Synthesis and Investigation of New Macrocyclic Diphosphine−Palladium(0) Complexes Based on the Barbiturate Binding Receptor

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A series of diphosphine ligands possessing a barbiturate-binding receptor have been synthesized with the goal of preparing new palladium(0) complexes for the Heck reaction, which position the alkene with respect to the metal center and thereby control the regioselectivity of the insertion step. Some of the diphosphines prepared were found to efficiently form macrocyclic bisphosphine palladium(0) complexes even though a 26-membered cycle is produced. A significant solvent effect for the oxidative addition of the Pd^0 complexes with phenyl iodide was noted in the case of one of the diphosphine ligands. This descrepancy may well be accounted for by the ability of the ligand when complexed to Pd^0 to possess different conformational preferences in the solvents tested, which influences the bite angle to the metal center. The receptors possessing an isophthaloyl connector bind barbital with affinities corresponding to those of the previously reported open receptors. However, upon complexation with $Pd(dba)_2$, none of the bidentate ligands revealed a capacity to bind barbital, reflecting again the conformational changes that occur upon coordination to Pd^0. The new palladium(0) complexes were tested for their ability to promote the Heck reaction between aryl halides and *n*-butyl acrylate. Whereas all the ligand:Pd^0 complexes were found to catalyze this reaction with reactivities similar to triphenylphosphine, in one case a higher reactivity was noted.

Introduction

The palladium(0)-catalyzed coupling of aryl iodides, bromides, or triflates with an olefin substrate, known as the Heck reaction, represents an important synthetic transformation for the preparation of arylalkenes on a laboratory and an industrial scale.[1] Traditionally, Pd^0-complexes with tertiary phosphine ligands have been studied and applied to the Heck coupling; however, the past few years have witnessed intensive efforts devoted to the design of new and more electron-donating ligands necessary for promoting the initial oxidative addition step in the catalytic cyclic with the cheaper but less reactive aryl chlorides.[2]

Less attention has been concentrated on providing a general method for controlling the regiochemical outcome of these reactions, where many factors come into play including the ligand type, solvent polarity, and substitution pattern of the alkene.[1,3,4] Fine-tuning of the catalyst and reaction conditions is therefore required

(1) For recent reviews, see: (a) Beletskaya, I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (c) Reetz, M. T. In *Transition Metal Catalyzed Reactions*; Davis, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999. (d) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (e) Brase, S.; DeMeijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (f) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447.

(2) For some recent examples, see: (a) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (c) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (d) Herrmann, W. A.; Bohm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141. (e) Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017. (f) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741. (g) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981. (h) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2000**, 201. (i) Calo, V.; Nacci, A.; Lopez, L.; Mannarini, N. *Tetrahedron Lett.* **2000**, *41*, 8973. (j) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (k) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619. (l) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, *11*, 1589. (m) Feuerstein, M.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 5923. (n) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989, and references therein.

(3) For a few recent examples of regiocontrolled arylation of alkenes bearing an internal coordinating group, see: (a) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (b) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544.

(4) For papers on the topic of insertion and regioselectivity, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Cabri, W.; Candiani, I. *Acc. Chem. Soc.* **1995**, *28*, 2. (c) Ludwig, M.; Stromberg, S.; Svensson, M.; Akermark, B. *Organometallics* **1999**, *18*, 970. (d) For a recent review on the topic of insertion and regioselectivity, see: Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, in press.

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for many cases in order to obtain higher regioselectivities. Whereas the Heck reaction works well for the arylation at the terminal position of electron-deficient olefins with monodentate ligands by the neutral pathway, there are no procedures for the preparation of the corresponding branched olefins. In contrast, protocols for the preparation of branched electron-rich alkenes are available employing bidentate ligands via the cationic pathway. For the obtention of linear products with electron-rich olefins, the most successful approach requires the incorporation of a chelating auxiliary. More problematic are the unfunctionalized 1-alkenes, where efficient methodology for their regioselective arylation is lacking.

We have recently commenced a program directed to the design of new Pd^0-ligand complexes that possess a receptor domain capable of binding and subsequently organizing the alkene substrate with respect to the metal center. Through the optimization of both the size of the receptor and positioning of the palladium(0) center it may therefore be possible to control the regioselectivity of the C−C bond forming step and thereby override any intrinsic directive properties of the olefin substrate. In this way, the regiochemistry may either be controlled for difficult alkenes, which are not regiospecific in the arylation step, or even potentially inverted compared to the normal products observed in the absence of such a receptor ligand.

As a suitable receptor ligand, our attention was first drawn to the barbiturate-recognizing hosts originally reported by Hamilton in 1988,[5] due to the well-documented exploitation of this host:guest system for numerous applications.[6] The host is built up of two appropriately separated 2,6-diaminopyridine units forming a cavity for the barbiturates, which ultimately binds by a six hydrogen bonding network, leading in general to strong complex formation in nonparticipating solvents.[7] With this host as the basis structure, we have therefore been interested in preparation of receptors incorporating two terminal triarylphosphine units capable of complexing palladium(0) and resulting in the formation of a metal-containing macrocycle, as schematically illustrated in Figure 1. Eventually, complexation of a suitable metal−host with an olefin covalently linked to a barbiturate unit via a temporary connector would subsequently position the alkene with respect to the metal center in much the same way as a chelating auxiliary and thereby potentially control the regioselectivity of the insertion step.[8]

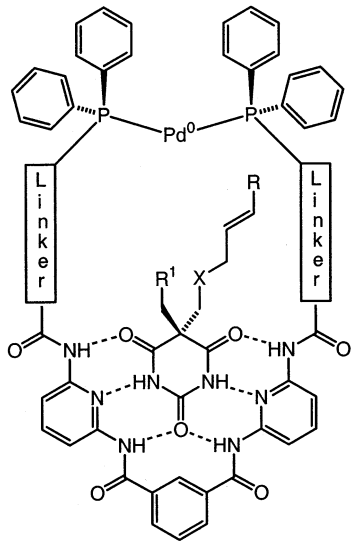


Figure 1. Macrocyclic bisphosphine palladium(0) complex possessing a barbiturate-recognizing moiety.

In this paper, we report our preliminary studies in this direction, revealing both the synthesis of several of such receptors, whereby phenyl groups of varying substitution patterns represent the linker, and their propensity to form macrocyclic complexes upon addition of $Pd^0(dba)_2$ (dba = *trans*,*trans*-dibenzylideneacetone), measured by ^{31}P NMR spectroscopy and cyclic voltammetry.[9] In addition, we disclose our investigation on the ability of these complexes to bind barbital and on their comparative reactivity in the oxidative addition with phenyl iodide, representing the first step in the catalytic cycle of the Heck reaction. Finally, the aptitude of these new complexes to promote the Heck reaction was explored, being an important requisite for the success of this project.

Results and Discussion

I. Synthesis of the Diphosphine Receptors. The bidentate phosphine ligands **1**−**3** first studied are illustrated in Figure 2. All contain the central barbiturate binding motif though modified at the terminal position with two aryl diphenylphosphine units of varying substitution pattern. The preparation of these compounds was easily performed by an initial amide-forming step between the three iodobenzoyl chlorides and the known diamine **7**[6d] in the presence of triethylamine (Scheme 1). A subsequent iodine to phosphorus exchange with diphenylphosphine promoted by palladium acetate in refluxing acetonitrile afforded the crystalline diphosphines **1** (mp 184−186 °C) and **2** (mp 174−176 °C) in good yields.[10] The rather unexceptional

(5) Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318.

(6) (a) Tecilla, P.; Dixon, R. P.; Slobodkin, G.; Alavi, D. S.; Waldeck, D. H.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9408. (b) Tecilla, P.; Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9586. (c) Tecilla, P.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1232. (d) Chang, S.-K.; Fan, E.; Van Engen, D.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 7640. (e) Aoki, I.; Harada, T.; Sakaki, T.; Kawahara, Y.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1341. (f) Aoki, I.; Kawahara, Y.; Sakaki, T.; Harada, T.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 927. (g) Motesharei, K.; Myles, D. C. *J. Am. Chem. Soc.* **1994**, *116*, 7413. (h) Tecilla, P.; Jubian, V.; Hamilton, A. D. *Tetrahedron* **1995**, *51*, 435. (i) Chin, T.; Gao, Z.; Lelouche, I.; Shin, Y. K.; Purandare, A.; Knapp, S.; Isied, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 12849. (j) Salameh, A. S.; Ghaddar, T.; Isied, S. S. *J. Phys. Org. Chem.* **1999**, *12*, 247. (k) Nabeshima, T.; Takahashi, T.; Hanami, T.; Kikuchi, A.; Kawabe, T.; Yano, Y. *J. Org. Chem.* **1998**, *63*, 3802. (l) Inoue, K.; Ono, Y.; Kanekiyo, Y.; Ishi-i, T.; Yoshihara, K.; Shinkai, S. *J. Org. Chem.* **1999**, *64*, 2933. (m) Ghaddar, T. H.; Castner, E. W.; Isied, S. S. *J. Am. Chem. Soc.* **2000**, *122*, 1233. (n) Rasmussen, B. S.; Elezcano, U.; Skrydstrup, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1723.

(7) For studies using synthetic receptors capable of binding ligands with high association constants via multiple hydrogen bonding, see: (a) Lehn, J.-M. *Supramolecular Chemistry-Concepts and Perspectives*; VCH: Weinheim, 1995. (b) Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; John Wiley and Sons: New York, 2000.

(8) For a few examples on the use of synthetic receptors for synthesis: (a) Rowe, H. L.; Spencer, N.; Philip, D. *Tetrahedron Lett.* **2000**, *41*, 4475. (b) Bassani, D. M.; Darcos, V.; Mahony, S.; Desvergne, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 8795. (c) Bach, T.; Bergmann, H. *J. Am. Chem. Soc.* **2000**, *122*, 11525.

(9) (a) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. (b) Amatore, C.; Jutand, A.; Meyer, G. *Inorg. Chim. Acta* **1998**, *273*, 76. (c) For a review, see: Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*−*180*, 511.

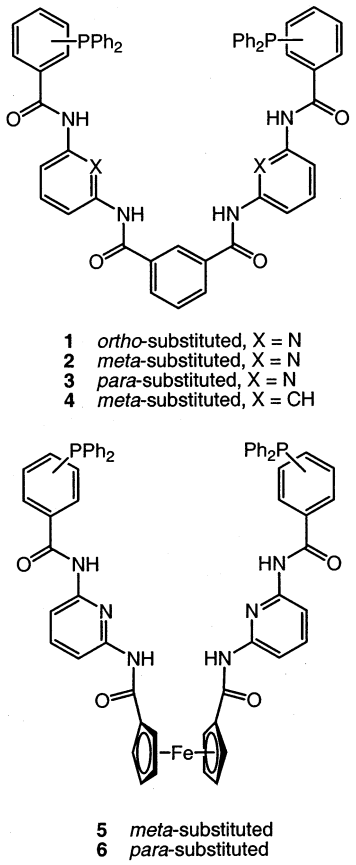
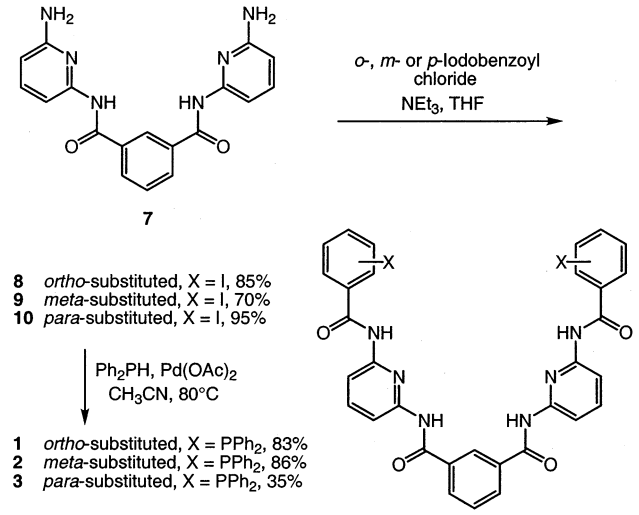


Figure 2. Receptor-containing diphosphines used for this study.

Scheme 1

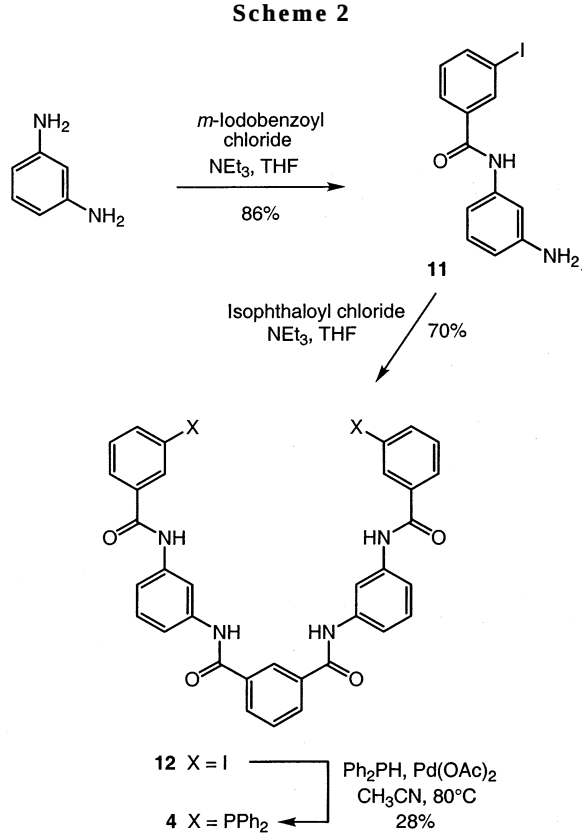


yield obtained for the *para*-substituted ligand **3** could be the result of the particularly low solubility of the diiodide **10** in the reaction conditions employed compared to its counterparts **8** and **9**.

In the subsequent investigation on the applicability of these ligands for promoting the Heck reaction (see section V), a series of similar ligands with small structurial variations were made, to study their effect on the reactivity of the Pd^0-complexes. For example, with

(10) (a) Herd, O.; Hessler, A.; Hingst, M.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69. (b) Bergbreiter, D. A.; Liu, Y.-S.; Furyk, S.; Case, B. L. *Tetrahedron Lett.* **1998**, *39*, 8799.

Scheme 2



ligand **4**, the pyridine rings have been replaced by benzene, and for ligands **5** and **6**, a ferrocene entity bridges the two 2,6-diamidopyridine units.

Adaptation of the same synthetic sequence to **4** as for ligands **1**−**3** proved less rewarding, as the monoacylation of 1,3-diaminobenzene with isophthaloyl chloride as reported for the effective preparation of **7** afforded only a 9% yield of the corresponding diamine. However, by reversing the synthetic sequence as indicated in Scheme 2, access to **4** was more satisfying. Hence, monoacylation of 1,3-diaminobenzene with *m*-iodobenzoyl chloride produced the amide **11** in 88% yield, which was coupled twice to isophthaloyl chloride. In constrast to the diphosphine **2**, ligand **4** proved exceptionally insoluble in both chloroform and THF, which complicated its purification by column chromatography. However, the crude product obtained after introduction of diphenylphosphine proved to be reasonably pure, as assessed by both ^1H and ^{31}P NMR spectroscopy.

Synthesis of the diphosphines **5** and **6** started with the double carboxylation of ferrocene via the dianion intermediate (Scheme 3). Conversion to its diacid chloride and amide formation with diaminopyridine afforded **14** in 66% yield. Subsequent acylation and introduction of diphenylphosphine afforded **5** and **6**.

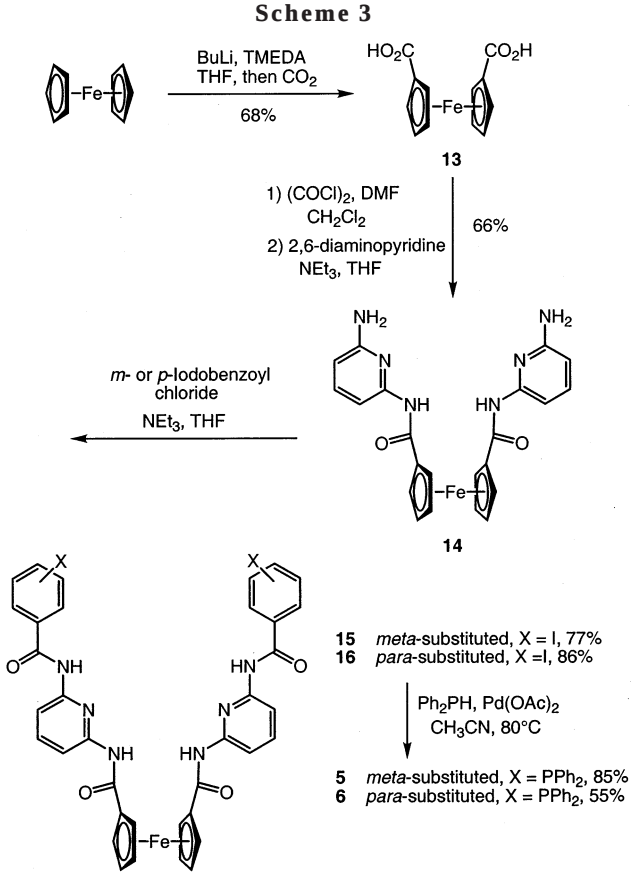
II. Investigation of the Palladium(0) Complexes Formed in Situ Between $Pd(dba)_2$ and the Bidentate Phosphine Ligands by ^{31}P NMR Spectroscopy and/or Cyclic Voltammetry. (a) $Pd(dba)_2$ and Ligand 2. The ability of the synthesized diphosphines to form macrocyclic complexes with Pd^0 was investigated by ^{31}P NMR with solutions of $Pd(dba)_2$ (14 mM) and 1 equiv of the ligand (Table 1).[9] In the event of bidentate complexation, the ^{31}P NMR spectrum will feature two doublets, which is indicative of two nonequivalent

Table 1. ^{31}P NMR Chemical Shifts[a] of Pd^0-Complexes Formed from the Mixture of Pd(dba)$_2$ + P,P and of the Complexes PhPdI(P,P) Generated from the Oxidative Addition with PhI

		P,P	Pd(dba)$_2$ + 1P,P → Pd(dba)(P,P)			PhPdI(P,P)
P,P	solvent	δ_0	δ_1	δ_2	δ_3	δ_4
2	$CDCl_3$	−4.78	23.76 (J_{PP} = 12 Hz) (J_{PP} = 10 Hz)	24.71 (J_{PP} = 12 Hz) (J_{PP} = 10 Hz)		24.15
2	THF	−4.20	24.34 (J_{PP} = 12 Hz) (J_{PP} = 10 Hz)	24.73 (J_{PP} = 12 Hz) (J_{PP} = 10 Hz)		24.37
2	DMF	−4.35	25.40	26.08	27.82[b]	24.03
1	$CDCl_3$	−8.97		22.94 (J_{PP} = 459 Hz)	44.71 (J_{PP} = 459 Hz)	n.m.[c]
1	THF	−8.40	−8.69	26.70[b]	29.84[b]	n.m.[c]
1	DMF	−9.31	−9.29	27.50[b]	31.16[b]	21.09

[a] Determined vs H_3PO_4 at 20 °C. [b] Broad singlet. [c] n.m. = not measured.

Scheme 3



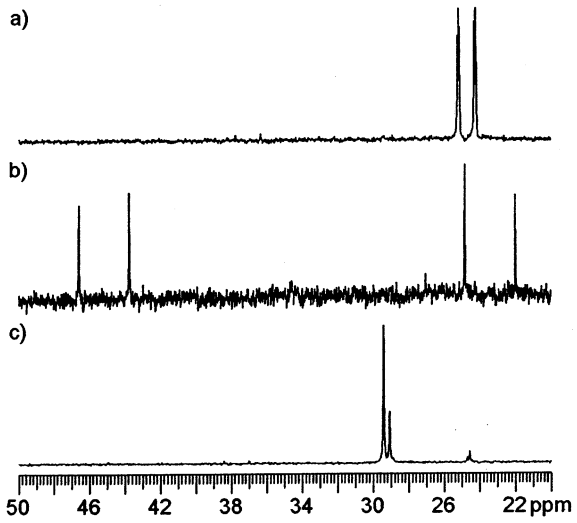


Figure 3. Partial ^{31}P NMR spectrum (162 MHz) in $CDCl_3$: (a) Pd(dba)$_2$ (14 mM) + diphosphine **2** after 10 min, (b) Pd(dba)$_2$ (14 mM) + diphosphine **1** after 24 h, (c) Pd(dba)$_2$ (14 mM) + diphosphine **3** after 24 h.

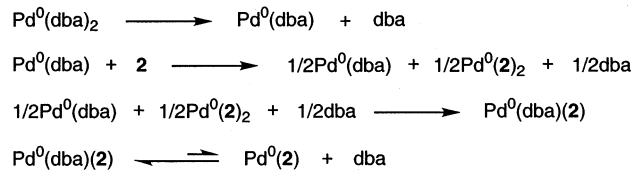
phosphorus compatible with the structure Pd^0(dba)(P,P) in which the dba ligand remains ligated to the Pd^0 center by only one C=C bond, as classically observed with other bidentate P,P ligands.[9a,c] The ^{31}P NMR spectrum of a mixture of a slight excess of ligand **2** with Pd(dba)$_2$ in $CDCl_3$ or THF exhibited after 10 min two double doublets of equal magnitude with coupling constants of approximately 12 and 10 Hz, the magnitude of which is indicative of a *cis*-geometry, which appeared stable even after 11 days (Figure 3a).[11] Macrocyclization by complexation is therefore both fast and efficient considering the formation of a 26-membered cycle. Further evidence for this ring size and not that of a dimeric or trimeric structure was gained from electrospray mass spectroscopy, where a peak corresponding to Pd^0(**2**) + Na^+ with loss of the dba ligand was observed.

Slightly more complicated was the ^{31}P NMR spectrum from an identical experiment in DMF where in addition to two broad singlets at δ_1 = 25.40 and δ_2 = 26.08 ppm of equal intensity representing the *cis*-macrocyclic Pd^0(dba)(**2**) species, a third signal was observed by a singlet at δ_3 = 27.82 ppm, implying the presence of a second complex displaying two equivalent phosphorus. Addition of excess dba (10 equiv) did not perturb the spectrum, thereby excluding the possibility that this peak arises from the formation of Pd^0(**2**), whereby dba has dissociated from the metal center. Exposure of the solution to oxygen or hydrogen peroxide did not produce signals that were comparable to the chemical shift of δ_3.

Addition of 100 equiv of PhI to the three solutions led to the disappearance of the above signals and the formation of a single signal at δ_4 ~24 ppm. Its appearance as a singlet suggests that the formed complex PhPdI(**2**) possesses a *trans*-configuration, as generally observed for monodentate ligands, but which is in contrast to the *cis*-preference previously reported for other bidentate ligands such as dppm, dppe, dppp, dppb, dppf, DIOP, and BINAP. The large ring size and thereby greater flexibility in the macrocyclic complex, PhPdI-

(11) It is difficult to explain the appearance of two double doublets, considering the nature of the Pd^0-complexes. We suggest the possible formation of two closely related dba-containing *cis*-macrocycles, the structures of which are elaborated upon in section IV.

Scheme 4



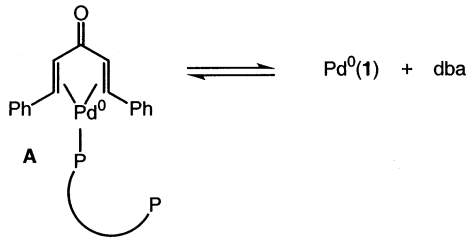
(**2**), compared to similar complexes with other bidentate ligands, could be the main reason for the generation of the thermodynamically more favored *trans*-relationship between the two phosphorus. In DMF, a small byproduct (approximately 5%) was also detected by the two singlets observed at $\delta = -4.99$ and 24.77 ppm, possibly attributed to the complex PhPdI(**2**)$_2$, in which only one of the phosphorus atoms of the ligand is bound to palladium. ^{31}P NMR spectroscopy performed on a 1:1 mixture of PhPdI(PPh_3)$_2$ and **2** indicated the same major product and byproduct as well as free PPh_3 ($\delta = -5.19$ ppm).

The kinetic evolution of the mixture Pd(dba)$_2$ + **2** in THF and DMF was monitored by cyclic voltammetry. When ligand **2** was added to a solution of Pd(dba)$_2$ (2 mM) in DMF (containing *n*-Bu_4NBF_4 0.3 M), two oxidation peaks of almost equal peak current were detected at +0.27 (O_1) and +0.78 V (O_2). After 10 min, the oxidation peak O_1 shifted to a slightly more positive potential of +0.30 V (O'_1), and the oxidation peak current of O_2 was approximately 4 times that of O'_1. This ratio was then constant with time. The oxidation peak O'_1 was plateau-shaped, suggesting the presence of two Pd^0 complexes involved in a fast equilibrium (CE mechanism).[9c] When 10 equiv of dba was added to the solution, only the oxidation peak O_2 was detected, indicating that the two Pd^0 complexes detected at O_2 and O'_1 were involved in an equilibrium with dba. Pd^0(dba)(**2**) formed at longer time (characterized by ^{31}P NMR spectroscopy, Table 1, and by the oxidation peak O_2) is then involved in an equilibrium with Pd^0(**2**) (oxidation peak O'_1) and dba (Scheme 4, last reaction). The complex Pd^0(**2**) could not be characterized by ^{31}P NMR spectroscopy (vide supra), suggesting that its thermodynamic concentration in the equilibrium with dba and Pd^0(dba)(**2**) (Scheme 4, last reaction) was very low. However, Pd^0(**2**) was detected by cyclic voltammetry. Indeed, its oxidation at O'_1 resulted in a shift of the equilibrium toward the formation of Pd^0(**2**) due to its consumption in the diffusion layer (CE mechanism).[9c] The oxidation current of Pd^0(**2**) at O'_1 reflected then its dynamic concentration. A 14-electron Pd^0 complex ligated to a bidentate P,P ligand[9a] as in Pd^0(**2**) is then detected and characterized for the first time by cyclic voltammetry performed in DMF.

As reported for other bidentate ligands,[9a] the formation of Pd^0(dba)(**2**) proceeds first via the fast formation of Pd^0(**2**)$_2$ generated at short times (t < 10 min, oxidation peak O_1, not detectable in ^{31}P NMR spectroscopy) (Scheme 4).

The oxidation peaks of Pd^0(dba)(**2**) and Pd^0(**2**) disappeared upon addition of 5 equiv of PhI, and a new oxidation peak appeared at +0.51 V, which was assigned to PhPdI(**2**), characterized by ^{31}P NMR spectroscopy (vide supra, Table 1). The location of the oxidation peak of PhPdI(**2**) between those of Pd^0(dba)(**2**) and Pd^0(**2**) excluded the monitoring of the kinetics of the oxidative addition by amperometry.[9a] UV spectroscopy was the best adapted and selected technique (vide infra) for this purpose.[9b]

Scheme 5



In THF, the mechanism of the formation of Pd^0(dba)(**2**) looked very similar (oxidation potentials of O_1 and O_2 at +0.34 and +0.83 V). However, the oxidation peak of Pd^0(**2**) was not detected. This suggests that the equilibrium between Pd^0(dba)(**2**), Pd^0(**2**), and dba (last reaction of Scheme 4) lies less in favor of Pd^0(**2**) in THF than in DMF, or is less labile in THF than in DMF with some kinetic consequences for the oxidative addition (vide infra).

(b) Pd(dba)$_2$ and Ligand 1. The *ortho*-substituted ligand **1** produced a macrocyclic *trans*-Pd^0(dba)(**1**) complex in $CDCl_3$ after 24 h of mixing with Pd(dba)$_2$, as observed by the formation of two doublets at $\delta_1 = 22.94$ and $\delta_2 = 44.71$ ppm with a large geminal *trans*-coupling constant of 459 Hz (Table 1, Figure 3b).[12] However, in DMF, three signals were detected, 1 h after mixing Pd(dba)$_2$ and 1 equiv of **1** and remained unchanged from 1 to 24 h. Two singlets of equal integration were observed at −9.21 ppm (δ_1) and 31.16 ppm (δ_3) (Table 1), and a third singlet was seen at 27.5 ppm (δ_2). A similar spectrum was obtained in THF (Table 1). Both the close vicinity of δ_1 when compared to the signal of the free ligand (Table 1) and the same intregration for δ_1 and δ_3 suggest that these two signals characterize a Pd^0 complex ligated by only one phosphorus of the ligand **1**, the second one being free. This complex did not exhibit any absorption band around 390 nm, as is always observed for the Pd^0(η^2-dba)(P,P) complex.[9c] Consequently, a structure such as **A** is proposed (Scheme 5) with a bis-ligation of dba, leading to a 16-electron complex, compatible with the ^{31}P NMR and UV spectroscopy data. The singlet at δ_2 characterizes a second complex displaying two equivalent phosphorus ligated to the Pd^0 center (Scheme 5) as in Pd^0(**1**). The coordination of the Pd^0 center by DMF (or THF) would enhance the stability of such a complex.

Complexes **A** and Pd^0(**1**) are involved in an equilibrium with dba (Scheme 5) since the ratio **A**/Pd^0(**1**) (determined by the integration of the corresponding ^{31}P NMR signals describe above) increased upon addition of dba to the 1:1 mixture of Pd(dba)$_2$ and **1** in DMF.

Upon addition of 100 equiv of PhI to the DMF solution, all three signals disappeared with the evolution of a new singlet at $\delta_4 = 21.09$ ppm ascribed to *trans*-PhPdI(**1**), as was done for the diphosphine **2**. This is also in favor of an equilibrium between complexes **A** and Pd^0(**1**) drawn by the oxidative addition of PhI to one (or to both) Pd^0 complex(es). A single macrocyclic Ph-Pd^{II}

(12) (a) Fahey, D. R. *J. Organomet. Chem.* **1973**, *57*, 385. (b) Ogilvie, F. B.; Jenkins, J. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 1916.

complex is indeed generated. Again, the *trans*-relationship between the two phosphorus is attributed to the large flexibility of the macrocyclic ring in comparison to other well-known bidentate ligands.

The two Pd^0 complexes described in Scheme 5 have been characterized by ^{31}P NMR and UV spectroscopy at long times, i.e., 1 h after mixing $Pd(dba)_2$ and 1 equiv of **1** (vide supra). The solution could be characterized at shorter times by UV spectroscopy. An absorption band was observed at 395 nm just after mixing, which usually characterizes a Pd^0 complex monoligated by dba, such as in Pd^0(dba)(**1**). However, such a complex was not stable since the absorbance at 395 nm continuously decreased with time. This suggests that the formation of complex **A** detected after 1 h reaction (Scheme 5) proceeds via the initial formation of Pd^0(dba)(**1**).

(c) Pd(dba)$_2$ and Ligands 3−6. Subjecting the *para*-isomer **3** to $Pd(dba)_2$ in $CDCl_3$ afforded a more complicated mixture upon complexation to Pd^0 according to the ^{31}P NMR spectrum, even when left standing over longer periods of time (Figure 3c). Hence, further work with this ligand was abandoned. On the other hand, ligands **4** and **6** produced more consistent results. Although these diphosphines proved to be sparingly soluble in either THF or $CDCl_3$, both afforded macrocyclic *cis*-complexes corresponding to Pd^0(dba)(**4**) or Pd^0(dba)(**6**) upon mixing with $Pd(dba)_2$ in DMF, as revealed by a set of small doublets at $\delta = 25.50$ and 26.40 ppm and $\delta = 27.24$ and 28.96 ppm, respectively A less well-defined system arose with the ligand **5**, which upon mixing with $Pd(dba)_2$ in $CDCl_3$ produced two signals as a sharp and broad singlet at $\delta = 24.30$ and 31.00 ppm, respectively, the origins of which were not pursued. In any event, the macrocyclization was supported by mass spectroscopy (ES), where a peak for Pd^0(**5**) + Na^+ was obtained. It is interesting to note the contrast in complexation between the *meta*- and *para*-substituted pairs of ligands, **2** and **3**, with **5** and **6**, which most likely reflect the differences in geometry and cavity size of the receptor complexes.

III. Rate Studies on the Oxidative Addition of PhI with the Palladium(0) Complex Formed in Situ between Pd(dba)$_2$ and the Bidentate Phosphine Ligand 2. A previous investigation of the reactivity of Pd^0 complexes generated from $Pd^0(dba)_2$ and a bidentate P,P ligand (1 equiv) in the oxidative addition of PhI in THF has established that both Pd^0(dba)(P,P) and Pd^0(P,P) were reactive but that Pd^0(P,P) was considerably more reactive than Pd^0(dba)(P,P).[9a,c] The overall reaction was slower in the presence of dba, by decreasing the concentration of the more reactive Pd^0(P,P).

The UV spectrum of a solution in DMF of Pd^0(dba)(**2**) formed in situ from $Pd^0(dba)_2$ (1 mM) and **2** (1 mM) exhibited an absorption band at 392 nm, characteristic of the dba monoligated to the Pd^0 center in Pd^0(dba)(**2**).[9b,c] The absorbance remained unchanged after addition of dba (10 equiv). Addition of PhI in excess to the UV cell at 25 °C resulted in the decay of the absorbance of Pd^0(dba)(**2**) versus time. The kinetics of the oxidative addition was then monitored by UV spectroscopy. Two reactions were first investigated with PhI (10 equiv) in the absence and then in the persence of added dba (10 equiv). The reaction was slower in the presence of added dba. The observed rate constants k_{obs} of the overall reaction are displayed in Figure 4. This deaccelerating effect of dba establishes that Pd^0(**2**) is the more reactive species. The reaction order in PhI was determined in the presence of added dba (10 equiv) by plotting the variation of k_{obs} versus the PhI concentration. A straight line was obtained, which went through origin (Figure 4), in contrast to what was observed with other P,P ligands.[9a,c] This established that the reaction order in PhI is +1 and that Pd^0(**2**) is the unique reactive species (Scheme 6). $k_{obs} = Kk$[PhI]/[dba]. $Kk = 0.008$ s^{-1}.

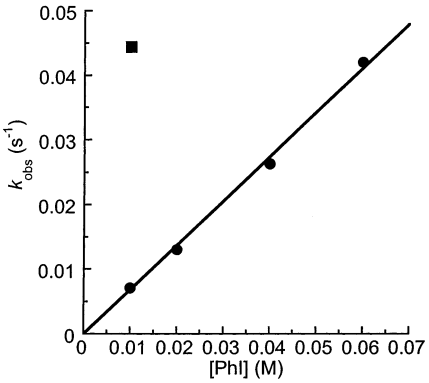
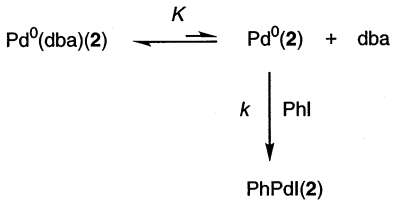


Figure 4. Kinetics of the oxidative addition of PhI to the Pd^0 generated from $Pd^0(dba)_2$ (1 mM) and **2** (1 mM) in DMF at 25 °C as monitored by UV spectroscopy at 392 nm. Plot of k_{obs} versus PhI concentration: (■) in the absence of added dba; (●) in the presence of added dba (10 equiv). $k_{obs} = Kk$[PhI]/[dba], slope = 0.685, $r = 0.998$.

Scheme 6



This oxidative addition was considerably slower in THF than in DMF and consequently was not quantified. This means that the concentration of Pd^0(**2**) was considerably higher in DMF than in THF. This is consistent with the observation of Pd^0(**2**) by cyclic voltammetry in DMF but not in THF (vide supra). Interestingly, this solvent effect was not observed for the similar reaction with triphenylphosphine as the ligand.[13]

The effect of barbital on the kinetics of the oxidative addition was tested. The rate constant was not significantly affected upon addition of barbital (1 equiv), suggesting that this molecule was not incorporated inside the ligand of the Pd^0-complex (vide infra).

IV. Determination of Binding Constants of Ligands 1−3, 5, and 6 with Barbital and Binding Studies with the Pd^0(dba)(2) Complex. Titration experiments were performed in $CDCl_3$ where complexation was expected to be greatest for the three solvents examined, measuring the typical large downfield shifts of the host's amide NH's (approximately 1.5 ppm) as a function of the barbiturate concentration. From the titration curve, the association constant (K_a) can there-

(13) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168.

Table 2. Binding Constants Determined for Barbital with Ligands 1−3, 5, and 6

receptor	K_a (M^{-1})[a]
1	7900
2	5100
3	7100
5	700
6	290

fore be extracted according to that previously reported. Initial experiments with ligands **1**−**3** and barbital afforded association constants in the range expected for open receptors of this type (Table 2). Less exceptional were the ligands **5** and **6**, displaying K_a's of less than 1000 M^{-1}, being indicative of barbital binding to only a single diaminopyridine unit of the receptor. This was somewhat unexpected, as simple molecular modeling revealed that a particular conformer of these hosts could be located with a sufficient cavity size for the binding of the barbiturate guests.

Of all the ligands tested, only the diphosphine **2** appeared suitable for further binding studies due to both its fast complexation with $Pd^0(dba)_2$, being independent of the three solvents examined, and its tendancy for *cis*-complex formation, which is a necessary requirement in the following Heck reactions. Whereas the Pd^0(dba)-(**2**) complex was initially studied by ^{31}P NMR, quite surprisingly, its ^1H NMR spectrum in $CDCl_3$ displayed some interesting hydrogen-bonding features in comparison to the uncomplexed **2**. For example, in **2** alone, the four amide protons are observed as two broad singlets at δ = 8.52 (2H) and 8.33 (2H) ppm. Upon treatment with $Pd(dba)_2$, these NH signals display a large downfield shift in addition to being split up into four sharp singlets representing one proton each (δ = 11.20, 10.34, 9.75, and 9.65 ppm), suggesting the involvement of some form of hydrogen-bonding event with these protons. Evidence for this process being intramolecular was gained by performing dilution experiments, resulting in the same large chemical shifts.

On the addition of excess barbital, no change was observed in the NH chemical shifts in either the Pd^0-(dba)(**2**) complex or barbital, implying that complexation cannot be made. Furthermore, addition of $Pd(dba)_2$ to a solution of the barbital:**2** system led to quick formation of Pd^0(dba)(**2**) and free barbital, indicating that complexation of Pd^0 to the diphosphine **2** is stronger than the six-point hydrogen-bonding complex between the host and guest. Hence, it appears that the binding of **2** to Pd^0 possibly results in either a considerable contraction of the cavity of the ligand or a pertubation from planarity required for the inclusion of the guest. The above chemical shifts observed for the amide protons upon complexation indicate some form of internal hydrogen bonding. We speculate as to whether the origins of these shifts are due to the tautomerization of one of the two terminal amides leading to the presence of tautomers **17a** and **17b**, as illustrated in Figure 5, where hydrogen bonding is favored to the pyridyl nitrogen. The driving force for this tautomerization could be the obtainment of more optimal Pd−P bond lengths and the P−Pd−P angle for the complexation of **2** to $Pd(dba)_2$. As discussed in section IIa, two sets of signals appear in the ^{31}P NMR spectrum, suggesting the possibility of two closely related *cis*-complexes formed

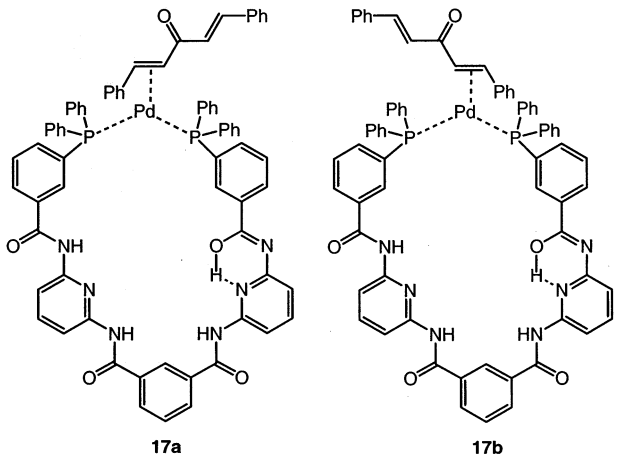


Figure 5. Proposed structure of Pd(dba)(**2**) in $CDCl_3$ and THF.

between **2** and $Pd(dba)_2$. The existence of the structures **17a** and **17b** provides a plausible explanation for this observation.[14]

Interestingly, when the ^1H NMR spectrum of the Pd^0(**6**)(dba) complex was examined, no significant downfield shifts were noted for the four amide protons, which may be consistent with the smaller cavity for this receptor and hence being more appropriate for the complexation to Pd^0.

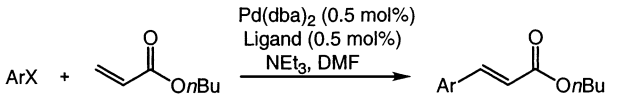
In any event, it appears that for all cases examined the barbiturate-binding site in the receptor is significantly perturbed upon complexation to palladium(0), thereby excluding the possibility for recognition of the barbiturate substrates. Diphosphines with larger and/or less rigid linkers are required in order that a particular conformer of the macrocyclic palladium(0) complex may be adapted to bind the barbiturate guest.

V. Heck Reaction Studies with the Ligands 1, 2, and 4−6. Finally, a small study was undertaken to examine whether this class of macrocyclic diphosphine-palladium(0) complexes could indeed promote the Heck reaction. These reactions were carried out with various aryl halides and *n*-butyl acrylate with 1:1 mixtures of the synthesized diphosphines and $Pd(dba)_2$ using triethylamine as the stoichiometric base. As the rates of oxidative addition were found to be highest in DMF, all reactions were performed in this solvent. The results were compared to those employing PPh_3 and are shown Table 3. Whereas PPh_3 and ligand **1** could only advance the reaction with phenyl iodide at 60 °C (entries 1−4), it was interesting to observe the aptitude of ligand **2** to promote the same reaction at room temperature (entry 6). More importantly, the $Pd(dba)_2$:**2** system exhibited sufficient catalytic activity for the same coupling with both an activated aryl bromide at 60 °C (entry 7) and an unactivated aryl bromide such as phenyl bromide at 120 °C (entry 8), providing in the latter case *n*-butyl cinnamate in an 85% isolated yield. With an activated aryl chloride the reaction proved also possible but required longer reaction times (entry 9). A product yield of 13% was obtained after 42 h at 120 °C along with recovered starting material.

Last, a few structural modifications were made on ligand **2** in order to examine what effect such changes

(14) We have so far not been successful in crystallizing the Pd^0-complexes with the diphosphine ligands **1**−**6**.

Table 3. Pd-Catalyzed Heck Reaction of Aryl Halides with *n*-Butyl Acrylate[a]



entry	ArX	ligand	temp (°C)	rxn time (h)	yield (%)[b]
1	PhI	PPh_3[c]	60	24	88
2	PhI	PPh_3[c]	20	48	*d*
3	PhI	**1**	60	24	89
4	PhI	**1**	20	48	*d*
5	PhI	**2**	60	3	87
6	PhI	**2**	20	30	82
7	(*p*-Ac)PhBr	**2**	60	24	48[e]
8	PhBr	**2**	120	24	85
9	(*p*-Ac)PhCl	**2**	120	42	13[e]
10	PhI	**4**	20	30	*d*
11	PhI	**5**	60	24	85
12	PhI	**5**	20	30	*d*
13	PhI	**6**	60	7	87
14	PhI	**6**	20	44	10
15	PhBr	**6**	120	24	47

[a] Reaction conditions: aryl halide (2.5 mmol), *n*-butyl acrylate (2.5 mmol), NEt_3 (2.75 mmol). [b] Isolated yield after column chromatography. [c] 1 mol % phosphine used. [d] No product detected according to TLC analysis. [e] ^1H NMR spectrum of the crude product mixture revealed the remaining material to be unreacted starting material.

would evoke on the activity of the palladium catalyst. However, replacement of the pyridyl rings with phenyl, as in the diphosphine **4**, or the isophthaloyl group with a ferrocene unit (diphosphine **5**) led only to ligands revealing a outcome comparable to PPh_3 in the same Heck reaction with phenyl iodide (Table 3, entries 10−12). The *para*-ligand **6** revealed only a slight improvement but still not quite as effective as the ligand **2** (entries 13−15).

These results establish that a Heck reaction performed from an aryl halide and an alkene containing an electron-withdrawing group may be efficiently catalyzed by a Pd ligated to a bibentate bisphosphine ligand (P,P), which are usually considered to be inappropriate[1b,4b] for such purposes due to the difficult deligation of one P in *cis*-ArPdX(P,P), required for the coordination of the olefin. However, in the present case, a *trans*-ArPdX(**2**) is formed in the oxidative addition as monitored by ^{31}P NMR. This suggests that the two phosphorus are less close to each other than in a *cis*-complex and that the deligation of one P should then be easier in this *trans*-complex than in a *cis*-complex.

Conclusion

In conclusion, we have prepared a series of diphosphine ligands possessing a barbiturate-binding receptor, where some were found to efficiently form macrocyclic bisphosphine palladium(0) complexes even though a 26-membered cycle is created. In one case, with ligand **2**, a significant solvent effect was observed for the oxidative addition of the Pd^0 complexes with phenyl iodide. Although the exact cause for this effect has not been deduced, it could be related to distinct conformational or tautomer preferences of the metal-containing macrocycle in the solvents tested, thereby giving rise to potentially different bite angles of the bidentate ligand to the metal center. Higher concentrations of the species responsible for the oxidative addition, namely, Pd(P,P)-(solvent), in the more ligating solvents such as DMF could also explain this effect.

Whereas the receptors possessing an isophthaloyl connector bind barbital with affinities corresponding to those of the previously reported open receptors, there are considerable deviations from the preferred conformer of the receptor for binding barbital upon complexation with $Pd(dba)_2$. More flexible linkers in the receptor are therefore required in order for these Pd^0 complexes to bind barbiturate guests. Such work is currently ongoing and will be reported in due course. Finally, these complexes were found to promote the Heck reaction with reactivities similar to triphenylphosphine. In one case, with Pd^0(dba)(**2**), a higher reactivity was noted.

Experimental Section

General Considerations. Unless otherwise stated, all reactions were carried out under argon. Dichloromethane was freshly distilled over P_2O_5, THF and diethyl ether from sodium/benzophenone, and acetonitrile from calcium hydride, whereas DMF was distilled under reduced pressure and stored over 4 Å molecular sieves. Reactions were monitored by thin-layer chromatography (TLC) analysis on Kieselgel 60 F_{254} (Merck). NMR spectra (^1H at 200 MHz and ^{13}C at 50 MHz) were recorded on a Varian Gemini 2000 spectrometer. Chemical shifts (δ in ppm) are given relative to those for Me_4Si. ^{31}P NMR spectra were recorded on a Bruker or Varian spectrometer (162 MHz) using H_3PO_4 as an external reference. ES mass spectra were recorded with a Micromass LC-TOF instrument. UV spectroscopy was recorded on a Beckman DU 7400 spectrometer. The electrochemical setup and electrochemical procedure for cyclic voltammetry and the UV studies were performed as previously published.[9] The complexation studies and monitoring by ^{31}P NMR were carried out as previously reported.[9] The ^1H NMR binding studies were performed employing standard methods.[7] The diamine **7** and $Pd(dba)_2$ were prepared according to published procedures.[5,9a]

***N,N′*-Bis[6-(2-iodobenzoylamino)pyridin-2-yl]isophthalamide (8). General Procedure for the Benzoylation of the Diamines 7 and 14.** Oxalyl chloride (1.75 mL, 20.2 mmol) and a catalytic amount of DMF (15 μL) were added to a solution of 2-iodobenzoic acid (2.12 g, 8.54 mmol) in CH_2Cl_2 (30 mL). After stirring for 1 h at 20 °C, the solvent was removed under reduced pressure, affording the crude benzoyl chloride, which was redissolved in THF (10 mL). To this solution were added the diamine **7** (686 mg, 1.97 mmol) and triethylamine (1.1 mL, 7.88 mmol) in THF (50 mL). An additional 20 mL of THF was added, and the reaction mixture was stirred at 20 °C for 18 h. After removal of the solvent under reduced pressure, ethyl acetate was added and the organic phase was washed with water. The aqueous phase was extracted once with ethyl acetate, and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness under vacuum. Column chromatography (ethyl acetate/CH_2Cl_2, 1:9) afforded **8** as light yellow crystals (1.35 g, 85% yield): mp 231−235 °C; ^1H NMR (DMSO-d_6) δ 10.72 (s, 2H, CONH), 10.60 (s, 2H, CONH), 8.54 (s, 1H, Ar), 8.15 (dd, 2H, J = 7.8, 1.4 Hz, Ar), 7.92−7.89 (m, 8H, Ar), 7.66 (t, 1H, J = 7.8 Hz, Ar), 7.47−7.42 (m, 4 H, Ar), 7.25−7.17 (m, 2H, Ar); ^{13}C NMR (DMSO-d_6) δ 169.1 (2C), 166.3 (2C), 151.3 (2C), 151.1 (2C), 143.4 (2C), 141.0 (2C), 139.8 (2C), 134.9 (2C), 132.3 (2C), 131.9 (2C), 129.6, 128.9 (4C), 128.3, 112.1 (2C), 111.8 (2C), 95.3 (2C); IR (KBr) ν 3264, 1677, 1583, 1505, 1446, 1300 cm^{-1}; MS (ES) calcd for $C_{32}H_{22}I_2N_6O_2$ 831.0 (M + Na), found 831.1.

***N,N′*-Bis[6-(2-{diphenylphoshanyl}benzoylamino)pyridin-2-yl]isophthalamide (1). General Procedure for the Introduction of Diphenylphosphine.** Triethylamine (733

μL, 5.26 mmol), Ph_2PH (322 μL, 1.85 mmol), and $Pd(OAc)_2$ (1.0 mL from a solution of 10.5 mg of $Pd(OAc)_2$ in 5 mL of CH_3CN, 9.4 μmol) were added to a solution of the diiodide **8** (709 mg, 0.88 mmol) in CH_3CN (15 mL). The reaction mixture was warmed to 85 °C in a closed tube and stirred for 2 h. Upon completion of the reaction, a clear red-colored solution is obtained, which was cooled and then poured into a separatory flask with CH_2Cl_2. The organic phase was washed with a saturated solution of NH_4Cl, dried (Na_2SO_4), and then evaporated to dryness under vacuum. Column chromatography (ethyl acetate/CH_2Cl_2, 1:19) afforded **1** as light yellow crystals (811 mg, 83% yield): mp 184−186 °C; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H, Ar), 8.42 (br s, 2H, CONH), 8.24 (br s, 2H, CONH), 8.14 (br d, 2H, J = 8.4 Hz, Ar), 8.05 (d, 2 H, J = 8.4 Hz, Ar), 7.88 (d, 2H, J = 8.4 Hz, Ar), 7.74−7.66 (m, 5H, Ar), 7.42−7.26 (m, 24H, Ar), 7.05−7.02 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 167.7 (2C), 164.9 (2C), 149.8 (2C) 149.7 (2C), 140.8 (d, 2C, J_{CP} = 24.5 Hz), 140.5 (2C), 137.0 (d, 2C, J_{CP} = 20.1 Hz), 136.6 (d, 4C, J_{CP} = 9.0 Hz), 134.6 (2C), 134.5 (d, 2C, J_{CP} = 5.7 Hz), 134.1 (d, 8C, J_{CP} = 20.1 Hz), 131.8 (2C), 130.9 (2C), 129.3 (2C), 129.2 (4C), 128.8 (d, 8C, J_{CP} = 7.2 Hz), 128.1 (d, 2C, J_{CP} = 4.7 Hz), 125.8 (2C), 110.8 (2C) 110.5 (2C); ^{31}P NMR ($CDCl_3$) δ −8.97; IR (KBr) ν 3394, 1685, 1585, 1501, 1446, 1302 cm^{-1}; MS (ES) calcd for $C_{56}H_{42}N_6O_4P_2$ 947.3 (M + Na), found 947.6.

***N,N′*-Bis[6-(3-iodobenzoylamino)pyridin-2-yl]isophthalamide (9).** The diiodide **9** was prepared according to the general procedure outlined for **8**, with the following quantities: 3-iodobenzoic acid (1.25 g, 5.04 mmol) in CH_2Cl_2 (25 mL), oxalyl chloride (1.75 mL, 20.2 mmol), diamine **7** (729 mg, 2.09 mmol), and triethylamine (1.2 mL, 8.36 mmol) in THF (40 mL). Column chromatography (ethyl acetate/CH_2Cl_2, 1:9) afforded **9** as colorless crystals (1.18 g, 70% yield): mp 272−275 °C; ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 4H, CONH), 8.51 (s, 1H, Ar), 8.24 (dd, 2H, J = 1.6, 1.6 Hz, Ar), 8.11 (dd, 2 H, J = 7.8 Hz, 1.4 Hz, Ar), 7.92−7.73 (m, 10 H, Ar), 7.62 (t, 1H, J = 7.8 Hz, Ar), 7.23 (t, 2 H, J = 7.8 Hz, Ar); ^{13}C NMR (DMSO-d_6) δ 166.1 (2C), 165.2 (2C), 151.2, 151.1 (4C), 141.3 (2C), 141.0 (2C), 137.2 (2C), 136.9 (2C), 134.9 (2C), 132.3 (2C), 131.4 (2C), 128.1 (4C), 112.5 (2C) 112.1 (2C), 95.55 (2C); IR (KBr) ν 3286, 1652, 1588, 1516, 1447, 1306 cm^{-1}; MS (ES) calcd for $C_{32}H_{22}I_2N_6O_2$ 831.0 (M + Na), found 831.1.

***N,N′*-Bis[6-(3-{diphenylphoshanyl}benzoylamino)pyridin-2-yl]isophthalamide (2).** The bisphosphine **2** was prepared according to the general procedure outlined for **1**, with the following quantities: diiodide **9** (150 mg, 0.19 mmol) in CH_3CN (3.5 mL), triethylamine (155 μL, 1.11 mmol), Ph_2PH (68 μL, 0.39 mmol), and $Pd(OAc)_2$ (204 μL from a solution of 10.2 mg of $Pd(OAc)_2$ dissolved in 5 mL of CH_3CN, 1.9 μmol). Column chromatography (ethyl acetate/CH_2Cl_2, 1:19) afforded **2** as colorless crystals (148 mg, 86% yield): mp 174−176 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (br s, 2H, CONH), 8.46 (br s, 1H, Ar), 8.33 (br s, 2H, CONH), 8.09−8.04 (m, 6H, Ar), 7.93 (br d, 2H, J = 8.4 Hz, Ar), 7.84−7.82 (m, 2H, Ar), 7.76 (t, 2H, J = 8.2 Hz, Ar), 7.59 (t, 1H, J = 7.8 Hz, Ar), 7.43−7.38 (m, 4H, Ar), 7.34−7.26 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$) δ 165.7 (2C), 164.9 (2C), 149.9 (2C) 149.6 (2C), 140.9 (2C), 139.2 (d, 2C, J_{CP} = 13.6 Hz), 137.2 (d, 2C, J_{CP} = 13.6 Hz), 136.3 (d, 4C, J_{CP} = 10.4 Hz), 134.6 (2C), 134.4 (d, 2C, J_{CP} = 7.6 Hz), 134.0 (d, 8C, J_{CP} = 19.8 Hz), 132.9 (d, 2C, J_{CP} = 19.8 Hz), 131.3 (2C), 129.4 (d, 2C, J_{CP} = 19.8 Hz), 129.3 (4C), 128.9 (d, 8C, J_{CP} = 7.2 Hz), 127.7 (3C), 126.1, 110.7 (2C) 110.4 (4C); ^{31}P NMR ($CDCl_3$): δ −4.78; IR (KBr) ν 3277, 1685, 1586, 1507, 1447, 1299 cm^{-1}; MS (ES) calcd for $C_{56}H_{42}N_6O_4P_2$ 947.3 (M + Na), found 947.7.

***N,N′*-Bis[6-(4-iodobenzoylamino)pyridin-2-yl]isophthalamide (10).** The diiodide **10** was prepared according to the general procedure outlined for **8**, with the following quantities: 4-iodobenzoic acid (1.19 g, 4.80 mmol) in CH_2Cl_2 (25 mL), oxalyl chloride (1.70 mL, 19.2 mmol), diamine **7** (528 mg, 1.52 mmol), and triethylamine (846 μL, 6.07 mmol) in THF (50 mL). The product was only slightly soluble in ethyl acetate; hence after extraction several times with ethyl acetate followed by combining the organic phases, a precipitate was obtained. This was filtered and washed with cold ethyl acetate, affording crude **10** as a light brown powder (1.23 g, 95%): mp 282−284 °C; ^{1}H NMR (DMSO-d_6) δ 10.56 (s, 2H, CONH), 10.49 (s, 2H, CONH), 8.50 (s, 1H, Ar), 8.10 (dd, 2H, J = 7.8, 1.4 Hz, Ar), 7.87−7.58 (m, Ar); ^{13}C NMR (DMSO-d_6) δ 166.1 (4C), 151.2 (2C) 151.1 (2C), 141.0 (2C), 138.4 (2C), 138.2 (2C), 134.9 (2C), 134.3 (4C), 131.9 (4C), 130.6 (2C), 112.4 (2C), 112.0 (2C), 100.8 (2C); IR (KBr) ν 3293, 1782, 1652, 1584, 1517, 1456, 1307 cm^{-1}; MS (ES) calcd for $C_{32}H_{22}I_2N_6O_2$ 831.0 (M + Na), found 831.0.

***N,N′*-Bis[6-(4-{diphenylphoshanyl}benzoylamino)pyridin-2-yl]isophthalamide (3).** The bisphosphine **3** was prepared according to the general procedure outlined for **1**, with the following quantities: diiodide **10** (294 mg, 0.36 mmol) in CH_3CN (1.5 mL), triethylamine (304 μL, 2.18 mmol), Ph_2PH (132 μL, 0.76 mmol), and $Pd(OAc)_2$ (499 μL from a solution of 8.2 mg of $Pd(OAc)_2$ in 5 mL of CH_3CN, 3.6 μmol). A reaction time of 20 h was allowed due to the low solubility of the diiodide. Column chromatography (ethyl acetate/CH_2Cl_2, 1:19) afforded **3** as colorless crystals (118 mg, 35% yield): mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (br s, 2H, CONH), 8.43 (m, 3H, Ar + CONH), 8.08 (d, 2H, J = 8.2 Hz, Ar), 8.03 (d, 4H, J = 7.6 Hz, Ar), 7.81 (d, 4H, J = 7.6 Hz, Ar), 7.75 (t, 2H, J = 8.2 Hz, Ar), 7.55 (t, 1H, J = 8.2 Hz, Ar), 7.38−7.30 (m, 24H, Ar); ^{13}C NMR ($CDCl_3$) δ 165.6 (2C), 164.7 (2C), 150.0 (2C), 149.6 (4C), 143.8 (d, 2C, J_{CP} = 14.3 Hz), 141.0 (2C), 136.2 (d, 4C, J_{CP} = 10.4 Hz), 134.6 (2C), 134.1 (d, 8C, J_{CP} = 20.1 Hz), 133.9 (2C), 133.7 (d, 4C, J_{CP} = 19 Hz), 131.1 (2C), 129.4 (4C), 128.9 (d, 8C, J_{CP} = 7.2 Hz), 127.3 (d, 4C, J_{CP} = 6.1 Hz), 126.2 (2C), 110.7 (2C), 110.3 (4C); ^{31}P NMR ($CDCl_3$) δ −4.75; IR (KBr) ν 3411, 1686, 1586, 1508, 1446, 1301 cm^{-1}; MS (ES) calcd for $C_{56}H_{42}N_6O_4P_2$ 947.3 (M + Na), found 947.6.

***N*-(3-Aminophenyl)-3-iodobenzamide (11).** Oxalyl chloride (0.40 mL, 4.59 mmol) and a catalytic amount of DMF (15 μL) were added to a solution of 3-iodobenzoic acid (250 mg, 1.02 mmol) in CH_2Cl_2 (20 mL). After stirring for 1 h at 20 °C, the solvent was removed under reduced pressure, affording the crude benzoyl chloride, which was redissolved in THF (10 mL). To this solution was added the *m*-diaminobenzene (170 mg, 0.79 mmol) and triethylamine (0.29 mL, 2.62 mmol) in THF (20 mL). The reaction mixture was stirred at 20 °C for 70 h. After removal of the solvent under reduced pressure, ethyl acetate was added and the organic phase was washed with water. The aqueous phase was extracted once with ethyl acetate, and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness under vacuum. Column chromatography (ethyl acetate/pentane, 1:2) afforded **11** as a colorless solid (240 mg, 88% yield): ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1H, CONH), 8.25 (t, 1H, J = 1,6 Hz, Ar), 7.92 (dd, 2H, J = 1.8, 7.8 Hz, Ar), 7.31 (t, 1H, J = 7,8 Hz, Ar), 7.08 (t, 1H, J = 1,8 Hz, Ar), 6.97 (t, 1H, J = 7,8 Hz, Ar), 6.86 (dt, 1H, J = 8.0, 1.2 Hz, Ar), 6.32 (dt, 1H, J = 7.8, 1.2 Hz, Ar), 5.10 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ 164.5, 149.8, 140.7, 140.3, 138.1, 136.7, 131.3, 129.7, 127.9, 110.8, 109.2, 106.9, 95.5; IR (KBr) ν 3448, 3354, 3239, 1648, 1610, 1546, 1494, 1441, 1327 cm^{-1}; HR-MS (ES) calcd for $C_{13}H_{11}N_2OI$ 360.9814 (M + Na), found 360.9815.

***N,N′*-Bis[3-(3-iodobenzoylamino)phenyl)isophthalamide (12).** Triethylamine (50 μL, 0.36 mmol) and isophthaloyl chloride (24 mg, 0.12 mmol) dissolved in THF (5 mL) were added to a solution of the amine **11** (91 mg, 0.27 mmol) in THF (25 mL). After stirring for 20 h at 20 °C, the solvent was removed under reduced pressure. Water was added, and the solid obtained was filtered and washed with water and then ethyl acetate. This afforded the crude diiodide **12** as a colorless powder (68 mg, 70% yield), which was sufficiently pure for the next step: ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 2H, CONH), 10.40 (s, 2H, CONH), 8.54 (s, 1H, Ar), 8.35 (t, 2H, J = 1.4 Hz, Ar), 8.31 (t, 2H, J = 1.4 Hz, Ar), 8.16 (dd, 2H, J = 7.6, 1.6 Hz, Ar), 7.97 (dt, 4H, J = 8.0, 1.6 Hz, Ar), 7.70 (dt, 1H, J = 7.6 Hz, Ar), 7.53 (t, 4H, J = 7.4 Hz, Ar), 7.34 (t, 4H, J = 8.0 Hz, Ar);

IR (KBr) ν 3304, 1648, 1607, 1538, 1489, 1428, 1327 cm^{-1}; HR-MS (ES) calcd for $C_{34}H_{24}I_2N_4O_4$ 828.9785 (M + Na), found 828.9774.

***N,N′*-Bis[3-(3-{diphenylphoshanyl}benzoylamino)phenyl]isophthalamide (4).** The bisphosphine **4** was prepared according to the general procedure outlined for **1**, with the following quantities: diiodide **12** (150 mg, 0.44 mmol) in CH_3CN (2 mL), triethylamine (250 μL, 1.79 mmol), Ph_2PH (160 μL, 0.92 mmol), and $Pd(OAc)_2$ (900 μL from a solution of 12 mg of $Pd(OAc)_2$ in 10 mL of CH_3CN, 4.8 μmol). A reaction time of 24 h was allowed due to the low solubility of the diiodide. During the course of the reaction a preciptitate was formed, which was filtered and then washed with water and dichloromethane. Drying afforded **4** as a light red powder (110 mg, 28% yield), which was sparingly soluble in THF, CH_2Cl_2, ethyl acetate, methanol, and ethanol, but soluble in DMF and DMSO: ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 2H, CONH), 10.39 (s, 2H, CONH), 8.53 (s, 1H, Ar), 8.32 (m, 4H, Ar), 8.14 (dd, 2H, J = 7.6, 1.6 Hz, Ar), 8.01 (dt, 2H, J = 8.2, 1.4 Hz, Ar), 7.89 (m, 2H, J = 7.8 Hz, Ar), 7.73−7.24 (m, 29 Ar); ^{31}P NMR (DMSO-d_6) δ −5.83; IR (KBr) ν 3218, 1644, 1605, 1527, 1435, 1316 cm^{-1}; MS (ES) calcd for $C_{58}H_{44}N_4O_4P_2$ 977.9 (M + Na), found 977.8.

1,1′-Ferrocenedicarboxylic Acid (13). *n*-BuLi (64.0 mL, 0.102 mol) was added dropwise to a solution of TMEDA (15.7 mL, 0.103 mol) and ferrocene (7.87 g, 42.2 mmol) in diethyl ether (260 mL) at 20 °C. After stirring overnight, CO_2 was bubbled through the orange slurry for 2 h. Water was added, and the mixture was extracted three times with CH_2Cl_2 and then acidified with concentrated aqueous HCl. The precipitate was filtered and dried, affording **13** as a yellow powder (7.07 g, 68% yield), which was sufficiently pure for the next step: ^{1}H NMR (DMSO-d_6) δ 4.69 (t, 4H, J = 2.0 Hz, Cp), 4.45 (t, 4H, J = 2.0 Hz, Cp); ^{13}C NMR (DMSO-d_6) δ 171.1 (2C), 73.5 (2C), 72.6 (4C), 71.3 (4C); IR (KBr) ν 2923, 1677, 1492, 1405, 1300 cm^{-1}; HR-MS (ES) calcd for $C_{12}H_{10}O_4Fe$ 296.9826 (M + Na), found 296.9841.

Bis(6-aminopyridin-2-yl)-1,1′-ferrocenedicarboxylic Amide (14). Oxalyl chloride (0.6 mL, 6.9 mmol) and a catalytic amount of DMF (15 μL) were added to a solution of diacid **13** (188 mg, 0.69 mmol) in CH_2Cl_2 (20 mL). After stirring for 1 h at 20 °C, the solvent was removed under reduced pressure, affording the crude benzoyl chloride, which was redissolved in THF (11 mL). To this solution were added the 2,6-diaminopyridine (445 mg, 4.14 mmol) and triethylamine (0.29 mL, 2.07 mmol) in THF (20 mL), and the reaction mixture was stirred at 20 °C for 16 h. After removal of the solvent under reduced pressure, ethyl acetate was added and the organic phase was washed with water. The aqueous phase was extracted once with ethyl acetate, and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness under vacuum, affording **14** as a brown powder (208 mg, 66% yield): ^{1}H NMR (DMSO-d_6) δ 9.43 (br s, 2H, CONH), 7.36 (t, 2H, J = 7.8 Hz, Pyr), 7.25 (dd, 2H, J = 7.8, 0.8 Hz, Pyr), 6.21 (dd, 2H, J = 7.8, 0.8 Hz, Pyr), 5.75 (br s, 4H, R-NH_2), 5.05 (t, 4H, J = 2.0 Hz, Cp), 4.41 (t, 4H, J = 2.0 Hz, Cp); ^{13}C NMR (DMSO-d_6) δ 167.6 (2C), 158.5 (2C), 150.4 (2C), 138.9 (2C), 103.6 (2C), 102.2 (2C), 77.6 (2C), 72.6 (2C), 70.1 (2C); IR (KBr) ν 3434, 3340, 3226, 1641, 1625, 1464 cm^{-1}; HR-MS (ES) calcd for $C_{22}H_{20}O_2N_6Fe$ (M + Na) 479.0895, found 479.0893.

***N,N′*-Bis[6-(3-iodobenzoylamino)pyridin-2-yl]-1,1′-ferrocenedicarboxylic Amide (15).** The diiodide **15** was prepared according to the general procedure outlined for **8** with the following quantities: 3-iodobenzoic acid (2.10 g, 8.47 mmol) in CH_2Cl_2 (40 mL), oxalyl chloride (7.3 mL, 83.7 mmol), and a catalytic amount of DMF, diamine **14** (1.01 g, 2.21 mmol), and triethylamine (1.2 mL, 8.60 mmol) in THF (60 mL). Column chromatography (CH_2Cl_2/MeOH, 50:1) afforded **15** as a reddish brown powder (1.56 g, 77%): ^{1}H NMR (DMSO-d_6) δ 10.48 (br s, 2H, CONH), 9.73 (br s, 2H, CONH), 8.30 (br s, 2H, Ar), 7.86 (m, 10H, Ar), 7.31 (br s, 2H, Ar), 5.11 (br s, 4H, Cp), 4.51 (br s, 4H, Cp); ^{13}C NMR (DMSO-d_6) δ 167.3 (2C), 164.0 (2C), 150.2 (2C), 149.8 (2C), 140.2 (2C), 139.6 (2C), 136.1 (2C), 135.9 (2C), 130.4 (2C), 127.1 (2C), 110.8 (2C), 110.4 (2C), 94.6 (2C), 77.1 (2C), 72.4 (2C), 70.0 (2C); IR (KBr) ν 3410, 1676, 1586, 1508, 1444 cm^{-1}; HR-MS (ES) calcd for $C_{36}H_{26}O_4N_6I_2Fe$ (M + Na) 938.9352, found 938.9321.

***N,N′*-Bis[6-(3-{diphenylphoshanyl}benzoylamino)pyridin-2-yl]-1,1′-ferrocenedicarboxylic Amide (5).** The bisphosphine **5** was prepared according to the general procedure outlined for **1**, with the following quantities: diiodide **15** (173 mg, 0.189 mmol) in CH_3CN (4 mL), triethylamine (158 μL, 1.13 mmol), Ph_2PH (69 μL, 0.396 mmol), and $Pd(OAc)_2$ (123 μL from a solution of 10.3 mg of $Pd(OAc)_2$ in 5 mL of CH_3CN, 1.9 μmol). Column chromatography (pentane/ethyl acetate, 2:1) afforded **5** as a yellowish brown powder (165 mg, 85% yield): ^{1}H NMR ($CDCl_3$) δ 8.33 (br s, 2H, CONH), 8.15 (br s, 2H, CONH), 7.98 (dd, 2H, J = 8.0, 0.7 Hz, Ar), 7.88 (dd, 2H, J = 8.0, 0.7 Hz, Ar), 7.82 (d, 4H, J = 8.6 Hz, Ar), 7.63 (t, 2H, J = 8.0 Hz, Ar), 7.41−7.30 (m, 24H, Ar), 4.84 (t, 4H, J = 2.0 Hz, Cp), 4.54 (t, 4H, J = 2.0 Hz, Cp); ^{31}P NMR ($CDCl_3$) δ −4.7; IR (KBr) ν 3409, 1677, 1585, 1507, 1444 cm^{-1}; HR-MS (ES) calcd for $C_{60}H_{46}O_4N_6P_2Fe$ (M + Na) 1055.2303 found 1055.2307.

***N,N′*-Bis[6-(4-iodobenzoylamino)pyridin-2-yl]-1,1′-ferrocenedicarboxylic Amide (16).** The diiodide **16** was prepared according to the general procedure outlined for **8** with the following quantities: 4-iodobenzoic acid (455 mg, 1.83 mmol) in CH_2Cl_2 (10 mL), oxalyl chloride (1.57 mL, 18.0 mmol), and a catalytic amount of DMF (15 μL), diamine **14** (205 mg, 0.44 mmol), and triethylamine (256 μL, 1.84 mmol) in THF (13 mL). Column chromatography (ethyl acetate/pentane, 1:1) afforded **16** as a reddish brown powder (344 mg, 86% yield): ^{1}H NMR (DMSO-d_6) δ 10.39 (br s, 2H, CONH), 9.74 (br s, 2H, CONH), 8.9 (m, 14H, Ar), 5.11 (br s, 4H, Cp), 4.51 (br s, 4H, Cp); ^{13}C NMR (DMSO-d_6) δ 167.4 (2C), 165.0 (2C), 150.4 (2C), 150.0 (2C), 139.7 (2C), 137.3 (4C), 133.4 (2C), 129.7 (4C), 110.8 (2C), 110.5 (2C), 100.0 (2C), 77.3 (2C), 72.5 (4C), 70.1 (4C); IR (KBr) ν 3407, 2924, 1676, 1585, 1508, 1443 cm^{-1}; HR-MS (ES) calcd for $C_{36}H_{26}O_4N_6I_2Fe$ (M + Na) 938.9352, found 938.9352.

***N,N′*-Bis[6-(4-{diphenylphoshanyl}benzoylamino)pyridin-2-yl]-1,1′-ferrocenedicarboxylic Amide (6).** The bisphosphine **6** was prepared according to the general procedure outlined for **1**, with the following quantities: diiodide **16** (760 mg, 0.83 mmol) in CH_3CN (8 mL), triethylamine (0.70 mL, 5.0 mmol), Ph_2PH (304 μL, 1.74 mmol), and $Pd(OAc)_2$ (518 μL from a solution of 18 mg of $Pd(OAc)_2$ in 5 mL of CH_3CN, 8.3 mmol). Column chromatography (CH_2Cl_2/MeOH, 60:1) afforded **6** as a brown powder (473 mg, 55% yield): ^{1}H NMR ($CDCl_3$) δ 8.30 (br s, 2H, CONH), 8.13 (br s, 2H, CONH), 7.98 (d, 2H, J = 8.0 Hz, Ar), 7.88 (d, 2H, J = 8.0 Hz, Ar), 7.81 (m, 4H, Ar), 7.63 (t, 2H, J = 8.0 Hz, Ar), 7.37 (m, 24H, Ar), 4.84 (t, 4H, J = 1.9 Hz, Cp), 4.54 (t, 4H, J = 1.9 Hz, Cp); ^{31}P NMR ($CDCl_3$) δ −4.74; IR (KBr) ν 3409, 1677, 1585, 1507, 1444 cm^{-1}; HR-MS (ES) calcd for $C_{60}H_{46}O_4N_6P_2Fe$ (M + Na) 1055.2303, found 1055.2307.

General Procedure for the Heck Coupling between the Aryl Halides and *n*-Butyl Acrylate. A Schlenk tube containing $Pd(dba)_2$ (7.2 mg, 12.5 μmol, 0.5 mol %) and the phosphine, either PPh_3 (6.6 mg, 25 μmol, 1.0 mol %) or the bidentate phosphines (11.6 mg, 12.5 μmol, 0.5 mol %), was purged with argon. DMF (800 μL) was added followed by triethylamine (383 μL, 2.75 mmol), *n*-butyl acrylate (358 μL, 2.5 mmol), and phenyl halide (2.5 mmol). The reaction mixture was stirred at 20, 60, or 120 °C over a period of time, as indicated in Table 3. Diethyl ether and water were added, and the aqueous phase was extracted three times with ether. The combined organic phases were dried ($MgSO_4$) and evaporated to dryness under vacuum. Column chromatography (ethyl acetate/pentane, 1:199) afforded *n*-butyl cinnamate as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 1H, J = 16.0 Hz, CH=CH), 7.56−7.51 (m, 2H, Ar), 7.41−7.36 (m, 2H, Ar), 6.44 (d, 1H, J = 16 Hz, CH=CH), 4.21 (t, 2H, J = 6.4 Hz, CH_2O), 1.77−

1.63 (m, 2H, CH_2), 1.50−1.35 (m, 2H, CH_2), 0.97 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.2, 144.7, 134.6, 130.4, 129.0 (2C), 128.2 (2C), 118.5, 64.6, 31.0, 19.4, 14.0; HR-MS (ES) calcd for $C_{13}H_{16}O_2$ 227.1048 (M + Na), found 227.1053.

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Note Added in Proof: We have recently prepared a homologue of the ligand **2**, which both complexes to palladium(0) and binds the guest, barbital. The ability of this complex to catalyze the Heck reaction and control regioselectivities is currently under investigation and will be reported in a separate paper.

Supporting Information Available: Copies of ^1H NMR spectra for compounds **1**−**6**. This material is available free of charge via the Internet at http//pubs.acs.org.

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