An Allylpalladium(IV) Intermediate in the Synthesis of Highly Substituted Benzoxepines and Benzopyrans via Reactions of Stable Pallada(II)cycles with Allyl Bromides

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Stable pallada(II)cycles $L_2Pd\text{-}1\text{-}C_6H_5\text{-}2\text{-}OCHCO_2Et$, featuring a Pd-bonded sp^3-hybridized stereogenic carbon and bipyridine or bis(imine) auxiliary ligands (L-L), reacted with allyl bromides via a Pd(II)−Pd(IV)-mediated process involving a direct C(sp^2)−H functionalization to afford highly substituted benzoxepines or benzopyrans. An allylpalladium(IV) complex, which was detected by low-temperature ^{1}H NMR analysis and characterized by X-ray crystallography, was shown to operate as an intermediate in the reaction sequence.

Introduction

Multistep cascade reactions catalyzed by palladium complexes are extremely useful tools in organic synthesis.[1] The traditional processes rely on catalytic cycles featuring palladium in oxidation states Pd(0) and Pd(II) and in most cases exploit intermediates with C(sp^2)−Pd bonds.[1] Recent developments have suggested that reactions involving Pd(IV) intermediates could give rise to synthetically attractive transformations.[2,3] Palladium(IV) complexes have been previously detected spectroscopically,[4a,g] isolated,[4b,d,h,k] and in some cases characterized by X-ray crystallography.[4b,c,e,i,l,m] However, the successful isolation and unambiguous characterization of a Pd(IV) intermediate, which could be converted into a complex organic molecule, remain extremely rare. Most recently, stable Pd(IV) intermediates arising via oxidation of Pd(II) complexes with hypervalent iodonium electrophiles have been isolated, characterized, and shown to participate in the overall C−H functionalization sequences.[5] Earlier, ^{1}H NMR data for a Pd(IV) complex generated via oxidative addition with benzyl bromide were reported,[6a] providing support for the proposed involvement of analogous catalytic intermediates in synthetically useful Pd-catalyzed cyclizations.[6b] Aiming to explore a formal annulation between two polyfunctional organic electrophiles, we envisioned that the hypothetical Pd(IV) intermediate **I** (Figure 1) with three C−Pd bonds, including a Pd-bonded stereogenic center, and an organic fragment featuring a reactive functional group (e.g., a double bond) could be generated and subsequently collapse to afford complex cyclic molecules with multiple stereogenic centers.

Herein, we provide a proof of concept for such a protocol, including the evidence for the formation of the proposed Pd(IV) intermediate **I** via oxidative addition of allyl bromides to the Pd(II) complexes **II** (Figure 1).[7] The stable palladacycles **II**, possessing a Pd-bonded sp^3-hybridized stereogenic carbon, reacted with allyl bromides to afford good yields of highly substituted benzoxepines **IV** and **V** or benzopyrans **VI** through a sequential formation of up to three C−C bonds, including a C(sp^2)−H functionalization event (Figure 1). Under optimized conditions, the Pd-bonded stereocenter in intermediates **I** and **II** was incorporated into the organic products **V** and **VI**. Spectroscopic data (low-temperature ^{1}H NMR) as well as X-ray crystallographic evidence confirmed the involvement of the reactive Pd(IV) intermediate **I** bearing the bipyridine ligand (L-L) in the reaction sequence. Structures of complexes **III** bearing both bipyridine and bis(imine) ligands and arising via C(sp^2)−C(sp^3) bond-forming reductive elimination from the Pd(IV) intermediates **I** were established by X-ray crystallography, and

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(1) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.

(2) (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1407. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 2300. A Pd(IV) intermediate was proposed for the arylation of C−H bonds with aryl iodides, see: (d) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(3) (a) Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601. (b) Catellani, M. *Synlett* **2003**, 298.

(4) For examples of studies stoichiometric in palladium, in which distinct Pd(IV) complexes were isolated or detected in solution, using aryl or alkynyl hypervalent iodonium oxidants, alkyl or benzyl halides, propargyl bromides, diaryl diselenide or halogens, see: (a) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Organometallics* **2006**, *25*, 3996. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (c) Campora, J.; Palma, P.; del Rio, D.; Lopez, J. A.; Valerga, P. *Chem. Commun.* **2004**, 1490. (d) Canty, A. J.; Patel, J.; Rodemann, T.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 3466. (e) Yamamoto, Y.; Kuwabara, S.; Matsuo, S.; Ohno, T.; Nishiyama, H.; Itoh, K. *Organometallics* **2004**, *23*, 3898. (f) Canty, A. J.; Denney, M. C.; Patel, J.; Sun, H.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **2004**, *689*, 672. (g) van Belzen, R.; Elsevier, C. J.; Dedieu, A.; Veldman, N.; Spek, A. L. *Organometallics* **2003**, *22*, 722. (h) Canty, A. J.; Jin, H.; Penny, J. D. *J. Organomet. Chem.* **1999**, *573*, 30. (i) Canty, A. J.; Hoare, J. L.; Patel, J.; Pfeffer, M.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 2660. (j) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83 and references cited therein. (k) Byers, P. K.; Canty, A. J. *J. Chem. Soc., Chem. Commun.* **1988**, 639. (l) Byers, P. K.; Canty, A. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1987**, 1093. (m) Byers, P. K.; Canty, A. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **198**6, 1722.

(5) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

(6) (a) Bocelli, G.; Catellani, M.; Ghelli, S. *J. Organomet. Chem.* **1993**, *458*, C12. (b) However, an alternative mechanistic pathway relying on transmetalation between two Pd(II) centers and lacking the involvement of Pd(IV) intermediates in analogous Pd-catalyzed reactions involving aryl halides as hypothetical oxidants for Pd(II) complexes was proposed and supported by computational studies; see: Cardemas. D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033.

(7) For rare reports on reactions of pallada(II)cycles with 2-propenyl bromide, leading to the in situ (^{1}H NMR) detection of a presumed Pd(IV) complex, see: (a) Canty, A. J.; Hoare, J. L.; Davies, N. W.; Trail, P. R. *Organometallics* **1998**, *17*, 2046. (b) de Graaf, W.; Boersma, J.; van Koten, G. *Organometallics* **1990**, *9*, 1479.

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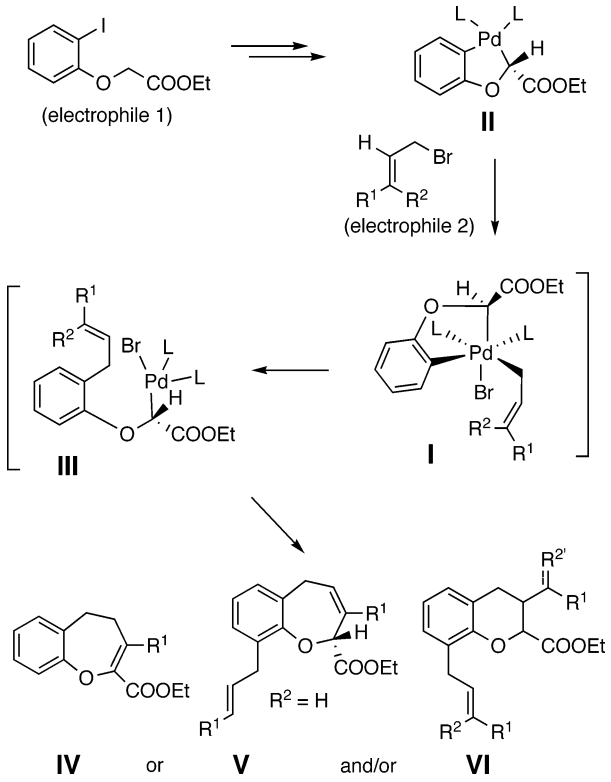
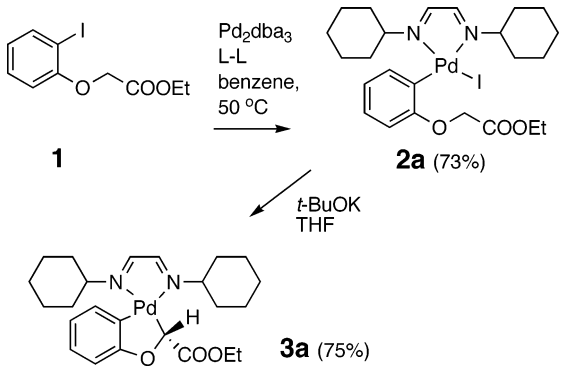


Figure 1. Overview of the results.

Scheme 1



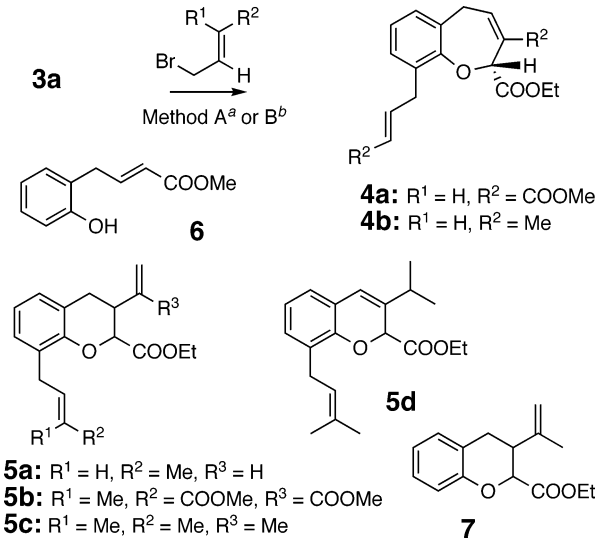
complexes **III** were converted to the functionalized heterocycles **IV**−**VI** under suitable conditions. The study documents the key elemental events of the multistep sequence and demonstrates the synthetic potential of reaction cascades exploiting Pd(0)−Pd(II)−Pd(IV) cycles.

Results and Discussion

The stable palladacycle **3a**, featuring a palladium-bonded sp^3-hybridized stereogenic carbon and the *N*,*N*′-dicyclohexylethylenediimine ligand, was prepared from aryl iodide **1** via complex **2a** by an established method[8] (Scheme 1), and the molecular structure of palladacycle **3a** was confirmed by X-ray crystallography. Palladacycle **3a** was treated with substituted allyl bromides at elevated temperatures (80−100 °C), either in solution (6−10 equiv of allyl bromides in 1,2-dichloroethane or acetonitrile) or in neat allyl bromide, to afford the racemic

(8) Pd(II) complexes bearing bipyridine and other N-based auxiliary ligands were frequently employed in the studies generating Pd(IV) complexes.[4] For the method for the preparation of complexes **2** and **3**, see: (a) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 4701. (b) Portscheller, J. L.; Malinakova, H. C. *Org. Lett.* **2002**, *4*, 3679.

Table 1.



entry	allyl bromide R¹	allyl bromide R²	solvent/ additive	time (h)/ temp (°C)	product (% yield)	
1	H	COOMe	DCE/*t*-BuOK[b]	20/95	**4a** (53)	
2			NA/NaBr[a]	1.5/85	**4a** (50)[c]	**6** (15)
3			NA/Cs_2CO_3[a]	2/95	**4a** (62)	
4	H	Me	NA/Cs_2CO_3[b]	2/115	**4b** (29)[d]	**5a** (35)
5			MeCN/Cs_2CO_3[b]	60/115	**4b** (40)[d]	**5a** (18)
6	Me	COOMe	NA/Cs_2CO_3[a]	3/100		**5b** (58)
7	Me	Me	DCE/Cs_2CO_3[b]	60/105		**7** (56)
8			DCE/*t*-BuOK[b]	2/115	**5c** (28)	**5d** (14)

[a] Method A: in neat allyl bromide, w/o Cs_2CO_3 (2.5 equiv) or *t*-BuOK (3.5 equiv) or NaBr (2.0 equiv). [b] Method B: in solution with Cs_2CO_3 (2.5 equiv) or *t*-BuOK (3.5 equiv). [c] Trace of benzoxepine lacking the allyl substituent in the aromatic ring was isolated.[10] [d] Trace of a disubstituted benzene was isolated.[11]

heterocycles **4**, **5**, and **7** in a single step (Table 1). It is notable that 2 equiv of the allylic electrophiles participated in the cyclization, resulting in functionalization of a $C(sp^2)$−H bond in the aromatic rings (vide infra). Bases and/or additives were employed to facilitate the intramolecular cyclization presumably terminated by β-hydride elimination (vide infra). The best results in the reaction of palladacycle **3a** with methyl 4-bromo-2-butenoate were achieved in neat allyl bromide in the presence of Cs_2CO_3, providing the benzoxepine **4a** (62%) as a single product via an unexpected 7-endo-trig cyclization (entry 3 of Table 1).[9] In the presence of NaBr, benzoxepine **4a** (50%) was accompanied by traces of a benzoxepine lacking the second allyl substituent in the aromatic ring[10] and the phenol **6** (15%) (entry 2 of Table 1). The reaction in solution (1,2-dichloroethane) afforded benzoxepine **4a** in a lower yield (53%; entry 1 of Table 1) as a single product. Palladium was recovered as complex **8** (45% yield; Chart 1) from reactions run in neat allyl bromides via precipitation with methylene chloride and as complex **9** (11% yield; Chart 1) after chromatographic separation of the meth-

(9) For examples of relatively rare 7-endo Heck reactions, and a discussion of the competition between 7-endo and 6-exo cyclization pathways in the Heck reactions, see: (a) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834. (b) Gibson, S. E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743.

(10) The benzoxepine with the structure shown below was isolated and identified by ^1H and ^{13}C NMR spectroscopy.

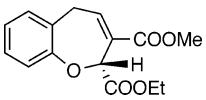
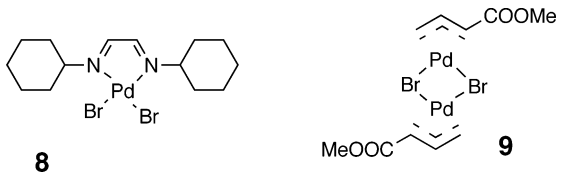


Chart 1



ylene chloride extracts of the crude precipitate. Structures of complexes **8** and **9** were determined by X-ray crystallography.

Replacement of the activating ester group with a methyl substituent or the presence of an additional terminal methyl group in the allyl bromide favored the 6-exo-trig cyclization leading to benzopyrans **5** and **7** (entries 4−8 of Table 1).[9] Treatment of palladacycle **3a** with the least hindered 1-bromo-2-butene in neat allyl bromide afforded comparable quantities of the 7-endo and 6-exo products **4b** (29%) and **5a** (35%), respectively, along with traces of a bis-allylated benzene byproduct[11] (entry 4 of Table 1). In contrast, the reaction in solution (MeCN) afforded the benzoxepine **4b** (40%) as a major product along with the benzopyran **5a** (18%) (entry 5, Table 1). The 3,3-disubstituted methyl 4-bromo-2-methyl-2-butenoate and 1-bromo-3-methyl-2-butene yielded the benzopyran **5b** (58%), along with a trace of an isomer arising from double-bond migration,[12] and the benzopyran **7** (56%), respectively (entries 6 and 7, Table 1). The application of a stronger base (e.g., *t*-BuOK vs Cs_2CO_3) increased the extent of the additional elaboration of the aromatic ring, providing the benzopyrans **5c** (28%) and **5d** (14%) instead of heterocycle **7** (compare entries 7 and 8 of Table 1). The benzopyrans **5** and **7** were isolated as single diastereomers. However, ^{1}H NMR NOE experiments[13] did not provide sufficient evidence for an unequivocal assignment of the relative stereochemistry in heterocycles **5** and **7** (Table 1).

Assuming the involvement of the Pd(IV) complex **I**, a plausible mechanism for the formation of heterocycles **4** and **5** is shown in Figure 2. Intermediate **VII** arising from **I** would undergo an intramolecular C(sp^2)−H activation (electrophilic palladation)[14] in the ortho position to afford the palladacycle **VIII**, under conditions favoring the C(sp^2)−H activation over an intramolecular Heck reaction. The resulting palladacycle **VIII** is poised for a second oxidative addition of allyl bromide,[7] yielding Pd(IV) intermediate **IX**, which collapses to complex **X**, providing the elaborated heterocycles **4** and **5** via 7-endo and 6-exo Heck cyclizations, respectively.[9] Substitution at the adjacent carbons (1, 2, 3) in products **4** and **5** supports the proposed ortho-metalation pathway, rather than an intermolecular electrophilic substitution on the corresponding 1,2-disubstituted heterocycles.[14]

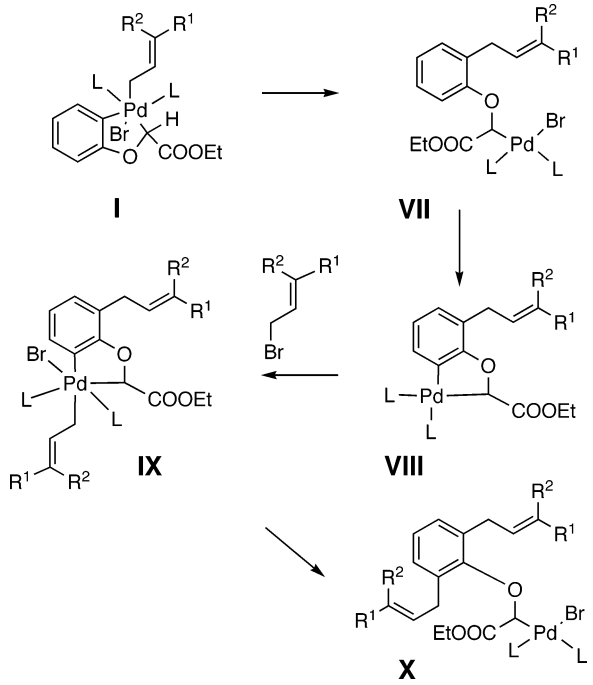
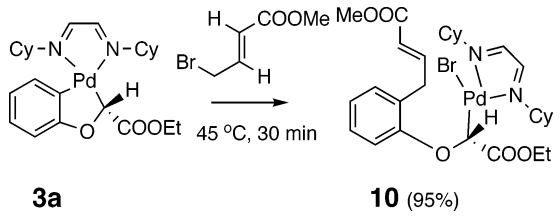


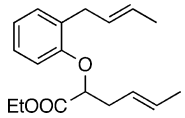
Figure 2. Proposed mechanism of the annulation reaction.

Scheme 2

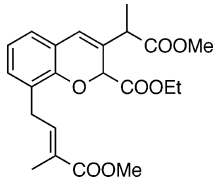


In a search for evidence for the proposed mechanistic pathway, isolation of the reactive intermediates **VII**−**X** was attempted. Low-temperature (0−8 °C) diffusion-controlled crystallization (EtOAc/pentane) of the crude product from the reaction between palladacycle **3a** and neat methyl 4-bromo-2-butenoate (45 °C, 30 min) afforded a single crystal, which was shown by X-ray crystallographic analysis to represent the proposed intermediate **VII**: e.g., the (*o*-allyl)arylpalladium(II) bromo complex **10** (Scheme 2). The solid-phase structure of complex **10** features an aromatic C−H bond (C6 in Figure 3) in close proximity to the palladium(II) center. A similar conformation of complex **10** in solution might contribute to the apparently facile palladation of the ortho position in the aromatic ring, leading to the proposed complex **VIII** (Figure 2). When palladacycle **3a** was allowed to react with neat methyl 4-bromo-2-butenoate for an extended time (45 °C, 20 h), formation of

(11) The 1,2-disubstituted benzene, the structure of which is shown below, was isolated and identified by ^{1}H and ^{13}C NMR spectroscopy. Its formation can be rationalized via C-allylation of the palladium ester enolate **VII** (Figure 2) with the allyl bromide.



(12) The benzopyran with the structure shown below was isolated and identified by ^{1}H and ^{13}C NMR spectroscopy. Its formation can be rationalized by *β*-hydride elimination following migratory insertion from intermediate **X** (Figure 2) occurring with the regiochemistry, giving rise to a benzopyran with an exocyclic double bond, which isomerizes to the more stable structure shown below.



(13) ^{1}H NMR NOE experiments performed on benzopyrans **5a**,**b** detected the following correlations: (i) the methine proton bonded to carbon C2 showed an NOE correlation to a proton on the vinylic carbon directly bonded to C3 (for **5a**) or to a terminal proton in the vinyl side chain bonded to carbon C3 (for **5b**). However, inspection of the molecular models of different conformations of benzopyrans **5a**,**b** revealed that these correlations could be present in both cis and trans heterocycles.

(14) Examples of palladation of aromatic rings directed by a heteroatom-containing substituent in the ortho position are well-known; see: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.

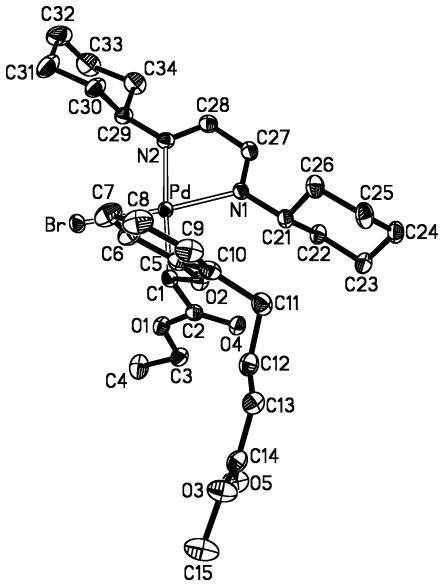


Figure 3. Thermal ellipsoid diagram of complex **10**. The ellipsoids are drawn at the 50% probability level.

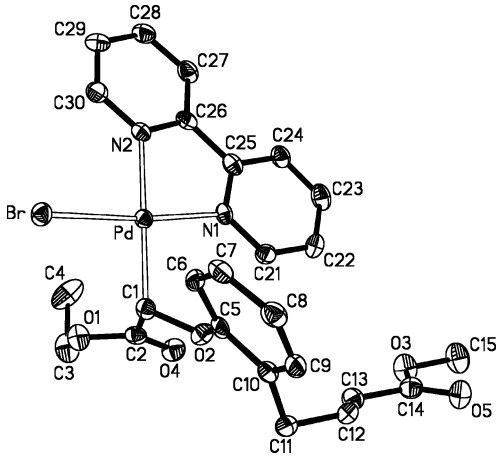
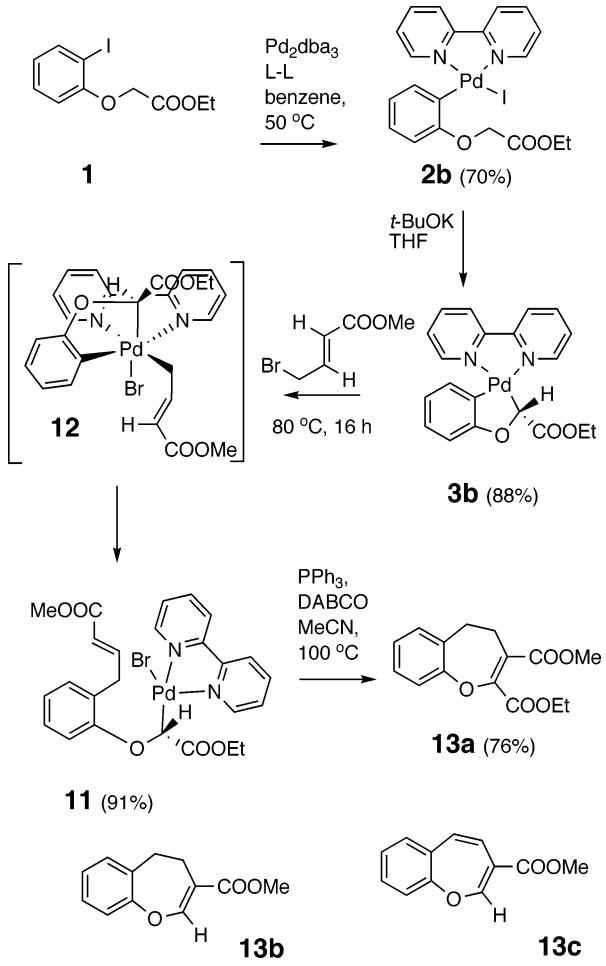


Figure 4. Thermal ellipsoid diagram of complex **11**. The ellipsoids are drawn at the 50% probability level.

benzoxepine **4a** was detected by GC analysis. However, due to the labile nature of the reactive intermediates, no evidence for the formation of a Pd(IV) intermediate en route from **3a** to **10** could be obtained.

Reasoning that less sterically demanding and more rigid bipyridine ligand will stabilize the reactive intermediates, palladacycle **3b** was prepared from aryl iodide **1** via complex **2b** by an established method[8] (Scheme 3). Indeed, the treatment of palladacycle **3b** with methyl 4-bromo-2-butenoate (2.0 equiv, 16 h, 80 °C) afforded the stable and robust arylpalladium(II) bromo complex **11** (Scheme 3). Molecular structures of palladacycle **3b** and complex **11** were confirmed by X-ray crystallographic analyses (Figure 4). The conversion of complex **11** into a benzoxepine via an intramolecular 7-endo-trig Heck reaction[9] required rather strenuous conditions, giving rise to byproducts **13b** and **13c**. The addition of bases (DABCO) and auxiliary phosphine ligands (PPh_3) allowed for a successful conversion of complex **11** into the single benzoxepine **13a** (MeCN, 100 °C, DABCO, PPh_3)[15] in good yield. Despite the loss of the stereogenic center via double-bond isomerization, the high-yielding formation of heterocycle **13a** demonstrates that complex **11** engages in reaction steps analogous to those proposed for the more labile complex **10**.

Scheme 3



Aiming to detect or isolate the presumed Pd(IV) intermediate en route from palladacycle **3b** to complex **11**, we treated the palladacycle **3b** with neat methyl 4-bromo 2-butenoate at 0 °C (8.5 h), during which time the cloudy solution turned clear. Precipitation with pentane and solvent decantation performed rapidly at −10 °C afforded a yellow solid, the ^{1}H NMR spectrum of which was recorded at −10 °C (see trace c in Figure 5). In addition to indicative signals for the remaining palladacycle **3b** (labeled # in traces a and c of Figure 5) and the emerging "open form" complex **11** (labeled % in traces b and c of Figure 5), as well as residual signals for allylic bromide and/or alcohol[16] (labeled × in trace c), signals (labeled ↓) indicating the presence of a significant concentration[16] of a distinct palladium complex containing the allyl substituent (CH_2-$CH{=}CHCO_2Me$) were detected (compare traces a−c of Figure 5). When it stood at room temperature, the $CDCl_3$ solution of the yellow solid (shown in trace c of Figure 5) was cleanly

(15) The minor benzoxepine products **13b**,**c** were isolated in variable quantities, depending on the reaction conditions, and were identified by ^{1}H and ^{13}C NMR spectroscopy. Heterocycle **13b** may arise via Pd-mediated decarboxylation following the formation of a benzoxepine substituted with the Pd atom at C-3 via readdition of the H−Pd−X complex to the double bond formed via β-hydride elimination. The heterocycle **13c** could arise via air oxidation of **13b**.

(16) A partial hydrolysis of the excess allyl bromide during the washing and decantation steps could account for the presence of the signal (singlet at 4.93 ppm) in ^{1}H NMR spectra in traces c and d. The ratios of Pd(IV) complex **12**, pallada(II)cycle **3b**, and the "open form" complex **11** in the yellow solid varied depending on the reaction conditions chosen. For example, reaction for 5 min at 30 °C afforded a mixture with a **12**:**3b**:**11** molar ratio of 3:4:1 (by ^{1}H NMR). Under optimum conditions (8.5 h, 0 °C) the molar ratio **12**:**3b**:**11** was 10:2:1.

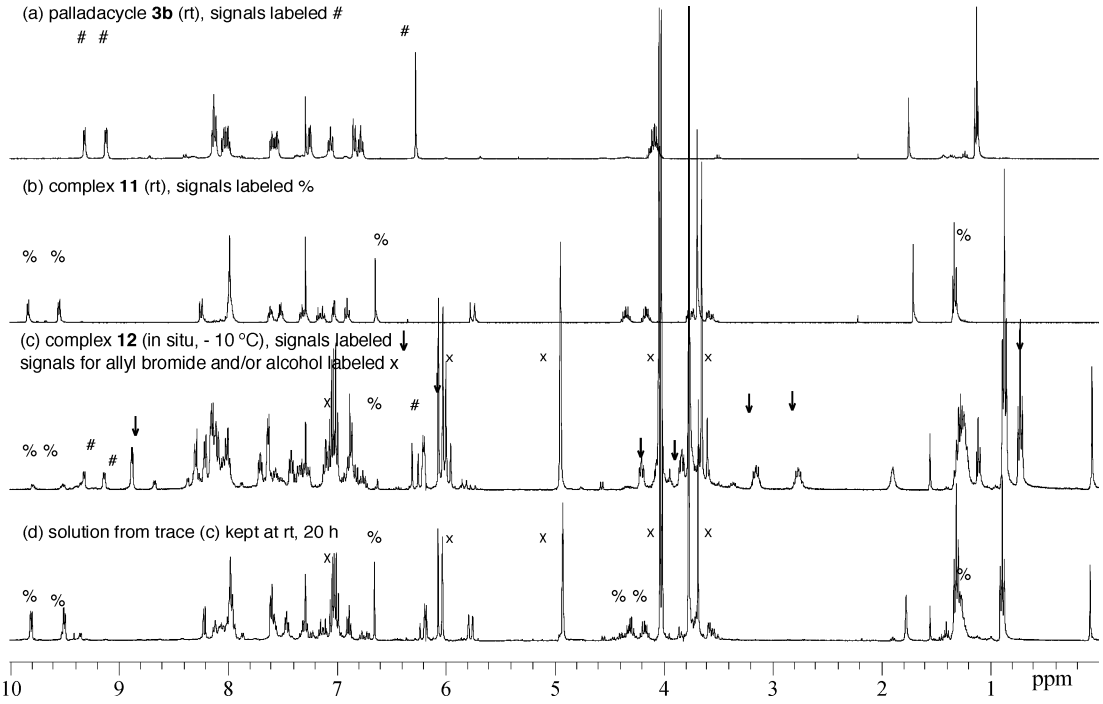


Figure 5. ^{1}H NMR (400 MHz, $CDCl_3$) of substrates and intermediates en route from **3b** to **11**.

converted to a solution of complex **11** (compare the spectral traces b−d of Figure 5). The key ^{1}H NMR signals (labeled ↓ in trace c of Figure 5) were assigned as follows: proton at 6.02 ppm (s, 1 H) as OCH_a(COOEt)Pd; protons at 4.22 ppm (t, J = 7.2 Hz, 1 H) and 3.85 (ddd, J = 15.6, 10.0, 6.8 Hz, 1 H) as the two protons H_b and H_c in the allyl fragment −CH_bH_cCH═CHCOOMe; protons at 3.15 ppm (dq, J = 7.2, 3.2 Hz, 1 H) and 2.82 (dq, J = 7.2, 2.8 Hz, 1 H) as methylene protons H_f and H_g in the ethyl ester group −C(═O)OCH_fH_gCH_3, in the structure of the Pd(IV) complex **12** (Scheme 3 and Figures 5 and 7)[17] operating as an intermediate en route from palladacycle **3b** to complex **11**.

Encouraged by these results, we attempted the purification and further characterization of complex **12**. The yellow solid obtained by the protocol described above was subjected to low-temperature (−30 °C), diffusion-controlled crystallization (ethyl acetate/pentane or ethyl acetate/hexane) to afford small and twinned single crystals of a palladium complex,[18] distinct from the palladacycle **3b** and the "open form" complex **11**. Single-domain crystals were obtained for two different solvent polymorphs. The asymmetric unit for one of these polymorphs contains two crystallographically independent Pd(IV)-containing molecules, and the asymmetric unit of the second polymorph contains just one.[18] Gratifyingly, the X-ray crystallographic analysis unequivocally indicated that a cis isomer of the proposed allylpalladium(IV) intermediate **12** was indeed formed (Scheme 3 and Figure 6).[18] All three molecules of **12** possess a distorted-octahedral geometry with the phenyl-*o*-(ethoxycarbonylmethyleneoxo) groups forming a five-membered chelate ring that contains the palladium and two (sp^3-hybridized carbon atom C7 and sp^2-hybridized carbon atom C(2)) of the three carbon atoms bonded to it. The five non-hydrogen atoms comprising this chelate ring in each of these three molecules are slightly noncoplanar (rms deviations from the respective least-squares mean planes range from 0.07 to 0.14 Å). The sp^3-hybridized carbon atom C7 deviates the most from each mean

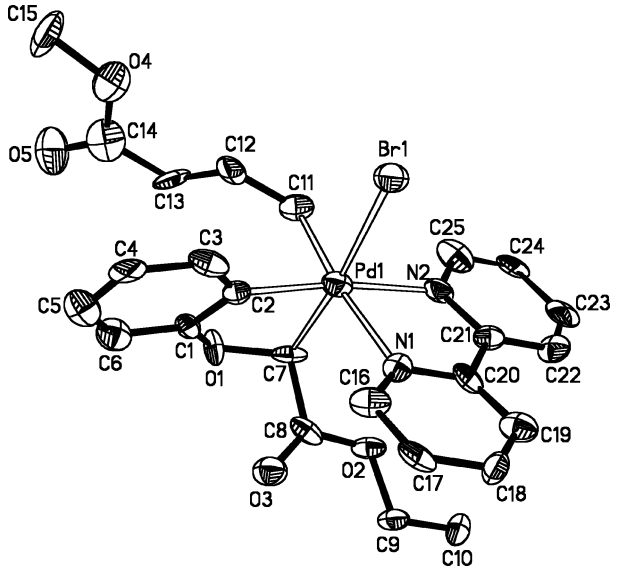


Figure 6. Thermal ellipsoid diagram of the allylpalladium(IV) complex **12**. The ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): Pd(1)−C(2), 2.002-(13); Pd(1)−C(7), 2.029(12); Pd(1)−C(11), 2.079(12); Pd(1)−N(1), 2.179(10); Pd(1)−N(2), 2.139(11); Pd(1)−Br(1), 2.606(2); C(2)−Pd(1)−C(7), 78.6(6); C(2)−Pd(1)−Br(1), 97.1(4); C(2)−Pd(1)−C(11), 88.4(5); C(11)−Pd(1)−N(2), 96.7(5); N(2)−Pd(1)−N(1), 75.7(4); N(1)−Pd(1)−C(2), 99.3(5).

(17) The assignments of protons in the structure of complex **12** as outlined in Figures 5 and 7 are supported by 2D NMR experiments (COSY, HSQC) recorded on the isolated complex **12**. Thus, COSY spectroscopy revealed correlations between (i) signals at 0.76 (t, J = 6.8 Hz, 3 H, CH_3), 3.15 (dq, J = 7.2, 3.2 Hz, 1 H_f), and 2.82 ppm (dq, J = 7.2, 2.8 Hz, 1 H_g) and (ii) signals at 7.36 (dt, J = 15.2, 9.0 Hz, 1 H_d), 4.22 (t, J = 7.2 Hz, 1 H_b), and 3.85 ppm (ddd, J = 15.6, 10.0, 6.8 Hz, 1 H_c). HSQC spectroscopy revealed correlations between (i) signals at 3.15 (H_f) and 2.82 ppm (H_g) and a single carbon at 59.8 ppm and (ii) signals at 4.22 (H_b) and 3.85 ppm (H_c) and a single carbon at 38.1 ppm.

(18) Although repeated attempts to grow larger high-quality single crystals of **12** were unsuccessful, the acquired small ((0.12−0.19) × (0.08−0.010) × 0.03 mm^3) single-domain crystals obtained for the two different solvent polymorphs gave acceptable yields of data to 2θ(Mo Kα) = 45.0°. Even though the lower yield of data for both polymorphs necessarily reduces the precision of the resulting structural parameters, all three molecules have the same Pd stereochemistry and consistent Pd−ligand bond lengths.

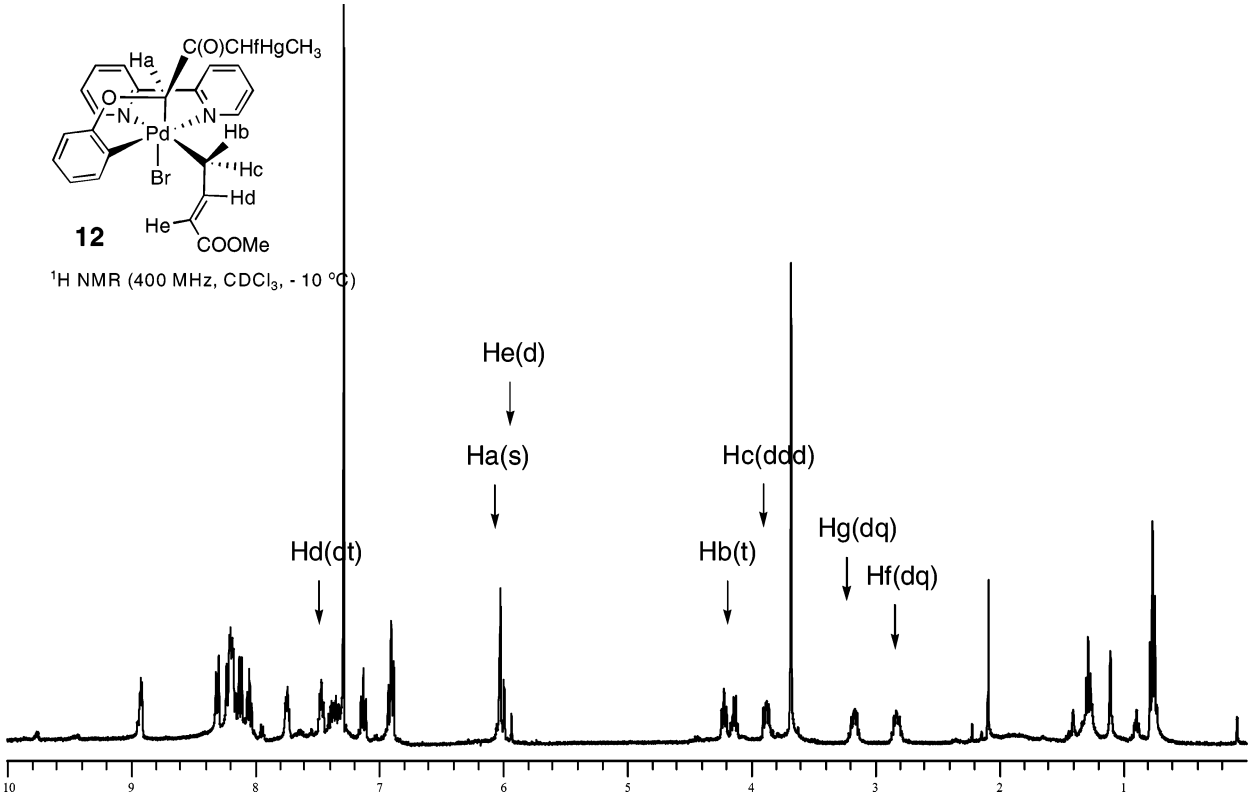


Figure 7. ^{1}H NMR spectra recorded for the crystallized complex **12** (400 MHz, $CDCl_3$, −10 °C).

plane (ranging from 0.11 to 0.23 Å) in one direction, and the oxygen atom has the next largest deviation (ranging from 0.10 to 0.19 Å), but in the opposite direction from the least-squares mean plane. The allyl substituent in complex **12** resides cis to the bromide ligand and cis to the aromatic carbon (C2) of the chelate ring. Both the allyl group and the coordinated aromatic carbon (C2) are positioned trans to the nitrogen atoms of the bipyridine ligand. The Pd−N, Pd−Br, and Pd−CH_2(allyl) bond lengths are in agreement with those found in related complexes,[19] and the Pd−C(sp^2) (aryl) and Pd−C(sp^3) (methylene) bond lengths Pd−C2 and Pd−C7, respectively, as well as the Pd−N bond lengths, are comparable to those found for the analogous square-planar pallada(II)cycle **3b**.[19]

The preferential formation of the cis isomer of complex **12** is in agreement with the cis structure assigned for a related benzylpallada(IV)cyclic complex by Catelani on the basis of NMR spectroscopic studies[6] but is in contrast with the generation of cis/trans isomer mixtures detected by NMR in reactions of palladacyclopentane with [Ph_2I][OTf].[4d] ^{1}H NMR spectra recorded on $CDCl_3$ solutions of the single crystals of complex **12** at low temperatures (−10 °C) (Figure 7) showed signals identical with those highlighted in trace c of Figure 5 and revealed that no isomerization of complex **12** occurred for 5 h at subzero temperatures in the $CDCl_3$ solution. Rather, a slow conversion of complex **12** into complex **11** was detected to occur even at subzero temperatures. In the spectrum of pure crystallized complex **12** (Figure 7) further assignments of the indicative ^{1}H NMR signals could be made for protons H_d (7.36 ppm (dt, J = 15.2, 9.0 Hz, 1 H_d)) and H_e (6.00 ppm (d, J = 15.2 Hz)) in the allyl fragment (−CH_2C*H_d*═C*H_e*COOMe).[17] The palladium(IV) complex **12** was sufficiently stable in solution to permit the collection of ^{13}C NMR data ($CDCl_3$, −10 °C), and the solid complex **12** could be handled at room temperature for short time periods, although prolonged standing of solid **12** at room temperature resulted in its conversion to complex **11**.[20]

Conclusions

In conclusion, a formal annulation between two electrophiles was studied in a stoichiometric mode exploiting the reactivity of stable pallada(II)cycles bearing bis(imine) or bipyridine ligands with allyl bromides. Highly substituted benzoxepines and benzopyrans featuring three new C−C bonds and up to two stereogenic centers were obtained in good yields via a multistep cascade sequence involving functionalization of a C(sp^2)−H bond. Studies of this transformation with a palladacycle bearing a rigid bipyridine ligand led to isolation of the rare reactive allylpalladium(IV) complex **12**, which was characterized by low-temperature ^{1}H and ^{13}C NMR analyses as well as by X-ray crystallography and could be converted into the stable palladium(II) complex **11** and subsequently into a benzoxepine heterocycle. Isolation of reactive palladium(IV) complexes that can give rise to complex organic products remains rare, and the present study demonstrates the potential of the protocols involving Pd(0)−Pd(II)−Pd(IV) interconversions for the generation of complex heterocyclic products.

Experimental Section

General Method for the Synthesis of Arylpalladium(II) Iodo Complexes 2a,b. To a solution of tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$; 1.0 mmol) in benzene (30−45 mL) at room temperature under argon was added the appropriate ligand

(19) Data published in ref 4m for complex Me_3Pd^{IV}(bipyridine)I indicate Pd−C(a−c) = 2.046, 2.034, and 2.040 Å, Pd−N(a,b) = 2.188 and 2.173 Å, and Pd−I = 2.834 Å. X-ray crystallographic analyses on pallada(II)-cycles **3a**,**b** (see the Supporting information) indicated the following. Complex **3a**: Pd−C(sp^2) = 2.013 Å, Pd−C(sp^3) = 2.026 Å, Pd−N(1,2) = 2.162, 2.123 Å. Complex **3b**: Pd−C(sp^2) = 1.991 Å, Pd−C(sp^3) = 2.043 Å, Pd−N(1,2) = 2.114, 2.126 Å.

(20) The half-life is approximately 3 h.

(3−4 mmol) followed by a solution of 2-{[(ethoxycarbonyl)-methylene]oxy}-1-iodobenzene (**1**; 2.2 mmol) in benzene (10 mL). The reaction mixture was warmed to the indicated temperature, stirred for the indicated time period, and filtered through a plug of Celite, and solvents were removed under reduced pressure to afford a crude product. The crude product was purified by flash chromatography over silica, with EtOAc/hexane (1:5) as eluent to remove dibenzylideneacetone (dba) and subsequently with EtOAc/hexane (1:1) to afford arylpalladium(II) complexes **2a**,**b** as bright yellow solids.

{2-[(Ethoxycarbonyl)methoxy]phenyl}iodo(*N,N′*-bis(cyclohexyl)ethylenediimine)palladium (2a). The treatment of $Pd_2(dba)_3$ (1.832 g, 2.0 mmol), *N,N′*-bis(cyclohexyl)ethylenediimine (1.320 g, 6.0 mmol), and 2-{[(ethoxycarbonyl)methylene]oxy}-1-iodobenzene (**1**; 1.346 g, 4.4 mmol) for 2 h at room temperature according to the method described above afforded the arylpalladium(II) iodo complex **2a** as a bright yellow solid (1.845 g, 73%): mp 126−128 °C (EtOAc/hexane 1:1); R_f = 0.43 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.96 (s, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 6.86 (t, J = 7.2 Hz, 1 H), 6.71 (t, J = 7.2 Hz, 1 H), 6.52 (d, J = 8.0 Hz, 1 H), 4.93 (d, J = 16.8 Hz, 1 H), 4.62 (d, J = 16.8 Hz, 1 H), 4.41 (t, J = 7.2 Hz, 1 H), 4.22−4.17 (m, 2 H), 3.11 (t, J = 7.2 Hz, 1 H), 2.24 (d, J = 11.2 Hz, 2 H), 2.02−1.83 (m, 4 H), 1.72 (t, J = 6.8 Hz, 2 H), 1.65−1.38 (m, 4 H), 1.29 (t, J = 6.8 Hz, 3 H), 1.29−1.13 (m, 4 H), 1.05−0.75 (m, 3 H), 0.75−0.55 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 160.2, 158.8, 157.0, 138.8, 130.3, 124.3, 121.3, 114.2, 67.2, 66.1, 65.4, 60.7, 34.5, 33.4, 33.3, 32.2, 25.6, 25.5, 25.4, 25.3, 25.1, 25.0, 14.3; IR (KBr, cm^{-1}) 2929 (s), 1757 (s), 1448 (s), 1186 (s); HRMS (ES$^+$) calcd M − I $C_{24}H_{35}N_2O_3Pd$ *m/z* 505.1682, found *m/z* 505.1675.

{2-[(Ethoxycarbonyl)methoxy]phenyl}iodo(*N,N′*-2,2′-dipyridyl)-palladium (2b). The treatment of $Pd_2(dba)_3$ (2.003 g, 2.18 mmol). 2,2′-dipyridyl (1.367 g, 8.75 mmol), and 2-{[(ethoxycarbonyl)-methylene]oxy}-1-iodobenzene (**1a**; 1.475 g, 4.817 mmol) for 1.6 h at 55 °C (oil bath) according to the method described above afforded the arylpalladium(II) iodo complex **2b** as a bright yellow solid (1.738 g, 70%): mp 195−198 °C (EtOAc/hexane 1:1); R_f = 0.59 (EtOAc/CH_2Cl_2 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (dd, J = 5.2, 0.8 Hz, 1 H), 8.14 (t, J = 8.0 Hz, 2 H), 8.02 (td, J = 7.6, 1.6 Hz, 1 H), 7.96 (td, J = 7.6, 1.6 Hz, 1 H), 7.77 (dd, J = 5.2, 0.8 Hz, 1 H), 7.48 (m, 2 H), 7.30 (t, J = 6.8 Hz, 1 H), 6.98 (t, J = 8.8 Hz, 1 H), 6.82 (td, J = 7.2, 1.2 Hz, 1 H), 6.64 (dd, J = 8.0, 1.2 Hz, 1 H), 4.95 (d, J = 16.4 Hz, 1 H), 4.72 (d, J = 16.8 Hz, 1 H), 4.16 (dq, J = 7.2, 3.6 Hz, 2 H), 1.23 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 160.2, 155.6, 154.0, 153.0, 151.0, 138.8, 138.7, 138.5, 132.1, 126.6, 126.4, 124.6, 122.1, 121.8, 121.5, 114.0, 67.0, 60.7, 14.2; IR (KBr, cm^{-1}) 1748 (s), 1442 (s), 1187 (s), 759 (s); HRMS (ES$^+$) calcd for $C_{20}H_{19}O_3PdN_2$ (M − I) *m/z* 441.0430, found *m/z* 441.0436.

General Procedure for the Synthesis of Pallada(II)cycles 3a,b. To a solution of the arylpalladium(II) iodo complex (1.0 mmol) in THF (22−40 mL) was injected simultaneously a 1 M solution of *t*-BuOK in THF (1.1−1.2 mmol). The resulting suspension was stirred for 5−15 min at room temperature under argon. Following a workup protocol specific for each pallada(II)cycle, palladacycles **3a**,**b** were obtained as yellow solids.

{[(Ethoxycarbonyl)methineoxy]-1,2-phenylene}[*N,N′*-bis(cyclohexyl)ethylenediimine]palladium (3a). Treatment of the palladium complex **2a** (0.632 g, 1.0 mmol) and a 1 M solution of *t*-BuOK in THF (1.1 mL, 1.1 mmol) as described above, followed by filtration through Celite and a small plug of basic alumina with methylene chloride as eluent, removal of solvents under reduced pressure, and trituration of the crude product with a hexane and ethyl acetate mixture, afforded palladacycle **3a** (0.370 g, 73%) as a yellow powder. Slow crystallization from a solution in $CDCl_3$ (0−10 °C) afforded a single crystal of **3a** suitable for X-ray crystallographic analysis (see data in the Supporting Information): mp 152−155 °C ($CDCl_3$, decomp); R_f = 0.29 (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 8.05 (s, 1 H), 7.13 (d, J = 7.5, 1 H), 6.98 (t, J = 7.6 Hz, 1 H), 6.77 (d, J = 7.9 Hz, 1 H), 6.67 (t, J = 7.4 Hz, 1 H), 6.03 (s, 1 H), 4.56 (t br, J = 9.5 Hz, 1 H), 4.17 (t br, J = 9.5 Hz, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 2.67 (d, J = 9.2 Hz, 1 H), 2.39 (d, J = 7.2 Hz, 1 H), 2.24 (d, J = 10.0 Hz, 1 H), 2.00−1.70 (m br, 8 H), 1.55−1.45 (m, 5 H), 1.32−1.16 (m, 4 H), 1.14 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 174.6, 157.9, 157.4, 137.5, 133.8, 126.4, 117.8, 108.6, 87.4, 65.11, 64.7, 59.5, 36.1, 33.6, 33.5, 31.5, 25.8, 25.6, 25.6, 25.5, 25.4, 25.3, 14.4; IR (KBr, cm^{-1}) 2929 (s), 1697 (s), 1166 (s); HRMS (ES$^+$) calcd for $C_{24}H_{35}N_2O_3Pd$ (M + H$^+$) *m/z* 505.1682, found *m/z* 505.1685.

{[(Ethoxycarbonyl)methineoxy]-1,2-phenylene}[*N,N′*-2,2′-dipyridyl]palladium (3b). Treatment of palladium complex **2b** (1.721 g, 3.0 mmol) and a 1 M solution of *t*-BuOK in THF (3.6 mL, 3.6 mmol) as described above, followed by removal of the solvents under reduced pressure, addition of CH_2Cl_2 (20 mL), filtration through Celite and a small plug of basic alumina with methylene chloride as eluent, final removal of solvents under reduced pressure, and trituration with ethyl ether, afforded palladacycle **3b** (1.177 g, 88%). A single crystal for X-ray crystallographic analysis was prepared by diffusion-controlled crystallization from an EtOAc/hexane mixture: mp 192−195 °C (EtOAc/hexane); R_f = 0.38 (EtOAc/CH_2Cl_2 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (d, J = 4.8 Hz, 1 H), 9.20 (d, J = 5.2 Hz, 1 H), 8.09 (t, J = 6.8 Hz, 2 H), 8.04 (td, J = 7.6, 1.6 Hz, 1 H), 8.00 (td, J = 7.6, 1.2 Hz, 1 H), 7.61 (t, J = 6.8 Hz, 1 H), 7.56 (t, J = 6.8 Hz, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.04 (t, J = 8.0 Hz, 1 H), 6.82 (dd, J = 8.0, 0.8 Hz, 1 H), 6.77 (t, J = 7.6 Hz, 1 H), 6.31 (s, 1 H), 4.18−4.02 (m, 2 H), 1.13 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 174.5, 155.4, 154.4, 152.3, 150.8, 139.6, 138.6, 138.3, 133.7, 126.0, 125.9, 125.8, 122.1, 121.5, 118.2, 108.5, 87.9, 59.6, 14.2; IR (KBr, cm^{-1}) 1697 (s), 1441 (s), 1168 (s), 756 (s); HRMS (ES$^+$) calcd for $C_{20}H_{19}O_3N_2Pd$ (M + H$^+$) *m/z* 441.0430, found *m/z* 441.0442.

{1-(Ethoxycarbonyl)-1-{2-(3-(methoxycarbonyl)-2-propenyl)-phenoxy]methyl}bromo[*N,N′*-bis(cyclohexyl)ethylenediimine]-palladium (10). A suspension of pallada(II)cycle **3a** (0.020 g, 0.040 mmol) in methyl *trans*-4-bromo-2-butenoate (0.20 mL, 1.67 mmol) was stirred for 20 min at 45 °C until a clear solution was formed. The reaction mixture was stirred for an additional 10 min and cooled to room temperature, and pentane (3 mL) was added. The liquid was decanted, and the remaining yellow solid was washed with pentane (2 × 3 mL) to afford complex **10** free of unreacted palladacycle **3a** (by ^{1}H NMR) as a yellow solid (0.026 g, 95%), which decomposed upon standing for several hours in $CDCl_3$ solution at room temperature under argon. A diffusion-controlled crystallization from EtOAc/pentane (3 days, 0 −5 °C) afforded a single crystal that was used for X-ray crystallographic analysis (data provided in the Supporting Information): mp 138−140 °C dec (EtOAc/pentane), R_f = 0.35 (EtOAc/hexanes 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1 H), 7.93 (s, 1 H), 7.79 (s, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.02 (dt, J = 15.5, 6.5 Hz, 1 H), 6.96 (d, J = 7.5 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1 H), 6.28 (s, 1 H), 5.79 (dd, J = 15.5, 0.5 Hz, 1 H), 4.56 (t, J = 11.5 Hz, 1 H), 4.31 (t, J = 11.5 Hz, 1 H), 4.15 (q, J = 7.0 Hz, 2 H), 3.61 (s, 3 H), 3.62−3.60 (m, 1 H), 3.47 (dd, J = 16.5, 6.5 Hz, 1 H), 2.20 (d, J = 11.5 Hz, 1 H), 2.03 (s br, 2 H), 1.82−1.64 (m, 9 H), 1.50−1.00 (m, 8 H), 1.25 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 167.0, 161.7, 156.9, 156.0, 147.6, 129.5, 128.3, 126.5, 121.8, 121.0, 115.3, 65.0, 64.4, 60.3, 60.1, 51.3, 35.9, 33.6, 33.5, 32.9, 32.6, 25.5 (2 carbons), 25.4, 25.2, 25.16, 25.1, 14.5; IR (KBr, cm^{-1}) 1714 (s), 1652 (s); HRMS (ES$^+$) calcd for $C_{29}H_{41}N_2O_5Pd$ (M$^+$ − Br) *m/z* 603.2050, found *m/z* 603.2053.

{1-(Ethoxycarbonyl)-1-[2-(3-(methoxycarbonyl)-2-propenyl)-phenoxy]methyl}bromo(*N,N′*-2,2′-dipyridyl)palladium (11). To a solution of the pallada(II)cycle **3b** (1.149 g, 2.608 mmol) in 1,2-dichloroethane (36 mL) was added methyl *trans*-4-bromo-2-butenoate (0.62 mL, 5.188 mmol). The reaction mixture was heated to 80 °C and stirred for 16 h. The solvent was partially removed under reduced pressure to afford a yellow powder, which was collected by filtration and washed with ethyl ether to afford complex **11** as a light yellow solid (1.478 g, 91%). Diffusion-controlled crystallization (EtOAc/pentane) at room temperature (3 days) afforded a single crystal of complex **11**, which was used for X-ray crystallographic analysis (data provided in the Supporting Information): mp 172−174 °C (EtOAc/pentane); $R_f = 0.44$ (EtOAc/CH_2Cl_2 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, $J = 5.2$ Hz, 1 H), 9.59 (d, $J = 5.6$ Hz, 1 H), 8.22 (d, $J = 8.0$ Hz, 1 H), 8.00−7.97 (m, 4 H), 7.61 (dt, $J = 6.8$, 2.4 Hz, 1 H), 7.51 (q, $J = 4.8$ Hz, 1 H), 7.30 (t, $J = 8.4$ Hz, 1 H), 7.13 (dt, $J = 15.6$, 6.4 Hz, 1 H), 7.03 (dd, $J = 7.2$, 0.8 Hz, 1 H), 6.91 (td, $J = 7.2$, 0.8 Hz, 1 H), 6.68 (s, 1 H), 5.77 (d, $J = 15.6$ Hz, 1 H), 4.33 (dq, $J = 7.2$, 10.2 Hz, 1 H), 4.18 (dq, $J = 7.2$, 10.2 Hz, 1 H), 3.74 (dd, $J = 16.0$, 6.4 Hz, 1 H), 3.73 (s, 3 H), 3.57 (dd, $J = 16.0$, 6.4 Hz, 1 H), 1.33 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 167.0, 155.5, 155.2, 153.6, 153.4, 151.6, 148.0, 138.9, 138.6, 129.8, 128.5, 126.9, 126.3, 125.9, 121.6, 121.5, 121.2, 120.9, 114.9, 60.2, 58.4, 51.3, 32.8, 14.4; IR (KBr, cm^{-1}) 1724 (s), 1701 (s), 1488 (s), 1444 (s), 1193 (s), 1035 (s), 765 (s); HRMS (ES^+) calcd for $C_{25}H_{25}N_2O_5Pd$ ($M^+ - Br$) *m/z* 539.0798, found *m/z* 539.0817.

***cis*-[(Ethoxycarbonyl)methineoxy-1,2-phenylene][*N,N′*-2,2′-dipyridyl][3-(methoxycarbonyl)-2-propenyl]bromopalladium (12).** The pallada(II)cycle **3b** (0.020 g, 0.0455 mmol) was treated with neat methyl *trans*-4-bromobutenoate (0.400 mL, 3.34 mmol) at 0 °C for 8.5 h, during which time the yellow solid of palladacycle **3b** gradually dissolved, forming a clear yellow solution. Cold pentane (5.0 mL, −10 °C) was added, and the resulting light yellow precipitate was separated by decantation, washed with cold pentane (3 × 5 mL, −10 °C), and dried in vacuo at −10 °C. ^{1}H NMR analysis on the solid indicated that it consisted of a mixture of the pallada(II)cycle **3b**, the arylpalladium(II)bromo complex **11**, and a new complex, e.g., the pallada(IV)cycle **12** in the molar ratio **12**:**3b**:**11** = 10:2:1, as well as some remaining allyl bromide and the corresponding allylic alcohol (see trace c in Figure 5). A portion (0.005 g) of the yellow solid prepared by this method was dissolved in cold ethyl acetate (−20 °C, 1.6 mL) and the solution was layered with cold pentane or hexane (5.0 mL) to establish diffusion-controlled crystallization conditions. On standing at −20 °C for 3 days, small light yellow crystals of pallada(IV)cycle **12** were formed, collected, and fully characterized (^{1}H NMR, ^{13}C NMR, COSY, HSQC recorded at −10 °C), including a single-crystal X-ray crystallographic analysis (data provided in the Supporting Information). In solution ($CDCl_3$) complex **12** underwent a slow conversion into the arylpalladium(II) bromide complex **11** both at −20 °C and at room temperature (over 16 h periods). The solid complex **12** has limited thermal stability at room temperature and undergoes a slow conversion into complex **11** (half-life approximately 3 h).

Analytical data for complex **12** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$, −10 °C) δ 8.88 (d, $J = 4.8$ Hz, 1 H), 8.29 (d, $J = 8.0$ Hz, 1 H), 8.25−8.14 (m, 3 H), 8.11 (d, $J = 7.6$ Hz, 1 H), 8.04 (t, $J = 7.8$ Hz, 1 H), 7.74 (t, $J = 6.4$ Hz, 1 H), 7.46 (t, $J = 6.4$ Hz, 1 H), 7.36 (dt, $J = 15.2$, 9.0 Hz, 1 H), 7.12 (t, $J = 7.6$ Hz, 1 H), 6.90 (t, $J = 9.0$ Hz, 2 H), 6.02 (s, 1 H), 6.00 (d, $J = 15.2$ Hz, 1 H), 4.22 (t, $J = 7.2$ Hz, 1 H), 3.85 (ddd, $J = 15.6$, 10.0, 6.8 Hz, 1 H), 3.66 (s, 3 H), 3.15 (dq, $J = 7.2$, 3.2 Hz, 1 H), 2.82 (dq, $J = 7.2$, 2.8 Hz, 1 H), 0.76 (t, $J = 6.8$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, −10 °C) δ 170.9, 167.2, 153.8, 153.6, 153.3, 150.2, 148.8, 147.9, 139.5, 139.2, 135.0, 127.4, 126.3, 126.2, 123.2, 122.3, 122.1, 121.3, 118.8, 111.4, 95.9, 59.8, 51.4, 38.1, 13.5. The limited stability of the complex at room temperature precluded the collection of melting point, HRMS, and IR data.

2-(Ethoxycarbonyl)-3-(methoxycarbonyl)-9-[3-(methoxycarbonyl)-2-*trans*-propenyl]-2,5-dihydro-1-benzoxepine (4a). Entry 1 (Table 1). To a solution of the pallada(II)cycle **3a** (0.025 g, 0.050 mmol) in 1,2-dichloroethane (0.5 mL) in a pressure tube equipped with a magnetic stirring bar was added neat methyl *trans*-4-bromobutenoate (0.036 mL, 0.300 mmol) and solid freshly sublimed *t*-BuOK (0.020 g, 0.178 mmol). The tube was purged with argon and capped, and the contents were stirred for 20 h at 95 °C (oil bath). The reaction mixture was cooled, diluted with methylene chloride, and filtered though a short plug of Celite, and solvents were removed under reduced pressure to afford the crude product, which was separated by flash chromatography over silica with EtOAc/hexane (1:9) as eluent to afford the benzoxepine **4a** (0.010 g, 53%) as a light yellow oil.

Entry 2 (Table 1). To a suspension of the pallada(II)cycle **3a** (0.050 g, 0.100 mmol) in neat methyl *trans*-4-bromobutenoate (0.20 mL, 1.674 mmol) in a pressure tube equipped with a magnetic stirring bar was added NaBr (0.021 g, 0.200 mmol). The reaction (1.5 h at 85 °C) and the workup were performed as described above to afford benzoxepine **4a** (0.019 g, 50%) as a light yellow oil and phenol **6** (0.003 g, 15%) as a colorless oil.

Entry 3 (Table 1). To a suspension of the pallada(II)cycle 3a (0.050 g, 0.100 mmol) in neat methyl *trans*-4-bromobutenoate (0.20 mL, 1.674 mmol) in a pressure tube equipped with a magnetic stirring bar was added Cs_2CO_3 (0.090 g, 0.277 mmol). The reaction (2 h at 95 °C) and the workup were performed as described above to afford the benzoxepine 4a (0.023 g, 62%) as a light yellow oil.

Analytical data for benzoxepine **4a** are as follows: $R_f = 0.33$ (EtOAc/hexane 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dt, $J = 15.5$, 7.0 Hz, 1 H), 6.96 (d, $J = 7.5$ Hz, 1 H), 6.87 (d, $J = 6.5$ Hz, 1 H), 6.82 (t, $J = 7.5$ Hz, 1 H), 6.41 (s, 1 H), 5.83 (d, $J = 15.5$ Hz, 1 H), 5.43 (s, 1 H), 4.13 (q, $J = 7.0$ Hz, 2 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.59 (dd, $J = 15.7$, 6.8 Hz, 1 H), 3.52 (dd, $J = 16.0$, 6.5 Hz, 1 H), 3.45 (d, $J = 16$ Hz, 1 H), 3.29 (d, $J = 16.5$ Hz, 1 H), 1.19 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.2, 167.1, 149.8, 147.3, 130.5, 125.5, 125.3, 124.9, 124.6, 121.6 (two carbons), 120.9, 74.9, 61.5, 52.2, 51.4, 38.9, 32.3, 14.0; IR (neat, cm^{-1}) 1732 (s), 1275 (s), 1192 (s); HRMS (ES^+) calcd for $C_{20}H_{22}O_7K$ ($M + K^+$) *m/z* 413.1003, found *m/z* 413.0983.

Analytical data for the phenol **6** are as follows: $R_f = 0.34$ (hexane/EtOAc 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.13 (m, 2 H), 7.11 (d, $J = 7.5$ Hz, 1 H), 6.91 (t, $J = 7.5$ Hz, 1 H), 6.78 (d, $J = 8.0$ Hz, 1 H), 5.83 (td, $J = 16.0$ Hz, 1.8 Hz, 1 H), 4.96 (s, 1 H), 3.73 (s, 3 H) 3.55 (dd, $J = 6.5$ Hz, 1.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 153.5, 147.1, 130.7, 128.2, 124.1, 121.7, 121.1, 115.5, 51.5, 32.9; IR (neat, cm^{-1}) 3250 (w br), 1720 (s), 1456 (m), 1274 (m); HRMS (ES^+) calcd for $C_{11}H_{13}O_3$ ($M + H^+$) *m/z* 193.0865, found *m/z* 193.0861.

2-(Ethoxycarbonyl)-3-methyl-9-(*trans*-2-butenyl)-2,5-dihydro-1-benzoxepine (4b) and 2-(Ethoxycarbonyl)-3-ethenyl-8-(*trans*-2-butenyl)-3,4-dihydro-2*H*-1-benzopyran (5a). Entry 4 (Table 1). To a suspension of the pallada(II)cycle **3a** (0.051 g, 0.100 mmol) in neat crotyl bromide (0.60 mL, 5.830 mmol) in a pressure tube equipped with a magnetic stirring bar was added Cs_2CO_3 (0.081 g, 0.250 mmol). The tube was purged with argon and capped, and the contents were stirred for 2 h at 115 °C (oil bath). The reaction mixture was cooled, diluted with methylene chloride, and filtered though a short plug of Celite. Solvents were removed under reduced pressure to afford a crude product, which was separated by flash chromatography over silica with methylene chloride/hexane (1:1) as eluent to afford benzoxepine **4b** (0.083 g, 29%) and benzopyran **5a** (0.010 g, 35%) as colorless oils.

Entry 5 (Table 1). To a solution of the pallada(II)cycle **3a** (0.051 g, 0.100 mmol) in acetonitrile (0.8 mL) in a pressure tube equipped with a magnetic stirring bar was added neat crotyl bromide

(0.100 mL, 1.00 mmol) and solid Cs_2CO_3 (0.081 g, 0.250 mmol). The reaction (60 h at 115 °C) and the workup were performed as described above (for entry 4) to afford the benzoxepine **4b** (0.012 g, 40%) and the benzopyran **5a** (0.005 g, 18%), both as colorless oils.

Analytical data for benzoxepine **4b** are as follows: $R_f = 0.60$ (EtOAc/hexane 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, J = 6.5, 2.5 Hz, 1 H), 6.86−6.80 (m, 2 H), 6.26 (s, 1 H), 5.65 (pent q, J = 7.5, 1.5 Hz, 1 H), 5.35 (pent t, J = 7.0, 1.0 Hz, 1 H), 5.21 (s, 1 H), 4.20−4.10 (m, 2 H), 3.49−3.28 (m, 2 H), 2.42 (sext, J = 7.5 Hz, 1 H), 2.27 (sext, J = 8.0 Hz, 1 H), 1.69 (dq, J = 6.0, 1.5 Hz, 3 H), 1.22 (s, 3 H), 1.20 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 149.5, 133.7 (two carbons), 129.3, 129.2, 127.9, 125.9, 124.2, 121.2, 119.4, 76.1, 61.2, 32.4, 26.1, 17.9, 14.1, 11.4; IR (neat, cm^{-1}) 1751 (s), 1731 (s), 1456 (s); HRMS (ES$^+$) calcd for $C_{18}H_{23}O_3$ (M + H$^+$) m/z 287.1647, found m/z 287.1650.

Analytical data for benzopyran **5a** are as follows: $R_f = 0.59$ (EtOAc/hexane 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 6.0 Hz, 1 H), 6.93 (d, J = 7.6 Hz, 1 H), 6.83 (t, J = 7.6 Hz, 1 H), 5.83 (ddd, J = 16.8, 10.4, 8.0 Hz, 1 H), 5.69−5.58 (m, 1 H), 5.56−5.48 (m, 1 H), 5.24 (dt, J = 16.8, 1.2 Hz, 1 H), 5.16 (dd, J = 10.4, 0.8 Hz, 1 H), 4.57 (d, J = 6.8 Hz, 1 H), 4.24 (qd, J = 7.2, 2.8 Hz, 2 H), 3.45−3.25 (m, 2 H), 2.97 (dt, J = 13.2, 7.2 Hz, 1 H), 2.89 (dd, J = 16.0, 5.2 Hz, 1 H), 2.74 (dd, J = 16.4, 7.6 Hz, 1 H), 1.69 (dd, J = 6.0, 1.6 Hz, 3 H), 1.29 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 150.6, 136.8, 129.3, 128.7, 127.7, 127.3, 125.9, 120.5, 119.8, 117.2, 77.7, 61.2, 38.7, 32.8, 29.3, 17.9, 14.2; IR (neat, cm^{-1}) 1751 (s), 1464 (s), 1194 (s); HRMS (ES$^+$) calcd for $C_{18}H_{23}O_3$ (M + H$^+$) m/z 287.1647, found m/z 287.1652.

2-(Ethoxycarbonyl)-3-[1-(methoxycarbonyl)-1-ethenyl]-8-[*trans*-3-methyl-3-(methoxycarbonyl)-2-propenyl]-3,4-dihydro-2*H*-1-benzopyran (5b). Entry 6 (Table 1). To a suspension of the pallada(II)cycle **3a** (0.051 g, 0.100 mmol) in neat methyl (*E*)-4-bromo-2-methyl-1-butenoate (0.15 mL, 0.214 g, 1.11 mmol) in a pressure tube equipped with a magnetic stirring bar was added Cs_2CO_3 (0.081 g, 0.25 mmol). The tube was purged with argon and capped, and the contents were stirred for 3 h at 100 °C (oil bath). The reaction mixture was cooled, diluted with methylene chloride, and filtered though a short plug of Celite, and solvents were removed under reduced pressure to afford a crude product, which was separated by flash chromatography over silica with EtOAc/hexane as eluent ((0.5−1):(9.5−9)) to afford the benzopyran **5b** (0.023 g, 58%) as a colorless oil: $R_f = 0.20$ (EtOAc/hexane 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, J = 7.5 Hz, 1 H), 6.95−6.91 (m, 2 H), 6.83 (t, J = 7.5 Hz, 1 H), 6.32 (s, 1 H), 5.69 (s, 1 H), 4.93 (d, J = 5.0 Hz, 1 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.53−3.49 (m, 3 H), 2.95 (t, J = 6.0 Hz, 2 H), 1.95 (d, J = 1.0 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 168.7, 166.6, 150.5, 140.5, 139.3, 127.9, 127.8, 127.7, 127.4, 126.5, 120.9, 120.0, 76.0, 61.4, 52.1, 51.7, 35.8, 29.2, 28.1, 14.1, 12.5; IR (neat, cm^{-1}) 1716 (br s), 1267 (s), 1195 (s), 740 (s); HRMS (ES$^+$) calcd for $C_{22}H_{27}O_7$ (M + H$^+$) m/z 403.1757, found m/z 403.1762.

2-(Ethoxycarbonyl)-3-(1-methyl-1-ethenyl)-3,4-dihydro-2*H*-1-benzopyran (7). Entry 7 (Table 1). To a solution of the pallada(II)cycle **3a** (0.051 g, 0.10 mmol) in 1,2-dichloroethane (1.0 mL) in a pressure tube equipped with a magnetic stirring bar was added neat 3-methyl-1-bromo-2-butene (0.20 mL, 1.70 mmol) and solid Cs_2CO_3 (0.050 g, 0.150 mmol). The tube was purged with argon and capped, and the contents were stirred for 60 h at 105 °C (oil bath). The reaction mixture was cooled, diluted with methylene chloride, and filtered though a short plug of Celite, and solvents were removed under reduced pressure to afford a crude product, which was separated by flash chromatography over silica with methylene chloride/hexane (1:9) as eluent to afford the benzopyran **7** (0.014 g, 56%) as a colorless oil: $R_f = 0.57$ (EtOAc/hexane 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (td, J = 7.8 Hz, 1.5 Hz, 1 H), 7.03 (d, J = 7.0 Hz, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 6.87 (t, J = 7.5 Hz, 1 H), 4.89 (t, J = 1.5 Hz, 1 H), 4.85 (s, 1 H), 4.64 (d, J = 7.5 Hz, 1 H), 4.23 (q, J = 7.5 Hz, 2 H), 2.89−2.81 (m, 3 H), 1.82 (s, 3 H), 1.27 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 152.8, 143.3, 129.2 (CH), 127.5 (CH), 120.9 (CH), 120.7, 116.5 (CH), 113.7 (CH_2), 76.9 (CH), 61.2 (CH_2), 41.9 (CH), 28.5 (CH_2), 20.2 (CH_3), 14.1 (CH_3); IR (neat, cm^{-1}) 1753 (s br), 1488 (m), 1197 (m); HRMS (ES$^+$) calcd for $C_{15}H_{19}O_3$ (M + H$^+$) m/z 247.1334, found m/z 247.1330.

2-(Ethoxycarbonyl)-3-(1-methyl-1-ethenyl)-8-(3-methyl-2-buten-1-yl)-3,4-dihydro-2*H*-1-benzopyran (5c) and 2-(Ethoxycarbonyl)-3-isopropyl-8-(3-methyl-2-buten-1-yl)-2*H*-1-benzopyran (5d). Entry 8 (Table 1). To a solution of the pallada(II)cycle **3a** (0.051 g, 0.100 mmol) in 1,2-dichloroethane (1.0 mL) in a pressure tube equipped with a magnetic stirring bar was added 1-bromo-3-methyl-2-butene (0.070 mL, 0.60 mmol) and freshly sublimed *t*-BuOK (0.046 g, 0.410 mmol). The tube was purged with argon and capped, and the contents were stirred for 2 h at 115 °C (oil bath). The reaction mixture was cooled, diluted with methylene chloride, and filtered though a short plug of Celite, and solvents were removed under reduced pressure to afford a crude product, which was separated by flash chromatography over silica with methylene chloride/hexane (1:5) as eluent to afford benzopyrans **5c** (0.009 g, 28%) and **5d** (0.004 g, 14%), both as colorless oils.

Analytical data for benzopyran **5c** are as follows: $R_f = 0.63$ (EtOAc/hexane 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 7.6 Hz, 1 H), 6.90 (d, J = 7.6 Hz, 1 H), 6.82 (t, J = 7.6 Hz, 1 H), 5.33 (tt, J = 6.0, 1.6 Hz, 1 H), 4.90 (t, J = 1.6 Hz, 1 H), 4.88 (s, 1 H), 4.67 (dd, J = 5.6, 2.0 Hz, 1 H), 4.24 (dq, J = 7.2, 2.8 Hz, 2 H), 3.38−3.30 (m, 2 H), 2.93−2.76 (m, 3 H), 1.84 (s, 3 H), 1.76 (s, 3 H), 1.71 (s, 3 H), 1.29 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 150.6, 143.6, 132.2, 129.8, 127.4, 126.8, 122.5, 120.5, 120.4, 113.6, 77.2, 61.2, 42.0, 29.7, 28.3, 25.8, 20.3, 17.8, 14.2; IR (neat, cm^{-1}) 1751 (s), 1463 (s), 1194 (s); HRMS (ES$^+$) calcd for $C_{20}H_{27}O_3$ (M + H$^+$) m/z 315.1960, found m/z 315.1955.

Analytical data for benzopyran **5d** are as follows: $R_f = 0.64$ (EtOAc/hexanes 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 6.8, 2.0 Hz, 1 H), 6.88−6.82 (m, 2 H), 6.29 (s, 1 H), 5.37 (tt, J = 7.2, 1.6 Hz, 1 H), 5.28 (s, 1 H), 4.20−4.11 (m, 2 H), 3.38 (d, J = 7.2 Hz, 2 H), 2.62 (sept, J = 6.8 Hz, 1 H), 1.76 (s, 3 H), 1.74 (s, 3 H), 1.26−1.18 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 149.6, 138.2, 132.4, 129.0, 128.5, 124.3, 122.5, 121.3, 121.2, 118.3, 75.1, 61.1, 30.7, 27.9, 25.8, 22.1, 20.3, 17.8, 14.0; IR (neat, cm^{-1}) 1751 (s), 1454 (s), 1184 (s); HRMS (ES$^+$) calcd for $C_{20}H_{27}O_3$ (M + H$^+$) m/z 315.1960, found m/z 315.1953.

Procedure for the Recovery of the Palladium(II) Complexes [*N*,*N*′-Bis(cyclohexyl)ethylenediimine]palladium Dibromide (8) and Bis[bromo(methyl η^3-butenoate)palladium(II)] (9). The crude reaction mixture obtained from the reaction of the palladacycle **3a** (0.051 g, 0.100 mmol) with neat methyl *trans*-4-bromobutenoate (0.15 mL) at 95 °C for 2 h as described in the protocols above in the absence of any additive was diluted with methylene chloride (3.0 mL). The resulting solid was collected by filtration and washed with cold methylene chloride to afford complex **8** (0.022 g, 45%) as an orange powder possessing minimal solubility in common organic solvents: mp 260 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (s br, 2 H), 2.95−1.85 (m, 2 H), 1.87 (d, J = 7.3 Hz, 4 H), 1.80−1.71 (m, 4 H), 1.58 (d, J = 12.0 Hz, 2 H), 1.27−1.06 (m, 10 H); IR (KBr, cm^{-1}) 3097 (s), 2937 (s), 2854 (s), 1591 (s), 1473 (s), 1001 (m).

Diffusion-controlled crystallization of complex **8** (*N*,*N*-dimethylacetamide/pentane, room temperature, 3 days) afforded a single crystal suitable for X-ray crystallographic analysis (data provided in the Supporting Information).

The filtrate obtained by the filtration of the original crude reaction mixture was collected, and solvents were removed under reduced

pressure to afford a crude product, which was separated by flash chromatography over silica with EtOAc/hexane mixtures as eluent, with the composition gradually changing from 5% EtOAc to 10% EtOAc to afford the benzoxepine **4a** (0.018 g, 49%), phenol **6** (0.003 g, 17%), and complex **9** (0.004 g, 11%) as a bright yellow solid: mp 185 °C dec; $R_f = 0.30$ (EtOAc/hexanes 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16−6.08 (m, 2 H), 4.35 (s br, 2 H), 3.78 (s, 6 H), 3.70 (d, $J = 8.4$ Hz, 2 H), 3.32 (d, $J = 13.2$ Hz, 2 H); IR (KBr, cm^{-1}) 1718 (s).

Diffusion-controlled crystallization of complex **9** (EtOAc/hexane, room temperature, 3 days) afforded a single crystal suitable for X-ray crystallographic analysis (data provided in the Supporting Information).

2-(Ethoxycarbonyl)-3-(methoxycarbonyl)-4,5-dihydro-1-benzoxepine (13a). To a solution of complex **11** (0.100 g, 0.16 mmol) in acetonitrile (5 mL) in a pressure tube at room temperature under argon was added 1,4-diazabicyclo[2.2.2]octane (DABCO; 0.0921 g, 0.82 mmol) and triphenylphosphine (0.099 g, 0.38 mmol). The pressure tube was purged with argon, capped, and heated in an oil bath (100 °C) for 24 h. The reaction mixture was cooled and filtered and the solvent was removed under reduced pressure to provide the crude product, which was purified by flash chromatography over silica with EtOAc/hexane (1:10) as eluent to afford the benzoxepine **13a** (0.034 g, 76%) as a colorless oil/solid: $R_f = 0.34$ (EtOAc/hexane 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, $J = 7.9$ Hz, 1 H), 7.55 (d, $J = 8.3$ Hz, 1 H), 7.45 (t, $J = 6.6$ Hz, 1 H), 7.32 (t, $J = 7.2$ Hz, 1 H), 4.46 (q, $J = 7.1$ Hz, 2 H), 3.65 (s, 3 H), 3.39 (t, $J = 7.8$ Hz, 2 H), 2.72 (t, $J = 7.8$ Hz, 2 H), 1.45 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 160.0, 154.5, 141.1, 128.3, 128.0, 127.9, 123.3, 121.2, 112.3, 61.3, 51.7, 33.9, 19.7, 14.4; IR (neat, cm^{-1}) 1728 (s), 1298 (s), 740 (s); HRMS (ES^+) calcd for $C_{15}H_{17}O_5$ ($M + H^+$) m/z 277.1076 found m/z 277.1068.

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Supporting Information Available: Text, figures, tables, and CIF files giving the general experimental protocol, a description of X-ray crystallographic studies on compounds **3a**,**b** and **8**−**12** and their crystal data, ^{1}H and ^{13}C NMR spectra of all new compounds prepared in this study, including data from 2D NMR experiments on complex **12**, and a description of the experiments described in Figure 5. This material can be found free of charge via the Internet at http://pubs.acs.org.

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