Mechanistic Studies of the Palladium-Catalyzed Ring Opening of Oxabicyclic Alkenes with Dialkylzinc

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Abstract: The mechanism of the palladium-catalyzed ring opening of oxabicyclic alkenes with dialkylzinc has been studied. Experiments which rule out a π-allyl mechanism were carried out. Trapping carbometalated products and synthesis and successful reaction of alkyl palladium species provided strong evidence in favor of an enantioselective carbopalladation as the key step in the mechanism. The studies also suggest that a cationic palladium species is responsible for carbopalladation of the alkene. The combination of palladium and dialkylzinc is unique in that the dialkylzinc functions both in the transmetalation to palladium and as a Lewis acid in forming the reactive cationic palladium species.

Introduction

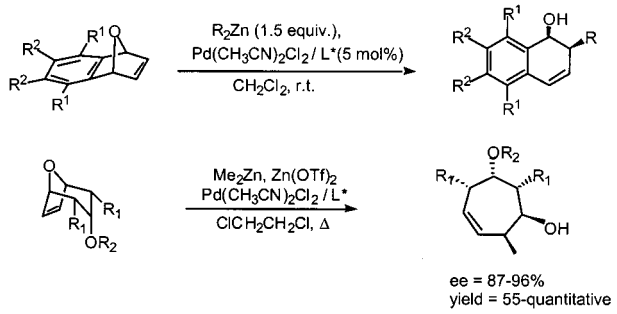
The use of stereochemically rigid oxabicyclic templates to achieve stereoselective functional group introduction in carbocyclic products has been investigated in our laboratory for some years. The products from ring opening of these substrates are potentially very useful in the synthesis of many natural products.[1] Recently we reported a highly enantioselective alkylative ring opening with dialkylzinc reagents catalyzed by palladium, which greatly extends the utility of the ring-opening methodology (Scheme 1).[2] We now report detailed studies on the mechanism of this transformation, which indicate that an enantioselective carbometalation is the predominant pathway for the reaction.

Carbopalladation and ring opening or ionization and alkylation were considered to be the two most likely reaction pathways. The enantiodetermining step would then either involve an enantioselective carbopalladation of the alkene or a selective ionization of the bridging carbon−oxygen bond. A reversible ionization and enantioselective alkylation was considered unlikely due to the release of strain upon opening the bridging carbon−oxygen bond.

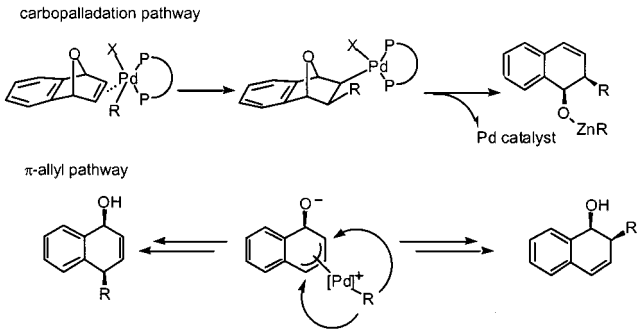
As shown in Scheme 2, a Pd(II) alkyl species could be involved in a carbopalladation of the alkene. Fiaud[3] and Hayashi[4] both propose a carbopalladation mechanism in their Pd(0)-catalyzed addition of aryl and alkenyl halides to bicyclic alkenes. Furthermore, Brookhart has also demonstrated that alkyl insertion into ethylene from a cationic Pd(II) species occurs in palladium-catalyzed polymerizations.[5] In the substrates we studied carbopalladation would be followed by elimination of the β-oxygen.[6]

Alternatively, an allylic substitution via a π-allyl palladium intermediate, in analogy with the well-documented results using allylic leaving groups, palladium catalysts and chiral ligands could also be occurring.[7] We observe overall retention, so a retention−retention or a double inversion pathway would be required. The intermediate formed, following the ionization, is closely related to the π-allyl species proposed by Trost in his work on desymmetrization of meso-diesters.[7b] However, the regioselectivity reported by Trost is the product from attack of the nucleophile distal to the alkoxide. No trace of this isomer was detected in our studies regardless of the substrate.

Scheme 1



Scheme 2



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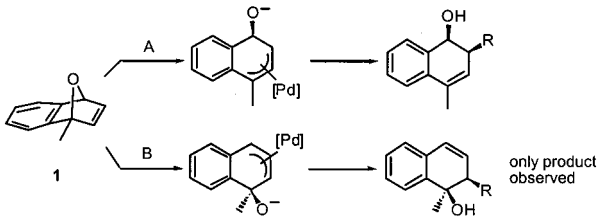
Scheme 3



Results and Discussion

1. Investigations into the π-Allyl Pathway. (a) Reactions of Oxabenzonorbornadiene with Palladium(0). If the π-allyl pathway were occurring a Pd(0) species would initiate the catalytic cycle. In reactions with $Pd(CH_3CN)_2Cl_2$ it is conceivable that displacement of a Pd−Cl with dialkylzinc could form a Pd(0) species via an in situ reductive elimination. However, when the reaction was attempted using Me_2Zn and catalytic $Pd_2(dba)_3$/dppf less than 25% conversion was observed after 24 h, whereas with $Pd(dppf)_2Cl_2$ the reaction is complete in less than 12 h. Also, when oxabenzonorbornadiene was reacted with sodium dimethyl malonate (1.5 equiv) and either $Pd_2(dba)_3$/dppf or $Pd(dppf)Cl_2/Et_2Zn$ (5 mol % to reduce Pd(II) to Pd(0)) no addition of the dimethyl malonate was detected.

(b) Reactions with Unsymmetrical Substrates. Additional evidence disfavoring an ionization mechanism is seen in the reaction of unsymmetrical substrate, **1**, substituted at the bridgehead (Scheme 3). If a Lewis acid promoted reaction was taking place ionization at the tertiary center would be expected to predominate (pathway A); however, products exclusively from pathway B were observed.

These results are better explained if a carbopalladation mechanism is occurring. The more sterically encumbered palladium would migrate to the less hindered carbon, while the smaller alkyl group would be transferred to the carbon next to the substituted bridgehead.

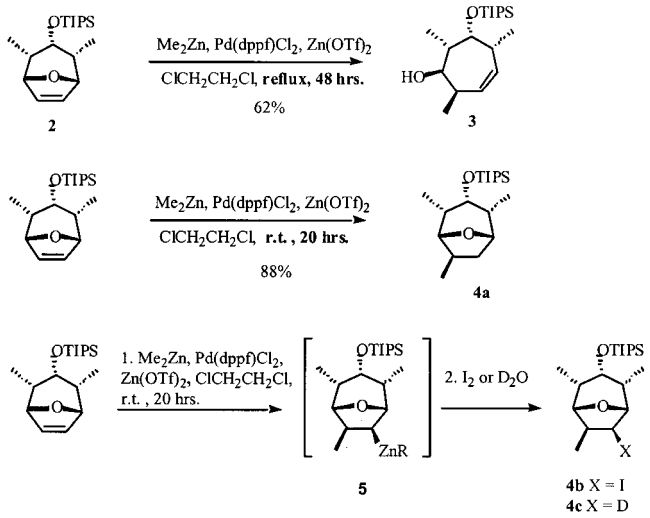
2. Evidence for a Carbopalladation Pathway. (a) Isolation and Reaction of Carbopalladated Products. Important evidence supporting a carbopalladation mechanism arose while studying the addition of Me_2Zn to the [3.2.1] oxabicycles where we found that addition of $Zn(OTf)_2$ improved the yield of the reaction. When the reaction of **2** was performed at ambient temperature instead of refluxing dichloroethane, the major product, **4a**, was one arising from a palladium-catalyzed carbozincation of the alkene followed by protonation (Scheme 4).

To confirm that a carbozincated intermediate, **5**, was indeed being formed, trapping experiments were carried out. When the reaction was quenched with dueterium oxide instead of water **4c** was isolated with incorporation of dueterium on the carbon adjacent to the methyl group. ^{1}H NMR showed less than 10% of **4a** present, which indicates that the organometallic intermediate is the major product prior to quenching.

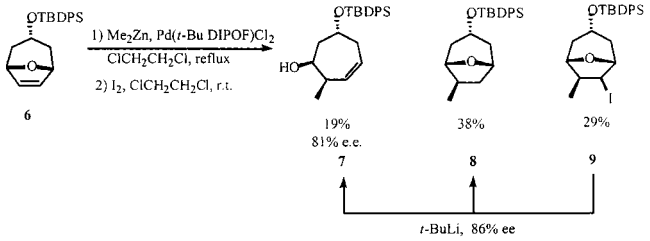
When the reaction was quenched with iodine, **4b** was isolated in 62% yield. An X-ray structure was obtained which confirmed the cis relationship between the methyl, iodide, and bridging oxygen. The cis iodide rules out the possibility of forming these products on workup by proto- or iodoetherification of **3**, and provides additional support for the formation of intermediate **5**.

Evidence that a carbopalladation was part of the catalytic cycle and not just a side reaction was obtained when similar results were observed using the chiral catalyst Pd(*t*-Bu-DIPOF)-Cl_2 with substrate **6** (Scheme 5). The carbometalated product

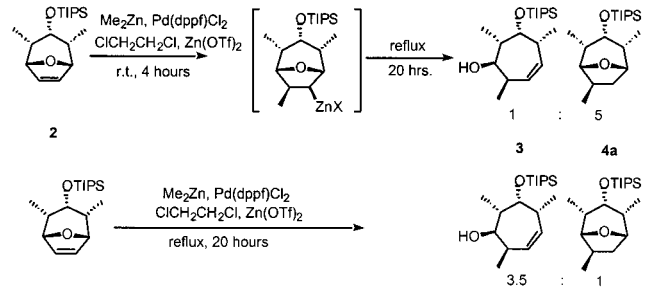
Scheme 4



Scheme 5



Scheme 6

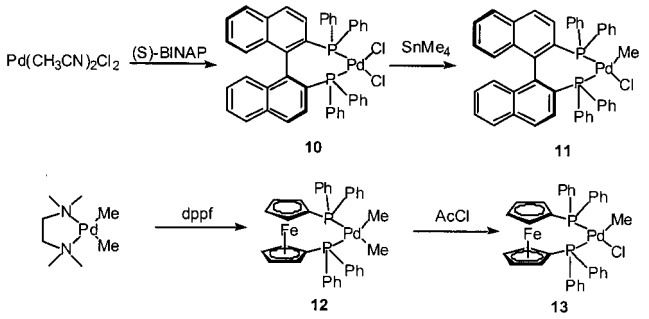


was trapped with iodine yielding the iodide **9** along with **7** and **8**. Ring opening by lithiation of **9** with *t*-BuLi gave a mixture of **7** and in similar enantiomeric excess to the direct conversion of **6** to **7** strongly supporting an enantioselective carbopalladation step.

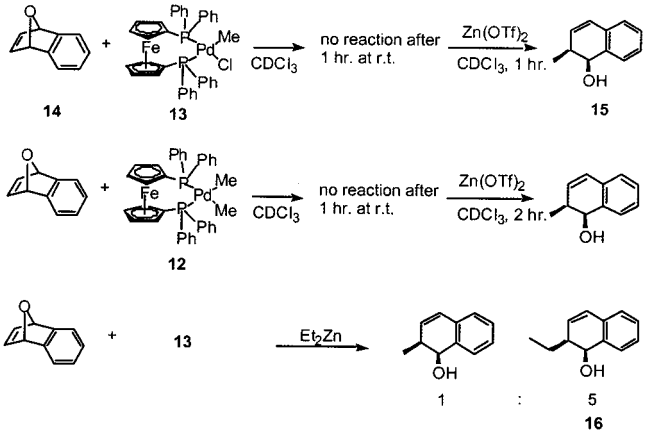
After carbopalladation it is conceivable that the organopalladium species directly undergoes a β-oxygen elimination.[6] Alternatively a transmetalation to zinc followed by ring opening could be occurring. To study this question substrate **2** was reacted with Me_2Zn, $Pd(dppf)Cl_2$, and $Zn(OTf)_2$ at room temperature to give what we assume is the carbozincated product in analogy to the results presented in Scheme 4 (via a carbopalladation and transmetalation). Subsequent heating to reflux for 20 h (Scheme 6) gave only 8% of the ring-opened product, **3**, whereas the reaction carried out entirely at reflux gave 40% of the ring-opened product after 20 h. This suggests that the ring opening via a palladium β-oxygen elimination is faster than ring opening from the zinc species. However, with certain substrates and conditions the transmetalation to zinc is competing with the ring opening.

(b) Synthesis and Reaction of Palladium Alkyl Species. To better understand the nature of the palladium intermediate

Scheme 7



Scheme 8



undergoing the carbopalladation we undertook the synthesis of palladium alkyl species **11**−**13** using the methods described by Vrieze and co-workers and van Koten and co-workers (Scheme 7).[8]

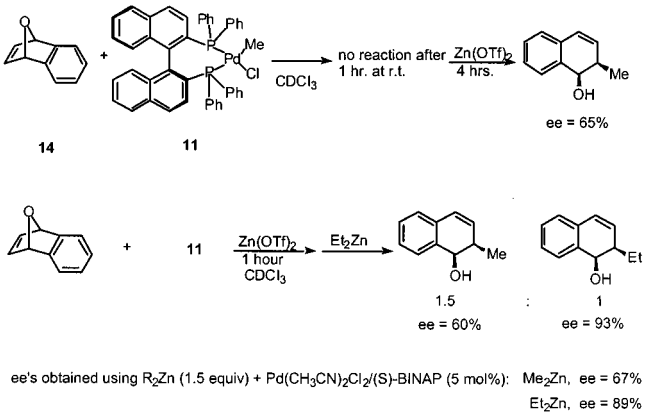
Treatment of **14** with a stoichiometric amount of **12** or **13** failed to induce any reaction; however, when $Zn(OTf)_2$ was added, rapid conversion to the ring-opened product was observed for both the methylchloropalladium species, **12**, and the dimethylpalladium species, **13** (Scheme 8).

When Et_2Zn was added to the reaction of **13** and **14** a 5:1 ratio of ethyl addition to methyl addition was observed. This is best explained if the rate of addition of the Et−Pd complex is much faster than that of the Me−Pd complex. This proposal is consistent with competition experiments in which we have observed that ethyl addition is >100 times faster than methyl addition. It is evident that diethylzinc both activates **13** leading to methyl addition and then participates in a rapid catalytic process.

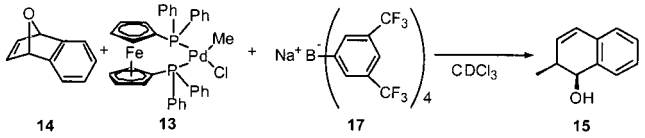
Palladium BINAP complex **11** reacted analogously to **12** and **13**, and the enantiomeric excesses of the methyl and ethyl addition products were similar to that observed in the catalytic reaction (Scheme 9).

These experiments provide strong evidence that $[RPdL_2]$ species are present in the catalytic cycle and undergo an enantioselective carbopalladation. It appears that both the alkylchloropalladium and dialkylpalladium species can react but both require the zinc as an activating agent. We speculated that perhaps the zinc species was acting as a Lewis acid to remove an alkyl or chloro group from the palladium creating a cationic intermediate that could then bind the substrate alkene. To test this hypothesis we performed a reaction with **13** and sodium

Scheme 9



Scheme 10



tetraarylborate, **17** ($NaB(Ar^F)_4$), a reagent Brookhart has shown forms a cationic palladium species in situ with concomitant formation of NaCl.[9] We found the resulting cationic palladium species underwent very rapid reaction with **14** to give complete conversion in less than an hour (Scheme 10). This suggests that the dialkylzinc or zinc triflate may form at least a small amount of a highly reactive cationic palladium species.

The proposal of a cationic palladium is in accordance with trends observed while studying additive effects on the yield of reaction with the [3.2.1] oxabicycles. During these reactions a Pd(0) black precipitate was frequently observed. The addition of Lewis bases such as excess phosphine, tetrabutylammonium chloride, or even THF to stabilize the palladium prevented formation of the Pd(0) precipitate but also inhibited the reaction. The addition of the Lewis acid, $Zn(OTf)_2$, which is more Lewis acidic than a dialkylzinc and is more apt to form the reactive cationic catalyst, resulted in higher yields and reduced amounts of precipitate.

(c) ^{1}H NMR Studies on the Effect of $Zn(OTf)_2$ on Pd(dppf)MeCl. To better understand the effect of the Lewis acidic species on the catalyst, ^{1}H NMR studies were undertaken and the results shown in Figure 1. Pd(dppf)MeCl, **13**, was used for the studies and trace A shows the spectrum of **13** in $CDCl_3$. There is a signal at 0.79 ppm from the methyl group and four cyclopentadienyl ring signals, two from the ring trans to the methyl and two from the ring trans to the chloride. Addition of $Zn(OTf)_2$ to **13** has an influence on the cyclopentadienyl resonances where a coalescence occurs but little change on the methyl signal (trace B). The result is similar to the spectrum obtained from addition of AgOTf to **13** (trace C) with small differences in the chemical shifts observed. Trace D shows the affect of the addition of $NaB(Ar^F)_4$ to **13**. Here again a coalescence in the cyclopentadienyl signals is observed, however in a slightly different pattern. The coalescence observed seems to suggest that in each of these cases there is partial or complete removal of the chloride to give a cationic palladium species. The differences in the spectra could be attributed to differences in the nature of the counterion, with the one obtained from $Zn(OTf)_2$ being more similar to that from AgOTf compared to $NaB(Ar^F)_4$.

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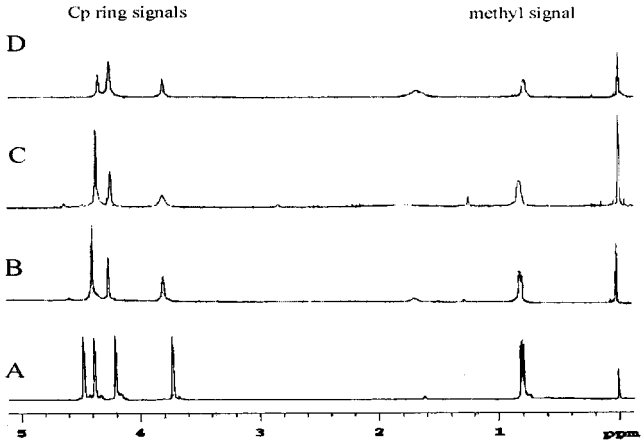
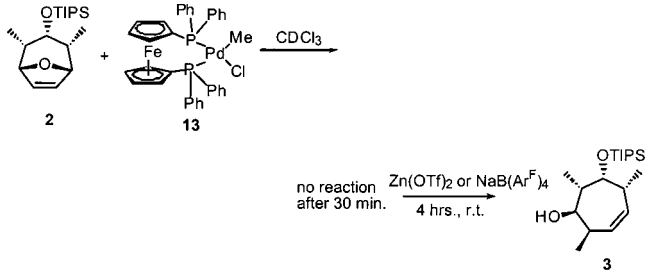


Figure 1. ^{1}H NMR of Pd(dppf)MeCl (A), Pd(dppf)MeCl + $Zn(OTf)_2$ (B), Pd(dppf)MeCl + AgOTf (C), and Pd(dppf)MeCl + $NaB(Ar^F)_4$ (D).

Scheme 11



(d) Attempts To Observe a Carbopalladated Intermediate. In hopes of observing a cationic palladium intermediate with substrate **2**, which did not undergo ring opening at room temperature, reaction with **13** and $Zn(OTf)_2$ or $NaB(Ar^F)_4$ was attempted (Scheme 11). To our surprise the ring-opened product, which normally could only be obtained at elevated temperature, was isolated. Thus, without the dialkylzinc species present for transmetalation, the carbopalladated intermediate undergoes rapid β-oxygen elimination to the ring-opened product.

3. Investigations into the Role of the Substrate Olefin. To investigate the importance of the substrate olefin on the reaction, different substrates were submitted to the reaction conditions. Without substrate present, addition of Et_2Zn to any of the palladium species in dichloromethane causes rapid formation of a black Pd(0) precipitate. The addition of Me_2Zn to Pd(dppf)-Cl_2 in the absence of substrate forms Pd(dppf)Me_2 which is stable at room temperature but upon heating also forms a black precipitate. Reaction with styrene gave no reaction, and substrates **19** and **20** seemed to react via Pd(0) mechanisms (Scheme 12).

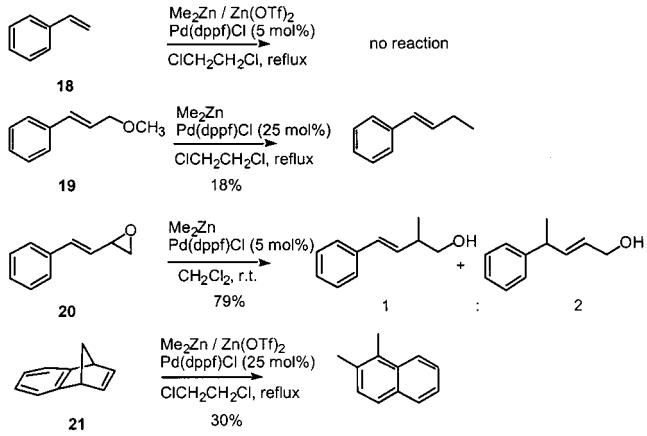
In contrast, reaction of **21** provided 1,2-dimethylnaphthalene which presumably proceeds via carbopalladation followed by β-carbon elimination. This result is similar to the ring-opening of cyclopropanes and cyclobutanes bearing a palladium at the β position.[10] Ring opening of these bicyclic substrates releases significant ring strain providing a driving force for the reaction.

Conclusion

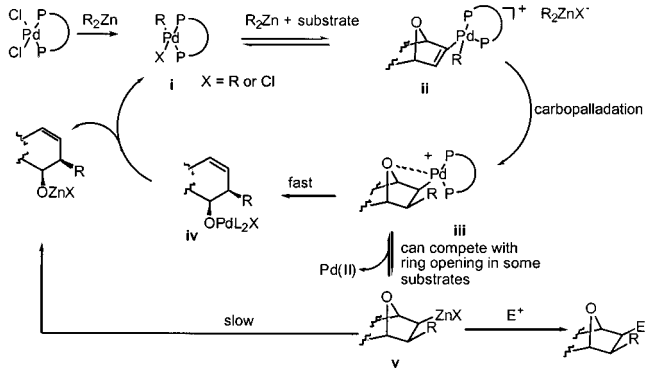
The mechanism we propose from the above evidence is summarized in Scheme 13. Pd(dppf)Cl_2 forms a palladium alkyl species, **i**, via transmetalation with the dialkylzinc which then binds the alkene substrate with loss of X^-, assisted by a Lewis acidic zinc agent. An enantioselective carbopalladation takes place to give intermediate **iii**, and β-oxygen elimination can then give the ring-opened product, **iv**, or transmetalation to zinc may occur which competes with ring opening and gives **v**. The zinc intermediate could potentially ring open, however it appears to do so at a slower rate.

In conclusion, these studies have helped provide insight into the mechanism of this new enantioselective reaction, and have been useful in the extension of this methodology. They also provide a better understanding of the interactions between alkyl palladium species and zinc. Reactions involving catalysis by cationic palladium are becoming more prevalent in the literature. Our studies show the important qualities of the dialkylzinc which functions both in the transmetalation to palladium and as a Lewis acid in forming the reactive cationic palladium species.

Scheme 12



Scheme 13



Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded using a Varian XL 400 spectrometer. IR spectra were obtained using a Nicolet DX FT-IR spectrometer. High-resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV.

Reactions of Oxabenzonorbornadiene (14) with Palladium(0). A flame-dried round-bottom flask was charged, under argon, with Pd_2dba_3 (6.3 mg, 0.007 mmol), dppf (7.6 mg, 0.14 mmol), and oxabenzonorbornadiene **14** (40 mg, 0.28 mmol). Distilled dichloromethane (5 mL) was added and stirred 1 h at room temperature. To this solution was added dimethylzinc (2.0 M in toluene, 0.21 mL, 0.42 mmol) which was stirred at room temperature for 24 h. The reaction was quenched with a few drops of water and the solution was stirred for 20 min, filtered through Celite, and evaporated to give the crude product. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes) to give (1*R*,2*R*)-2-methyl-

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1,2-dihydronaphth-1-ol (**15**, 11 mg, 25% yield) as a white solid. R_f = 0.33 on silica gel (hexanes:ethyl acetate 7:3); mp 64−65 °C; IR ($CHCl_3$) 3456 (s), 3030 (m), 2966 (s), 1588 (w), 1485 (m), 1454 (m), 1364 (m), 1280 (m), 831 (w), 788 (s), 760 (s), 679 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, d, J = 7.2 Hz), 7.30−7.22 (2H, m), 7.12 (1H, d, J = 7.2 Hz), 6.52 (1H, dd, J = 9.5, 2.3 Hz), 5.80 (1H, dd, J = 9.5, 2.5 Hz), 4.57 (1H, dd, J = 7.8, 4.8 Hz), 2.67−2.63 (1H, m), 1.57 (1H, d, J = 7.8 Hz), 1.25 (3H, d, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.6, 132.4, 128.6, 127.7, 127.4, 126.7, 126.6, 71.8, 35.4, 14.2; HRMS calcd for $C_{11}H_{12}O$ $(M)^+$ 160.0888, found 160.0888.

Attempts to add dimethyl malonate were carried out as above except with the addition of a solution of sodium dimethyl malonate (formed by addition of NaH (8 mg, 0.33 mmol) to dimethyl malonate (38 μL, 0.33 mmol) in THF at room temperature) to the substrate and catalyst in THF at room temperature.

(1*R*,2*R*)-1,2-Dimethyl-1,2-dihydronaphth-1-ol. A flame-dried, round-bottom flask was charged, under argon, with $Pd(dppf)Cl_2$ (3 mg, 0.004 mmol) and **1** (73 mg, 0.46 mmol). Distilled dichloromethane (13 mL) was added prior to addition of dimethylzinc (2.0 M in toluene, 0.28 mL, 0.56 mmol) and the mixture was stirred at room temperature for 16 h. The reaction was quenched with a few drops of water and the solution was stirred 20 min, filtered through Celite, and evaporated to give the crude product, which was purified by flash chromatography on silica gel (10% ether in hexanes) to give the product (50 mg, 62% yield) as an oil. R_f = 0.36 on silica gel (hexanes:ether 7:3); IR (neat) 3450, 3031, 2966, 1484, 1452, 1364, 788, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.1 Hz, 1H), 7.23 (m, 2H), 7.03 (d, J = 6.8 Hz, 1H), 6.36 (d, J = 9.6 Hz, 1H), 5.97 (dd, J = 9.6, 5.2 Hz, 1H), 2.42 (quint., J = 5.2 Hz, 1H), 1.82 (1H, OH), 1.51 (s, 3H), 1.01 (d, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 133.8, 132.1, 127.9, 127.4, 126.3, 125.6, 123.7, 73.9, 41.0, 28.1, 13.2; HRMS calcd for $C_{12}H_{14}O$ $(M)^+$ 174.1045 found 174.1043.

(1*R*,2*R*)-1-Methyl-2-ethyl-1,2-dihydronaphth-1-ol. A flame-dried, round-bottom flask was charged, under argon, with $Pd(dppf)Cl_2$ (15 mg, 0.02 mmol) and **1** (73 mg, 0.46 mmol). Distilled dichloromethane (8 mL) was added prior to addition of diethylzinc (1.0 M in hexanes, 0. 64 mL, 0.64 mmol) and the mixture was stirred at room temperature for 4 h. The reaction was quenched with a few drops of water and the solution was stirred 20 min, filtered through Celite, and evaporated to give the crude product, which was purified by flash chromatography on silica gel (10% ether in hexanes) to give the product (68 mg, 78% yield) as an oil. R_f = 0.4 on silica gel (hexanes:ether 7:3); IR (neat) 3447, 3033, 2963, 1588, 1461, 1384, 790, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H), 7.23 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 10.0 Hz, 1H), 6.11 (dd, J = 9.8, 5.8 Hz, 1H), 2.22 (m, 1H), 1.77 (1H, OH), 1.75 (m, 1H), 1.50 (s, 3H), 1.26 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 132.4, 132.1, 127.9, 127.2, 126.2, 126.1, 123.3, 74.4, 47.6, 29.3, 21.5, 11.7; HRMS calcd for $C_{13}H_{16}O$ $(M)^+$ 188.1201, found 188.1203.

Ring Opening and Carbometalation of *endo*-2,4-Dimethyl-3-(triisopropylsilyl)oxy-8-oxabicyclo[3.2.1]oct-6-ene (2). A flame-dried, round-bottom flask was charged, under argon, with $Pd(dppf)Cl_2$ (6.5 mg, 0.008 mmol), $Zn(OTf)_2$ (58 mg, 0.16 mmol), and substrate **2** (50 mg, 0.161 mmol). Distilled dichloroethane (6 mL) was added and the reaction solution brought to the appropriate temperature. A solution of dimethylzinc (2.0 M in toluene, 0.12 mL, 0.24 mmol) was then added dropwise. After the reaction was complete it was cooled to room temperature and quenched with a few drops of water and the solution was stirred 15 min, filtered through a short plug of Celite, and concentrated. The crude mixture was purified by flash chromatography on silica gel (10% Et_2O in hexanes) to give the product.

When the reaction was carried out at reflux product **3** was obtained in 62% yield as an oil. R_f = 0.33 on silica gel (hexanes:ethyl ether 8:2); IR (neat) 3403, 2945, 2865, 1653, 1461, 1382, 1212, 1089, 887, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddd, J = 11.5, 7.5, 1.6 Hz, 1H), 5.34 (dd, J = 11.5, 5.3 Hz, 1H), 4.19 (dd, J = 5.0, 3.6 Hz, 1H), 3.65 (td, J = 7.0, 2.0 Hz, 1H), 2.73 (m, 1H), 2.51 (quint. d, J = 7.3, 3.5 Hz, 1H), 2.26 (quint., J = 7.0 Hz, 1H), 1.60 (dd, J = 7.0, 6.8 Hz, 1H), 1.17 (d, J = 7.5 Hz, 3H), 1.14 (d, J = 7.3 Hz, 6H), 1.07 (br s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 132.0, 77.2, 71.2, 45.6, 42.6, 36.6, 18.4, 17.6, 16.1, 14.4, 12.8; HRMS calcd for $C_{26}H_{36}O_2Si$ $(M)^+$ 326.263281, found 326.264109; M(m/z) 309, 283, 265, 135, 123, 103, 95, 75, 61.

When the reaction was carried out at room temperature product **4a** was obtained in 88% yield as a white solid. R_f = 0.5 on silica gel (hexanes:ethyl ether 8:2); IR ($CHCl_3$) 2951, 1458, 1057, 1015, 909, 881, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (t, J = 4.0 Hz, 1H), 3.98 (dd, J = 7.6, 3.2 Hz, 1H), 3.47 (d, J = 2.8 Hz, 1H), 2.70−2.61 (m, 1H), 2.47 (dd, J = 11.7, 8.6 Hz, 1H), 2.00−1.91 (m, 1H), 1.16 (m, 1H), 1.13(br s, 21H), 1.00 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.2, 80.0, 74.4, 40.4, 40.3, 34.8, 32.1, 23.6, 18.9, 14.1, 14.0, 13.9; HRMS calcd for $C_{16}H_{31}O_2Si$ $(M - C_3H_7)^+$ 283.2093, found 283.2098.

When the reaction was carried out at room temperature for 20 h followed by addition of iodine (2 equiv) and stirring an additional 2 h product **4b** was obtained in 62% yield as a white solid. R_f = 0.6 on silica gel (hexanes:ethyl ether 8:2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (d, J = 8.0 Hz, 1H), 4.43 (d, J = 3.2 Hz, 1H), 4.04 (t, J = 3.8 Hz, 1H), 3.57 (d, J = 3.2 Hz, 1H), 2.64 (quint., J = 7.4 Hz, 1H), 1.91 (m, 2H), 1.22 (d, J = 7.6 Hz, 3H), 1.13(br s, 21H), 1.08 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 92.1, 85.6, 73.8, 41.6, 39.5, 35.8, 35.1, 29.4, 18.6, 13.7, 13.6, 13.5; HRMS calcd for $C_{16}H_{30}O_2SiI$ $(M - C_3H_7)^+$ 409.1060, found 409.1069.

Ring Opening and Carbometalation of *endo*-3-(*tert*-Butyldiphenylsilyl)oxy-8-oxabicyclo[3.2.1]oct-6-ene (6). A flame-dried, round-bottom flask was charged, under argon, with $Pd(CH_3CN)_2Cl_2$ (5 mol %) and (*S*)-*t*-Bu-(*S*)-DIPOF (5 mol %). Distilled dichloroethane (1 mL) was added, the solution was stirred at room temperature for 1 h, and then substrate **6** (50 mg, 0.137 mmol) in dichloroethane (6 mL) was added via cannula and heated to reflux. A solution of dimethylzinc (2.0 M in toluene, 0.14 mL, 0.28 mmol) was then added and stirred at reflux for 20 h. The reaction was cooled to room temperature and a solution of iodine (2 equiv) in dichloroethane was added and stirred 60 min. The reaction was quenched with a few drops of water and the solution was stirred for 15 min, filtered through a short plug of Celite, and concentrated. The crude mixture was purified by flash chromatography on silica gel to afford products **7**, **8**,[11] and **9**.

Product **7** was obtained in 19% yield as an oil, and the ee was determined to be 81% using HPLC analysis on a CHIRACEL OD column, λ = 254 nm. Retention times in 0.5% ^{i}PrOH in hexanes were 9.4 min (major) and 15.6 min (minor). R_f = 0.27 on silica gel (hexanes:ethyl ether 8:2); IR (neat) cm^{-1} 3443, 2954, 2923, 2867, 1649, 1451, 1109, 1067; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.44−7.34 (m, 6H), 5.62−5.56 (m, 1H), 5.30−5.25 (m, 1H), 3.86−3.81 (m, 1H), 3.73 (br s, 1H), 2.58−2.48 (m, 1H), 2.40−2.22 (m, 3H), 1.86 (td, J = 10.4, 2.8 Hz, 1H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 135.8, 135.1, 134.4, 134.2, 129.6, 129.5, 127.9, 127.5, 72.4, 65.8, 47.6, 38.2, 38.0, 26.9, 19.1, 18.9; HRMS calcd for $C_{20}H_{23}O_2Si$ $(M - C_4H_9)^+$ 323.1467, found 323.1482.

Product **8** was obtained in 38% yield as an oil. R_f = 0.51 on silica gel (hexanes:ethyl ether 8:2); IR (neat) 3155, 2972, 1486, 1381, 1103, 913, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64−7.62 (m, 4H), 7.46−7.40 (m,2H), 7.39−7.35 (m, 4H), 4.34 (dd, J = 7.6, 3.5 Hz, 1H), 4.08 (t, J = 4.6 Hz, 1H), 3.80 (d, J = 3.6 Hz, 1H), 2.95−2.85 (m, 1H), 2.72 (dd, J = 11.6, 8.8 Hz, 1H), 1.89−1.81 (m, 2H), 1.65 (d, J = 14.4 Hz, 1H), 1.46 (ddd, J = 11.4, 8.0, 3.8 Hz, 1H), 1.56 (dd, J = 14.4, 1.0 Hz, 1H), 1.09 (s, 9H), 1.07(d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (4C), 134.3 (2C), 129.9 (2C), 127.8 (4C), 81.3, 75.1, 66.0, 38.8, 38.7, 38.6, 36.3, 27.2 (3C), 23.4, 19.3; HRMS calcd for $C_{20}H_{23}O_2Si$ $(M - C_4H_9)^+$ 323.1467, found 323.1466.

Product **9** was obtained in 29% yield as an oil. R_f = 0.62 on silica gel (hexanes:ethyl ether 8:2); IR (neat) 3148, 2930, 1817, 1795, 1638, 1483, 1468, 1382, 1102, 990, 941, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.67 (m, 4H), 7.45−7.35 (m, 6H), 4.21 (t, J = 5.9 Hz, 1H), 4.08 (t, J = 5.7 Hz, 1H), 3.77 (br s, 1H), 3.70 (t, J = 6.6 Hz, 1H), 3.24 (quint., J = 6.6 Hz, 1H), 2.46 (AB, J_{AB} = 15.4 Hz, 1H), 2.11 (td, J = 14.8, 6.0 Hz, 1H), 1.81 (td, J = 14.8, 4.8 Hz, 1H), 1.49 (d, J_{AB} = 15.4 Hz, 1H), 1.15 (d, J = 7.1 Hz, 3H), 1.12 (s, 9H); ^{13}C

(11) This product was obtained by protonation of the carbometalated product by water, presumably because the iodination was slow and incomplete. Quenching the reaction with D_2O instead of iodine gave only **7** with a deuterium next to the methyl along with ring-opened product.

NMR (100 MHz, $CDCl_3$) δ 136.3 (2C), 136.2 (2C), 134.3, 134.0, 129.9, 129.8, 127.8 (2C), 127.7 (2C), 80.2, 78.6, 64.4, 44.3, 39.0, 34.9, 29.9, 27.5 (3C), 19.3, 18.9; HRMS calcd for $C_{20}H_{22}O_2SiI$ $(M - C_4H_9)^+$ 449.0434, found 449.0427.

Ring opening of **9** was achieved by addition of *t*-BuLi (1.7M in pentane, 46 μL, 0.08 mmol) to substrate **9** (20 mg, 0.04 mmol) in distilled THF at −78 degrees. This solution was allowed to slowly warm to room-temperature overnight. Work up was done with water and ether, and the ether layer was separated, dried (Na_2SO_4), and evaporated to give crude **7** and **8** in a 1:1.5 ratio. The ee of **7** was determined to be 86% by HPLC analysis as described above.

[(*S*)-BINAP]Pd(CH_3)Cl (11).[12] To a flame-dried, round-bottom flask, under argon, was added $Pd(CH_3CN)_2Cl_2$ (33 mg, 0.13 mmol) and (*S*)-BINAP (80 mg, 0.13 mmol) and 4 mL of distilled dichloromethane. The mixture was stirred 1 h at room temperature and then $SnMe_4$ (36 μL, 0.26 mmol) was added and stirring was continued for 65 h at room temperature. The reaction mixture was filtered through Celite, evaporated, washed with ether (3 × 5 mL), and dried in vacuo to give product **11** (71 mg, 70% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.75 (m, 2H), 7.54−7.21 (m, 18H), 7.03 (m, 2H), 6.79−6.53 (m, 8H), 0.77 (dd, J = 7.8, 3.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6−125.1 (aromatic C), 16.9 (d, J = 97.3 Hz); ESMS calcd for $C_{45}H_{35}P_2Pd$ $(M - Cl)^+$ 743, found 743.[13]

[1,1′-Bis(diphenylphosphino)ferrocene]Pd(CH_3)$_2$ (12). To a flame-dried, round-bottom flask, under argon, was added (TMEDA)Pd(CH_3)$_2$[14] (200 mg, 0.8 mmol) and dppf (444 mg, 0.8 mmol) and 7 mL of distilled benzene. This was stirred at room temperature for 30 min and then the benzene was removed in vacuo. The crude was washed with pentane and dried in vacuo to give product **12** (550 mg, 99% yield) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 8H), 7.35 (m, 12H), 4.22 (t, J = 1.6 Hz, 4H), 4.09 (t, J = 1.6 Hz, 4H), 0.13 (d, J = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0 (d, J = 28.2 Hz), 134.6 (t, J = 6.8 Hz), 129.6, 127.9 (t, J = 4.5 Hz), 79.5 (d, J = 38.8 Hz), 74.7 (t, J = 5.3 Hz), 71.6, 8.5 (dd, J = 14.4, 107.9 Hz); ESMS calcd for $C_{36}H_{34}P_2FePd$ $(M)^+$ 690, found 690.[13]

[1,1′-Bis(diphenylphosphino)ferrocene]Pd(CH_3)Cl (13). To a flame-dried, round-bottom flask, under argon, was added **12** (250 mg, 0.36 mmol) and 5 mL of distilled benzene. Acetyl chloride (0.1 mL, 1.4 mmol) was added at room temperature and the reaction mixture was stirred for 1 h. The reaction mixture was then evaporated in vacuo to give product **13** (250 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 4H), 7.65 (m, 4H), 7.43−7.29 (m, 12H), 4.48 (s, 2H), 4.38 (s, 2H), 4.20 (s, 2H), 3.74 (s, 2H), 0.79 (dd, J = 7.8, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9 (d, J = 12.2 Hz), 134.3 (d, J = 12.2 Hz), 133.6 (d, J = 31.9 Hz), 132.8 (d, J = 53.2 Hz), 130.7 (d, J = 3.0 Hz), 129.9 (d, J = 2.3 Hz), 128.0 (d, J = 10.7 Hz), 127.9 (d, J = 9.1 Hz), 77.6 (d, J = 7.1 Hz), 75.7 (d, J = 11.4 Hz), 74.7 (d, J = 9.1 Hz), 72.9 (d, J = 6.9 Hz), 72.3 (d, J = 4.5 Hz), 16.8 (d, J = 98.8 Hz); ESMS calcd for $C_{35}H_{31}P_2FePd$ $(M - Cl)^+$ 675, found 675.[13]

General Procedure for Reactions of Palladium Alkyl Species. The reactions in Schemes 8−11 were carried out as follows: A flame-dried, round-bottom flask, under argon, was charged with substrate **14** or **2** (1 equiv), palladium species **11**, **12**, or **13** (1 equiv), and $CDCl_3$ (stored over molecular sieves). A small aliquot was taken after 1 h and diluted in $CDCl_3$ for ^{1}H NMR analysis. Then $Zn(OTf)_2$ or Et_2Zn or $NaB(Ar^F)_4$ (1 equiv) was added and the mixture was stirred at room temperature. Aliquots were taken after 1−4 h for ^{1}H NMR analysis to determine percent conversion of substrate to product.

The ^{1}H NMR of products **15** and **3** is given above. Product **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, d, J = 6.9 Hz), 7.28−7.19 (2H, m), 7.10 (1H, d, J = 7.1 Hz), 6.52 (1H, dd, J = 9.7, 2.5 Hz), 5.81 (1H, dd, J = 9.6, 1.8 Hz), 4.62 (1H, dd, J = 7.3, 4.5 Hz), 2.39−2.32 (1H, m), 1.84 (1H, dquin, J = 13.6, 7.5 Hz), 1.63 (1H, dquin, J = 13.6, 7.5 Hz), 1.52 (1H, d, J = 7.3 Hz), 1.11 (3H, t, J = 7.4 Hz). The enantiomeric excess of products **15** and **16** was determined by HPLC analysis on a CHIRACEL OD column, λ = 254 nm. Retention times for **15** in 1.25% ^{i}PrOH in hexanes were 33.6 and 35.3 min (major) and for **16** in 1.25% ^{i}PrOH in hexanes were 14.5 and 16.3 min (major).

^{1}H NMR Studies on Pd(dppf)MeCl. A flame-dried, round-bottom flask, under argon, was charged with Pd(dppf)MeCl (7.1 mg, 0.01 mmol) and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol), AgOTf (2.5 mg, 0.01 mmol), or $NaB(Ar^F)_4$ (8.8 mg, 0.01 mmol). $CDCl_3$ (2 mL, stored over molecular sieves) was added with stirring at room temperature. After 10 to 30 min the salts were allowed to settle and an aliquot was taken for ^{1}H NMR analysis. The ^{1}H NMR of Pd(dppf)MeCl is given above. For Pd(dppf)MeCl + $Zn(OTf)_2$ signals are seen at δ 4.39 (4H), 4.24 (2H), 3.81 (2H), 0.79 (3H). For Pd(dppf)MeCl + AgOTf signals are seen at δ 4.38 (4H), 4.26 (2H), 3.82 (2H), 0.82 (3H). For Pd(dppf)MeCl + $NaB(Ar^F)_4$ signals are seen at δ 4.35 (2H), 4.25 (4H), 3.81 (2H), 0.79 (3H).

General Procedure for Reactions with Olefins 18−21. A flame-dried, round-bottom flask, under argon, was charged with $Pd(dppf)Cl_2$ and $Zn(OTf)_2$ (105 mg, 0.29 mmol). Distilled dichloromethane or dichloroethane (2 mL) was added and after 10 min at room temperature the substrate (0.29 mmol) in 4 mL of the reaction solvent was added via cannula. The reaction was heated to the appropriate temperature and dimethylzinc (2.0 M in toluene, 0.22 mL, 0.44 mmol) was added. After 20 h the reaction was cooled to room temperature and quenched by addition of a few drops of water. This was stirred 15 min and then filtered through Celite and evaporated to give crude product.

1-Phenylbutene. The reaction was carried out as above with substrate **19** in refluxing dichloroethane with 25 mol % $Pd(dppf)Cl_2$ and no $Zn(OTf)_2$. The crude product was purified by flash chromatography on silica gel (hexanes) to give 18% yield of product. R_f = 0.65 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.16 (m, 5H), 6.38 (d, J = 16.0 Hz, 1H), 6.27 (d, J = 16.0, 6.4 Hz, 1H), 2.23 (quint., J = 7.2 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H).

2-Methyl-4-phenylbut-3-enol and 4-Methyl-4-phenylbut-2-enol. The reaction was carried out as above with substrate **20** at room temperature in dichloromethane with 5 mol % $Pd(dppf)Cl_2$ and no $Zn(OTf)_2$. The crude product was purified by flash chromatography on silica gel (40% ethyl acetate in hexanes) to give a mixture of isomers in 79% yield. R_f = 0.3 (40% ethyl acetate in hexanes)

1,2-Dimethylnaphthalene. The reaction was carried out as above with substrate **21** in refluxing dichloroethane with 25 mol % $Pd(dppf)Cl_2$. The crude product was purified by flash chromatography on silica gel (hexanes) to give product in 30% yield. R_f = 0.4 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 2.61 (s, 3H), 2.49 (s, 3H).

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Supporting Information Available: Crystallographic data and ORTEP diagram for the X-ray structure of compound **4b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Recrystallization from dichloromethane/hexanes gave crystals suitable for obtaining an X-ray structure.

(13) Electrospray mass spectrometry was the only method mild enough to give molecular ion signals without loss of ligand. The pattern and intensity of the isotope peaks for M^+ were calculated and matched the experimental data giving good evidence for the molecular formula.

(14) (TMEDA)Pd(CH_3)$_2$ was prepared according to the procedure in ref 8b.