), 7.24 (dt, J_d = 13.3, J_t = 1.8, 1 H), 6.94 (s, 1 H), 6.00 (s, 2 H), 4.52 (s, 2 H), 4.33 (dd, J = 3.2, 1.7, 2 H); ^{13}C NMR (100 MHz) 148.48, 148.13, 139.65, 138.10, 132.54, 118.51, 109.08, 101.75, 86.13, 76.64, 65.75; IR 2893 (m), 1534 (s), 1503 (s), 1478 (s); MS (EI) 363 (M^+, 56), 261 (100); TLC R_f 0.27 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{11}H_{10}INO_5$ (363.108): C, 36.39; H, 2.78; N, 3.86; I, 34.95. Found: C, 36.43; H, 2.80; N, 3.89; I, 34.78.

(*Z*)-6,7-(Methylenedioxy)-4-(nitromethylene)-3,4-dihydro-1*H*-2-benzopyran ((*Z*)-2) and 6,7-(Methylenedioxy)-4-(nitromethyl)-3,4-dihydro-1*H*-2-benzopyran (10). Iodo nitroalkene **9** (1.45 g, 4.0 mmol) and Ag_2CO_3 (2.21 g, 8.0 mmol, 2.0 equiv) were suspended in freshly distilled benzene (200 mL). $Pd(OAc)_2$ (898 mg, 4.0 mmol, 1.0 equiv) was added to the solution followed by the addition of triphenylphosphine (2.10 g, 8.0 mmol, 2.0 equiv). The mixture was allowed to stir at rt for 10 h. The reaction mixture was filtered through Celite and washed through with benzene (25 mL). Without concentration the mixture was purified by column chromatography (benzene, benzene/EtOAc (10/1)) to provide crude (*Z*)-**2** and **10**. Nitroalkene (*Z*)-**2** was recrystallized from EtOAc (20 mL), and the mother liquor was concentrated *in vacuo* and further purified by column chromatography (hexane/EtOAc (6/1, 4/1)). Recrystallization (EtOAc (5 mL)/pentane (1 mL)) afforded a combined yield of 400 mg (43%) of nitroalkene (*Z*)-**2** as a yellow solid. Recrystallization of **10** from hexane/EtOAc afforded 380 mg (40%) of nitroalkane **10** as a light yellow solid. Data for (*Z*)-**2**: mp 161–162 °C (EtOAc); ^{1}H NMR (400 MHz) 7.44 (t, J = 2.2, 1 H), 7.05 (s, 1 H), 6.65 (s, 1 H), 6.05 (s, 2 H), 5.20 (d, J = 2.2, 2 H), 4.59 (s, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 151.55, 148.33, 146.14, 135.62, 130.45, 120.34, 105.96, 104.11, 102.59, 68.02, 67.86; IR ($CHCl_3$) 3023 (w), 1504 (s), 1482 (s), 1322 (s); MS (EI) 235 (M^+, 100); TLC R_f 0.30 (benzene). Anal. Calcd for $C_{11}H_9NO_5$ (235.196): C, 56.17; H, 3.86; N, 5.96. Found: C, 56.12; H, 3.89; N, 5.90. Data for **10**: mp 108–109 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 6.62 (s, 1 H), 6.47 (s, 1 H), 5.94 (q, J = 1.2, 2 H), 4.77 (dd, J = 12.9, 9.8, 1 H), 4.72, 4.66 (ABq, J = 14.9, 2 H), 4.47 (ddd, J = 12.9, 4.9, 1.2, 1 H), 4.07 (dd, J = 12.1, 1.5, 1 H), 3.78 (ddd, J = 12.1, 2.9, 1.2, 1 H), 3.40 (dddd, J = 9.8, 4.6, 2.9, 1.5, 1 H); ^{13}C NMR (100 MHz) 147.28, 146.62, 128.19, 123.90, 108.26, 104.41, 101.04, 78.05, 67.94, 65.74, 36.51; IR 2897 (m), 1555 (s), 1504 (s), 1484 (s), 1240 (s); MS (EI) 237 (M^+, 43), 149 (100); TLC R_f 0.38 (benzene). Anal. Calcd for $C_{11}H_{11}NO_5$ (237.212): C, 55.70; H, 4.67; N, 5.90. Found: C, 55.72; H, 4.68; N, 5.91.

(*E*)- and (*Z*)-6,7-(Methylenedioxy)-4-(nitromethylene)-3,4-dihydro-1*H*-2-benzopyran (2). Nitroalkane **10** (237 mg, 1.0 mmol) was dissolved in THF (10 mL), and the solution was cooled to 0 °C. To the solution was slowly added *n*-butyllithium (1.55 M in hexane, 710 μL, 1.1 mmol). The resulting suspension was stirred for 15 min at 0 °C, and then a solution of benzeneselenenyl bromide (472 mg, 2.0 mmol, 2.0 equiv) in THF (2.5 mL) was added. After 1 h at 0 °C, the reaction mixture was diluted with EtOAc (100 mL) and was washed with water (2 × 25 mL) and brine (25 mL). The aqueous layers were back-extracted with EtOAc (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the selenide as a yellow oil. The crude selenide was dissolved in THF (20 mL), the solution was cooled to 0 °C, and a solution of aqueous hydrogen peroxide (30%, 4 mL) was added. The reaction mixture was allowed to warm to rt and stir for 3 h. The bright yellow solution was diluted with CH_2Cl_2 (100 mL) and was washed with water (2 × 25 mL) and brine (25 mL). The aqueous layers were back-extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified by column chromatography (hexane/EtOAc (4/1)) and recrystallization (EtOAc/hexane) to afford 122 mg (52%) of nitroalkene (*Z*)-**2** and 52 mg (22%) of nitroalkene (*E*)-**2** (15/1, *E*/*Z*, HPLC) as yellow solids. Data for (*Z*)-**2**: mp 161–163 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.44 (t, J = 2.2, 1 H), 7.05 (s, 1 H), 6.65 (s, 1 H), 6.05 (s, 2 H), 5.20 (d, J = 2.2, 2 H), 4.59 (s, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 151.06, 147.84, 145.67, 135.13, 129.96, 119.85, 105.47, 103.62, 102.09, 67.53, 67.37; IR ($CHCl_3$) 2906 (w), 1505 (s), 1482 (s), 1322 (s); TLC R_f 0.29 (benzene). Anal. Calcd for $C_{11}H_9NO_5$ (235.196): C, 56.17; H, 3.86; N, 5.96. Found: C, 56.01; H, 3.72; N, 6.14. Data for (*E*)-**2**, (*Z*)-**2** mixture: mp 122–124 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.44 (t, J = 2.2, 0.1 H), 7.14 (s, 0.9 H), 7.05 (s, 0.1 H), 6.84 (s, 0.9 H), 6.65 (s, 0.1 H), 6.55 (s, 0.9 H), 6.05 (s, 0.2 H), 6.02 (s, 1.8 H), 5.20 (d, J = 2.2, 0.2 H), 4.80 (s, 1.8 H), 4.60 (s, 0.2 H), 4.30 (d, J = 1.0, 1.8 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 150.79, 146.83, 136.48, 133.81, 119.64, 108.43, 104.70, 102.38, 69.26, 69.14; IR 2903 (w), 1505 (m), 1484 (m); MS (EI) 235 (M^+, 100); TLC R_f 0.35 (benzene); HPLC (Supelco LC-Si, 1.5 mL/min, hexane/EtOAc, 8/1) t_R (*Z*)-**2** 7.74 min (6.6%), t_R (*E*)-**2** 10.10 min (93.4%). Anal. Calcd for $C_{11}H_9NO_5$ (235.196): C, 56.17; H, 3.86; N, 5.96. Found: C, 56.03; H, 3.74; N, 5.93.

Isomerization of (*Z*)-6,7-(Methylenedioxy)-4-(nitromethylene)-3,4-dihydro-1*H*-2-benzopyran ((*E*)-2). Nitroalkene (*E*)-**2** (15/1, *E*/*Z*) (24 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and the solution was cooled to −78 °C. To the solution was added $SnCl_4$ (35 μL, 0.3 mmol, 3.0 equiv), and the resulting deep, purple solution was stirred at −78 °C for 30 min. The reaction was quenched with a 1 N solution of NaOH in methanol (1.2 mL), diluted with CH_2Cl_2 (100 mL), and was washed with water (3 × 25 mL) and brine (25 mL). The aqueous layers were back-extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford 24 mg (100%) of nitroalkene (*Z*)-**2** (65/1, *Z*/*E*, HPLC) as a yellow solid. Data for (*Z*)-**2**: mp 161–163 °C; ^{1}H NMR (400 MHz) 7.44 (t, J = 2.2, 1 H), 7.05 (s, 1 H), 6.65 (s, 1 H), 6.05 (s, 2 H), 5.20 (d, J = 2.2, 2 H), 4.60 (s, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 151.55, 148.33, 146.15, 135.62, 130.45, 120.34, 105.96, 104.11, 102.59, 68.02, 67.86;

IR ($CHCl_3$) 2964 (w), 1482 (s), 1322 (s); TLC R_f 0.29 (benzene); HPLC (Supelco LC-Si, 1.5 mL/min, hexane/EtOAc, 8/1) t_R (*Z*)-**2** 7.75 min (98.5%), t_R (*E*)-**2** 10.04 min (1.5%).

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Supplementary Material Available: Complete ^1H and ^{13}C NMR assignments and IR and MS data for all characterized compounds (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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