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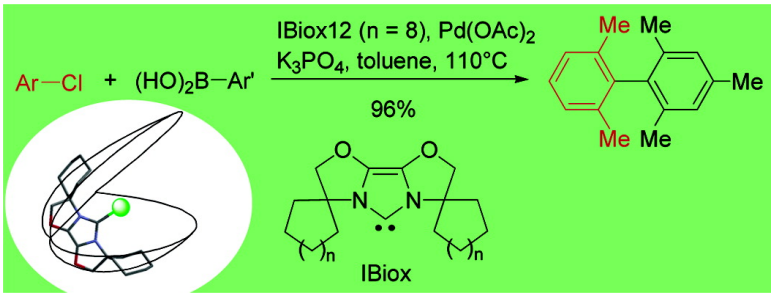

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Sterically Demanding, Bioxazoline-Derived N-Heterocyclic Carbene Ligands with Restricted Flexibility for Catalysis

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Abstract: A unique family of N-heterocyclic carbenes derived from bioxazolines (IBiox) suitable for application in transition-metal catalysis is described. The ligands are electron rich, sterically demanding, and have restricted flexibility. Their usefulness has been demonstrated in the Suzuki−Miyaura cross-coupling of sterically hindered aryl chlorides and boronic acids. For the first time, tetraortho-substituted biaryls with methyl and larger ortho-substituents have been synthesized from aryl chlorides using the Suzuki−Miyaura method.

Introduction

The Suzuki−Miyaura cross-coupling reaction has become an attractive standard process for biaryl formation.[1] Its popularity results from the wide functional group tolerance, as well as the low toxicity and robustness of the reagents involved. Many catalyst systems have been developed to increase the scope of this important transformation and allow the reaction to proceed under milder conditions.[1−10] For a long time, the use of unactivated aryl chlorides as substrates in Suzuki−Miyaura cross-couplings was not feasible. Instead, more costly and less readily available aryliodides and arylbromides had to be used. Buchwald[4] and Fu[5] were the first to independently develop catalyst systems based on electron-rich, sterically demanding phosphine ligands, which allow the Suzuki−Miyaura cross-coupling of many unactivated aryl chlorides. The application of N-heterocyclic carbene (NHC)[11] ligands in the reaction was first reported by Herrmann in 1998.[7] Subsequently, palladium complexes of many N-heterocyclic carbene (NHC)[11] ligands were found to be competent catalysts for the Suzuki−Miyaura coupling of unactivated aryl chlorides,[7−10] with sterically demanding ligands, such as IMes or IAd, being especially useful.

Ortho-substituted biaryls are important substructures of biologically active compounds and organic functional materials.[1] Unfortunately, the linking of sterically hindered carbon centers is notoriously difficult and the formation of multi-ortho-substituted biaryls under mild conditions has remained elusive.[12] Recently, we described the IBiox6 ligand, a bioxazoline-derived NHC, which contains a tricyclic, rigid backbone as the key structural element and substituents next to the nitrogen atoms

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(3) For a survey of the rational design of catalysts for the Suzuki−Miyaura coupling, see: Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201.

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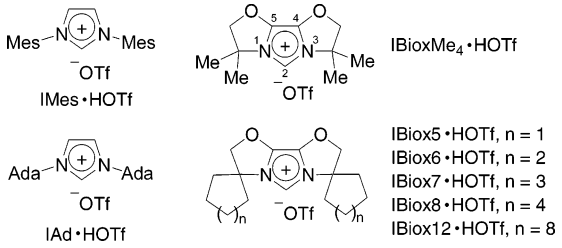
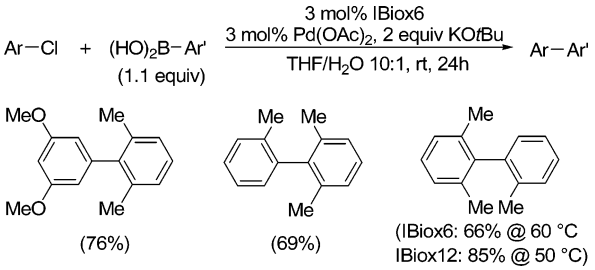
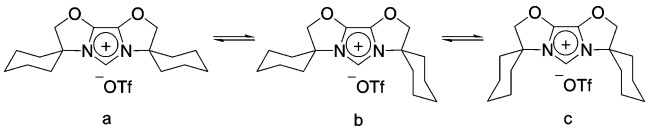


Figure 1.

Scheme 1. Suzuki−Miyaura Couplings of Sterically Hindered Substrates at Ambient Temperature



Scheme 2. Reasonable Conformations of IBiox6·HOTf; Conformations a and b Were Proven by NMR/X-ray Analysis



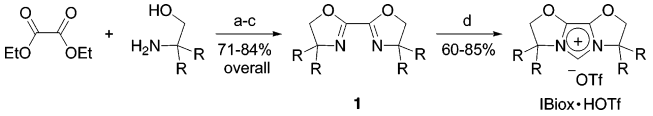
placed in close proximity to a carbene-coordinated metal that determine its catalytic properties (Figure 1). Using this ligand, we were able to form di- and triortho-substituted biaryls at ambient temperature with nonactivated aryl chlorides as substrates (Scheme 1).[9,13]

NMR and X-ray structural analysis showed that IBiox6·HOTf exists in the form of at least two different conformers which rapidly interconvert at room temperature (Scheme 2). We reasoned that the flexible steric bulk caused by chair flipping of the cyclohexyl rings proves beneficial in the catalytic cycle of the Suzuki−Miyaura coupling reaction and that the sterically more demanding conformations would favor the formation of a catalytically active monoligated $Pd(IBiox6)_1$ species.[14] However, while IBiox6·HOTf was successfully employed for the synthesis of many different biaryls, the challenging formation of tetraortho-substituted biaryls remained out of reach. Here, we report the synthesis of a family of differently substituted IBiox ligands, the investigation of their electronic and steric properties, as well as their successful application in the formation of tetraortho-substituted biaryls from aryl chlorides.

Results and Discussion

The investigation began with the synthesis of a series of IBiox ligands, with differing carbocycle ring sizes, ranging from

Scheme 3. Synthesis of the IBiox·HOTf Salts[a]



[a] (a) Toluene, 80 °C; (b) $SOCl_2$, toluene, 90 °C; (c) NaOH, THF, EtOH, 80 °C; (d) AgOTf, chloromethyl pivalate, CH_2Cl_2; **1**, 40 °C.

IBiox5·HOTf (two cyclopentyl rings) to IBiox12·HOTf (two cyclododecyl rings) (Figure 1). We also prepared the open-chain tetramethyl-substituted ligand $IBioxMe_4$·HOTf for comparison. The ligands were all synthesized from the corresponding readily available amino alcohols.[15] Amide formation of the amino alcohols with diethyl oxalate, followed by chlorination and base-mediated cyclization, gave the bioxazolines[16] **1** in good overall yield of around 75% (Scheme 3). Purification of the products is simply achieved by washing or crystallization. Early on, we realized that standard methods for imidazolium salt formation, as used for bisimines, are not applicable to bioxazolines.[17] We found that bioxazolines could be successfully converted into imidazolium salts by using a combination of AgOTf and chloromethyl pivalate. It is also worth noting that the use of AgOTf also facilitates the formation of other imidazolium salts such as IMes·HOTf.[18] Optimum results for the imidazolium system were obtained by preforming the alkylating reagent from AgOTf and chloromethyl pivalate, and by removal of the AgCl formed. Under the optimized protocol, AgOTf and chloromethyl pivalate were stirred in CH_2Cl_2 for 45 min in the dark, followed by filtration, and subsequent addition of the filtrate to the bioxazolines **1**. Subsequently, the reaction mixture was stirred for 24 h at 40 °C, resulting in yields above 60% (Scheme 3).

Overall, this method has proven to be very reliable for the cyclization of bioxazolines, imineoxazolines, and bisimines. It has the advantage that it leads to the formation of the triflate salts, which are soluble in CH_2Cl_2 and THF, and can be chromatographed. This is in stark contrast to the much less soluble standard imidazolium chlorides.

The substitution pattern of the 4,5-dialkoxy-substituted 1,3-disubstituted imidazolium salts has important implications, both sterically and electronically (Figure 2).

First, the NHC ligands have an unambiguous binding mode. Because the imidazolium core of the IBiox·HOTf is tetrasubstituted, only C2 of the imidazolium ring is accessible for coordination to a metal. A number of recent publications report the possibility of the involvement of NHC binding modes other than through C2.[19]

(13) Subsequently, two other catalyst systems have been reported for Suzuki−Miyaura reactions of sterically hindered aryl chlorides at ambient temperature, the latter being exceptionally practical and general: refs 8e and 4d. However, none of these systems has been reported to allow the successful formation of tetraortho-substituted biaryls from aryl chlorides.

(14) The importance of monoligated Pd(0) complexes as catalytically active species in Suzuki−Miyaura cross-coupling has been proposed. See, for example: (a) ref 5b; (b) ref 6e; (c) Hu, Q.-S.; Lu, Y.; Tang, Z.-Y.; Yu, H.-B. *J. Am. Chem. Soc.* **2003**, *125*, 2856. For the successful application of an interesting sterically demanding NHC ligand in a difficult Sonogashira coupling, see: (d) Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 3317.

(15) The amino alcohols were prepared starting from the commercially available ketones by formation of the corresponding hydantoins, hydrolysis ((a) Palacin, S.; Chin, D. N.; Simanek, E. E.; MacDonald, J. C.; Whitesides, G. M.; McBride, M. T.; Palmore, G. T. R. *J. Am. Chem. Soc.* **1997**, *119*, 11807), and reduction ((b) Aurich, H. G.; Biesemeier, F.; Geiger, M.; Harms, K. *Liebigs Ann. Chem.* **1997**, 423. (c) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517). This method allows the convenient synthesis of large gram quantities of amino alcohol.

(16) (a) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (b) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257.

(17) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.

(18) The reaction of the corresponding bisimine with AgOTf (1.2 equiv) and chloromethyl-ethyl ether (1.4 equiv) in CH_2Cl_2 (0.17 M) at 40 °C leads to the smooth formation of IMes·HOTf in 83%. Related systems react equally well.

(19) (a) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046. (b) Chianese, A. R.; Kovacevic, A.; Zeglis, B. M.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2004**, *23*, 2461.

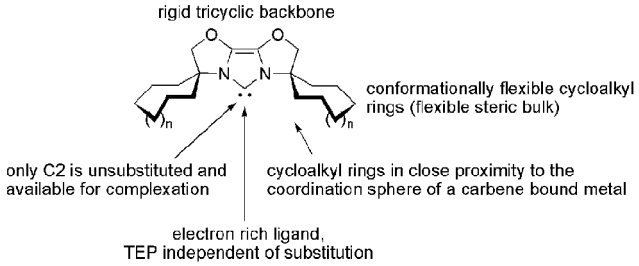


Figure 2. Characteristics of the IBiox ligand system.

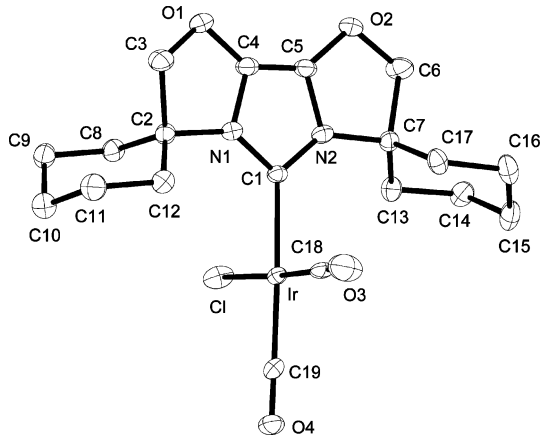
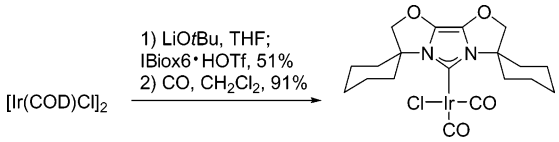


Figure 3. X-ray structure of (IBiox6)Ir(CO)$_2$Cl. Selected distances (Å) and angles (deg): Ir−C1 2.072(3), Ir−C18 1.897(4), Ir−C19 1.892(3), Ir−Cl 2.351(1), plane(Ir, C1, C18, C19, Cl)/plane(Ir, C1, N1, N2, C4, C5) 89.9(1)°.

Scheme 4. Synthesis of the (IBiox6)IrCl(CO)$_2$ Complex



The 4,5-dioxygen substitution also has an influence on the electronic properties of the ligands. According to Crabtree, the average carbonyl stretching frequency of Ir(CO)$_2$Cl(L) complexes can be used as a measure of the electron-donor power of ligands, quantified in terms of Tolman's electronic parameter (TEP).[20] We first looked at IBiox6. The (IBiox6)Ir(CO)$_2$Cl-complex was synthesized in 46% overall yield and was shown by X-ray analysis to contain a cis and a trans coordinated CO group (Scheme 4, Figure 3). The IR spectrum of (IBiox6)Ir(CO)$_2$Cl (measured in CH_2Cl_2) shows two CO stretching bands (2065 and 1982 cm^{-1}) of similar intensity, consistent with this. The average ν(CO) (2024 cm^{-1}) corresponds to a TEP of 2054 cm^{-1}, following Crabtree's linear fit procedure.[21] This puts IBiox6 electronically close to electron-rich phosphines, such as P*t*Bu$_3$ (TEP = 2056.1 cm^{-1}),[20] and shows them to be a little less electron rich than standard NHC ligands (TEP = 2050 cm^{-1}). Three further (IBiox)Ir(CO)$_2$Cl-complexes were prepared, and similar values were obtained (Table 1). Thus, it seems that the oxygen atoms cause a slight electron-withdrawing effect, at least as far as the metal is concerned, and that this is independent of the length of the alkyl substituents. The ^{1}H and ^{13}C NMR spectra of the IBiox·HOTf salts also indicate that

Table 1. Vibrational CO Frequencies and Calculated[21] TEP for (IBiox)Ir(CO)$_2$Cl-Complexes (TEP = 0.722[$\nu_{average(CO)}$] + 593 cm^{-1})

ligand	ν(CO) [cm^{-1}]	ν(CO) [cm^{-1}]	TEP [cm^{-1}]
IBioxMe$_4$	1982	2066	2054
IBiox6	1982	2065	2054
IBiox8	1981	2064	2053
IBiox12	1980	2064	2053

Table 2. Selected ^{1}H and ^{13}C NMR Data (in ppm) for the Bioxazoline-Derived Imidazolium Triflates

	C2–*H*	OC*H*$_2$	C2	OCN	C$_{quart}$	OCH$_2$
IBioxMe$_4$·HOTf	8.71	4.76	112.4	125.2	64.6	88.4
IBiox5·HOTf	8.83	4.83	112.6	125.7	73.6	87.6
IBiox6·HOTf	8.93	4.82	113.2	124.8	67.5	85.9
IBiox7·HOTf	8.83	4.75	112.4	124.9	71.3	87.1
IBiox8·HOTf	8.82	4.78	113.0	125.0	71.5	87.6
IBiox12·HOTf	8.71	4.73	114.5	125.2	70.9	87.3

the electronic character of the IBiox ligands is largely independent of the substitution pattern. Similar chemical shifts are obtained for key groups of the bioxazoline-derived imidazolium cores (Table 2).

The uniformity of the IR and NMR data within the series means that the steric bulk of the ligand can be varied without affecting the electronic character. It is important to note that this is not the case for most other monodentate ligand systems. For example, increasing the size of a trialkyl phosphine ligand significantly changes both its steric and its electronic properties (e.g., for PEt$_3$, P*i*Pr$_3$, P*t*Bu$_3$: Tolman's cone angle = 132°, 160°, 182° and TEP = 2061.7, 2059.2, 2056.1 cm^{-1}, respectively).[20]

In addition, the IBiox ligands have a rigid tricylic core, which presents a highly anisotropic face to the metal. To estimate the steric demand of the IBiox ligands, X-ray quality crystals were grown and structurally analyzed for all IBiox·HOTf salts prepared (Figure 4). Comparison of the structures reveals that, whereas the central imidazolium ring is strictly planar, the oxazolium five-membered rings can take up slightly different conformations in which the methylene groups C3 and C6 lie slightly (±0.2 Å) out of the plane of the central ring. The differences are so small that the tricycle can be largely considered rigid. Figure 4 gives an indication of some of the conformations available to the cycloalkyl substituents. For all salts, the arrangements of the α-C atoms with respect to the central tricycle are almost identical. The arrangement of the remaining atoms is constrained by spiro attachment to the central core and the ring nature of the substituents. It is likely that, when a metal is bonded to the C2 of the imidazolium ring, the cycloalkyl rings of the ligands surround and influence the coordination sphere of the metal, the effect increasing with the size of the cycloalkyl group. It is important to note that, whereas the cycloalkyl rings are constrained close to the IBiox ligand core, further away they can exist in several favorable conformations. This can be clearly seen in the structures of IBiox5·HOTf, IBiox6·HOTf, and IBiox12·HOTf, where the cycloalkyl rings adopt different conformations on either side of the imidazolium salt. It is tempting to suggest that while shielding the metal the IBiox ligands are adaptable, allowing the coordination sphere of the metal to expand or contract.[22]

To investigate this further, we compared the effectiveness of the IBiox ligands in the challenging Suzuki−Miyaura coupling

(20) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(21) Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2003**, *22*, 1663. See also: ref 19b.
(22) Burgess, K. *Chem. Ind.* **2003**, 32 (17th November).

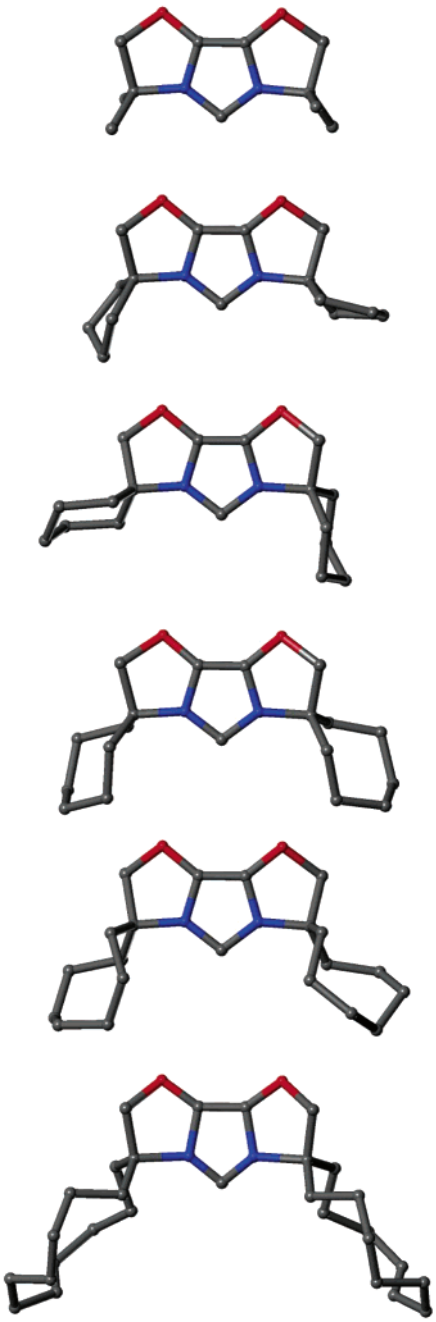
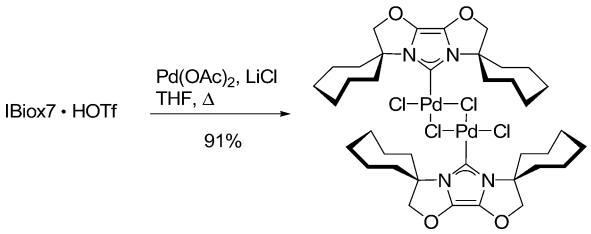


Figure 4. X-ray structures of the IBiox triflate salts.

of 1-chloro-2,6-dimethylbenzene and 2,4,6-trimethylbenzeneboronic acid. Preliminary experiments identified two useful solvent/base systems: dioxane/Cs_2CO_3 and toluene/K_3PO_4, with the latter combination generally giving slightly superior results. Using the toluene/K_3PO_4 system and an excess of the aryl boronic acid (1.5 equiv), a combination of $Pd(OAc)_2$ and IBioxMe$_4$·HOTf, IBiox5·HOTf, or IBiox6·HOTf gave only small amounts of the desired cross-coupled product (Figure 5). In these cases, the main product was 2,4,6-trimethylbenzene formed by protodeboronation, which is a well-known side reaction of sterically demanding substrates.[23] Use of IBiox7·HOTf and IBiox8·HOTf resulted in significantly increased

Scheme 5. Synthesis of $[(IBiox7)PdCl_2]_2$



product formation. Gratifyingly, still more product was formed by using the IBiox12 ligand (96%). It is important to note that under the same conditions IMes·HOTf and IAd·HOTf failed to provide substantial amounts of product (Figure 5).

To demonstrate the efficacy and generality of this catalytic system, we prepared several biaryl derivatives from sterically hindered aryl chlorides and aryl boronic acids. In all cases, around 3% homocoupling of the boronic acid was obtained, presumably originating from the reduction of the Pd(II) precatalyst. Whereas water was tolerated and sometimes even beneficial in the synthesis of di- and triortho-substituted biaryls at ambient temperature,[9] the use of strictly anhydrous conditions was found to be important for tetraortho-substituted biaryls, because it minimized the competing protodeboronation of the aryl boronic acid.[24] Thus, the use of dry reagents such as finely ground, flame-dried K_3PO_4 gave optimum results.[25] As shown in Table 3, IBiox12 proved to be an excellent ligand for the synthesis of tetraortho-substituted biaryls in good yields. Many different ortho-substituents, including methyl, ethyl, fluorine, and methoxy, can be accommodated. These results represent the first Suzuki−Miyaura cross-coupling of aryl chlorides to give tetraortho-substituted biaryls with ortho-substituents that are methyl or larger. A phosphine-based catalyst system for the synthesis of tetraortho-substituted biaryls by Suzuki−Miyaura cross-coupling has only recently been reported by Buchwald, but only aryl bromides and anthracenyl chloride have been successfully used as substrates.[4d,g]

To shed some light onto the mode of action of the IBiox ligands, we looked at the formation of catalytically active monocarbene−palladium complexes. Many standard methods were screened, such as heating IBiox·HOTf salts with $Pd(OAc)_2$ and $Na(OAc)_2$ in DMSO, or treating the preformed carbene with palladium complexes. However, optimum results were obtained by heating the IBiox7·HOTf together with $Pd(OAc)_2$ and an excess of LiCl in THF to 100 °C for 2 days (Scheme 5). $[(IBiox7)PdCl_2]_2$ was cleanly formed in 91% yield. X-ray structural analysis of the complex clearly reveals that IBiox7 is a sterically demanding ligand and that it surrounds the metal like an oyster shell, while leaving enough space for the coordination plane of palladium (Figure 6). As is usually observed, palladium adopts a square-planar coordination, and two Pd complexes are bridged by two chlorine atoms. Interestingly, the (IBiox12)Pd-complex could not be prepared in an analogous method. Instead, it was best prepared in 45% yield by heating a dioxane solution of IBiox12·HOTf, $Pd(OAc)_2$, Cs_2CO_3, and an excess of LiCl at 100 °C for 24 h. X-ray structural analysis of this complex showed the same binding motif for IBiox12 as for IBiox7 (Figures 6, 7). As for the IBiox7 complex, the large

(23) For example, see: (a) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034. (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(24) Cammidge, A. N.; Crépy, K. V. L. *J. Org. Chem.* **2003**, *68*, 6832.

(25) Commercial sources provide boronic acids of substantially different dryness. Recrystallization may be advisable in some cases.

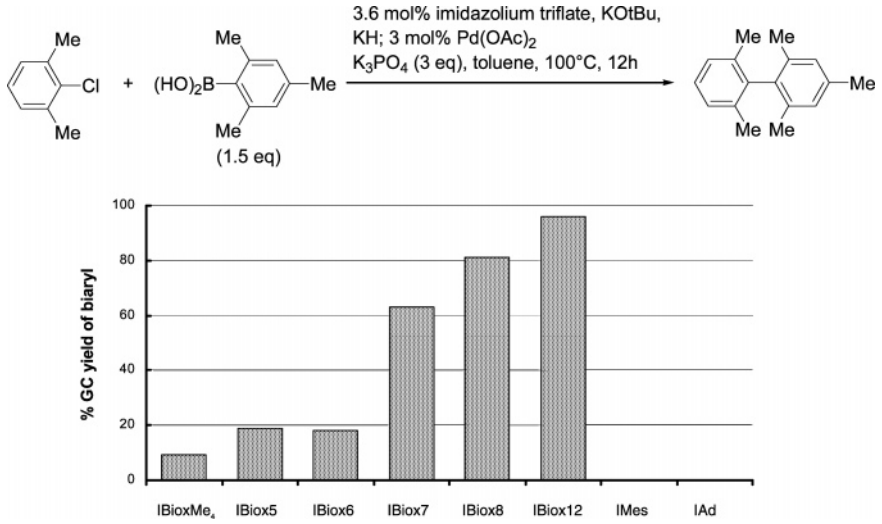


Figure 5. Screening of ligands for Suzuki−Miyaura cross-coupling of sterically hindered substrates.

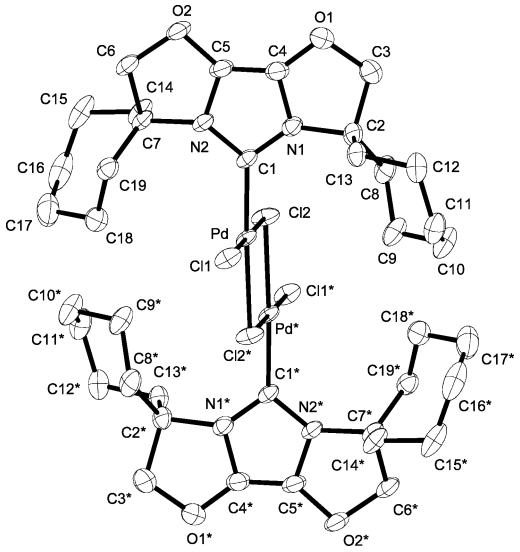


Figure 6. X-ray structure of $[(IBiox7)PdCl_2]_2$. Selected distances (Å) and angles (deg): Pd−C1 1.943(2), Pd−Cl1 2.2856(4), Pd−Cl2 2.3344(4), Pd−Cl2* 2.4201(4), C8···Pd 3.673(2), plane(Pd, C1, Cl1, Cl2, Cl2*)/plane(Pd, C1, N1, N2, C4, C5) 83.4(1)°.

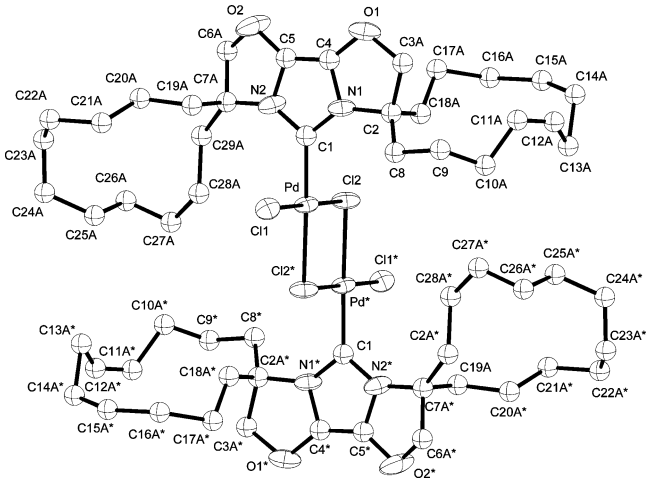


Figure 7. X-ray structure of $[(IBiox12)PdCl_2]_2$, showing one of the conformations of the disordered cyclododecyl rings. Selected distances (Å) and angles (deg): Pd−C1 1.944(5), Pd−Cl1 2.285(1), Pd−Cl2 2.337(1), Pd−Cl2* 2.415(1), C8···Pd 3.627(6), plane(Pd, C1, Cl1, Cl2, Cl2*)/plane-(Pd, C1, N1, N2, C4, C5) 85.5(1)°.

cycloalkyl rings substantially shield the metal. However, because the cyclododecyl rings are significantly larger, the two IBiox12 ligands in the dimer are not independent of each other and one of the cyclododecyl rings of each IBiox ligand moves toward its NHC backbone to prevent unfavorable steric interaction. This difference in conformation strikingly demonstrates the flexibility of the cycloalkyl rings. Furthermore, one of the conformations found for IBiox12 in $[(IBiox12)PdCl_2]_2$ resembles conformation b of imidazolium salt IBiox6·HOTf (Scheme 2) and the conformation proposed for its catalytically active palladium complex.[9] It is interesting to note that there is a relatively short Pd···C contact (3.6 Å) between the nondisordered β C atom (C8 in Figure 7) of the cyclododecyl ring and the metal, indicative of a weak C−H···Pd interaction. Most importantly, both complexes were found to be catalytically active (3 mol %, entries 3,4 of Table 3).

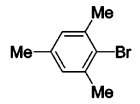
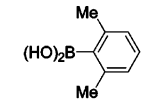
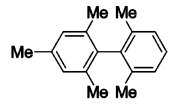
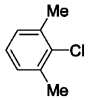
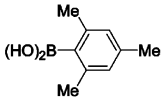
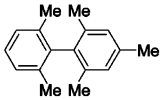
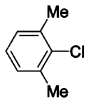
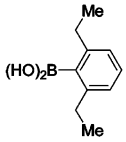
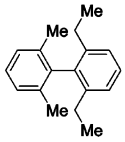
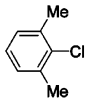
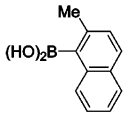
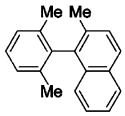
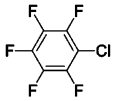
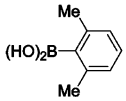
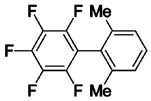
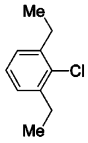
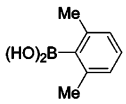
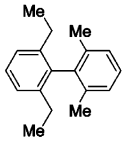
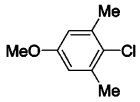
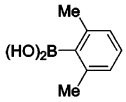
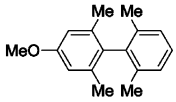
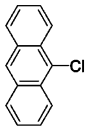
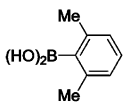
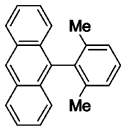
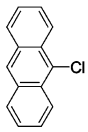
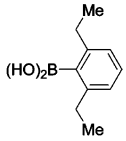
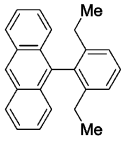
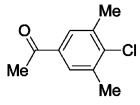
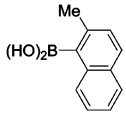
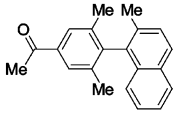
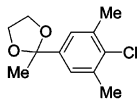
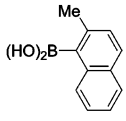
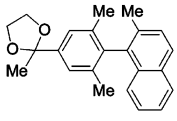
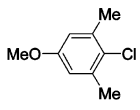
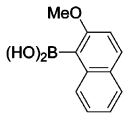
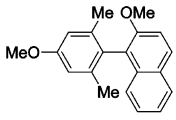
Many beneficial features for catalysis can be attributed to the IBiox ligand system. The ligands are electron rich, facilitating the oxidative addition of the metal complex with aryl chlorides. The ligands are sterically demanding, favoring the formation of coordinatively unsaturated metal species. The catalytically active metal is shielded, but not completely, allowing space within the coordination sphere of the metal. In the case of nickel complexes, the influence of sterically demanding NHC ligands on the coordination number has been demonstrated.[26] However, while electron richness and sterical bulk are important, a certain degree of ligand flexibility seems to be the key to successful application in the Suzuki−Miyaura transformation, because classical rigid ligands such as IAd·HOTf failed to provide the desired products. Flexible steric bulk allows the ligands to adapt to the changing needs of the catalytic cycle. Thus, whereas a less sterically demanding ligand is favorable for oxidative addition and transmetalation, reductive elimination should benefit from more demanding conformations around the metal center.

Conclusions

We have demonstrated the usefulness of a new class of bioxazoline-derived NHC ligands, IBiox. These ligands are

(26) Dorta, R.; Stevens, E. D.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 10490.

Table 3. Suzuki−Miyaura Couplings of Aryl Chlorides Resulting in Tetraortho-Substituted Biaryls[a]

entry	ArX	Ar'B(OH)$_2$	Product	Yield
1				91
2				96
3				71[b]
4				87[c,d]
5				75
6				78
7				89
8				82
9				83
10				87
11				65[d]
12				69
13				70
14				47

[a] Reaction conditions: 1.0 mmol of ArX, 1.5 mmol of Ar′B(OH)$_2$, 3 mmol of K_3PO_4, 3.6 mol % of IBiox12 (from IBiox12·HOTf, KH, cat. KO*t*Bu), 3 mol % of Pd(OAc)$_2$ in THF, toluene (3 mL), 110 °C, 16 h; yield of isolated products. [b] 3 mol % of complex [(IBiox7)PdCl$_2$]$_2$. [c] 3 mol % of complex [(IBiox12)PdCl$_2$]$_2$. [d] 0.5 mmol scale.

easily prepared, electron rich, and sterically demanding as a consequence of their characteristic tricyclic backbone, while being flexible, with restricted degrees of freedom. These favorable characteristics should render them attractive for application in many transition-metal-catalyzed processes. These ligands have been successfully employed in the Suzuki−Miyaura cross-coupling of sterically hindered aryl chlorides and aryl boronic acids to give tetraortho-substituted biaryls.

Experimental Section

General Remarks. The solvents used were purified by distillation over the drying agents indicated and were transferred under argon: tetrahydrofuran (THF) (Na), CH_2Cl_2 (P_4O_{10}), toluene (Na/K). For flash chromatography, Merck silica gel 60 (230−400 mesh) was used. All commercially available compounds were used as received. All reactions were set up under an atmosphere of argon; K_3PO_4 was ground with a mortar and flame-dried. Noncommercial aryl boronic acids were synthesized from the corresponding aryl Grignard by quench with $B(OMe)_3$ and acidic hydrolysis. Noncommercial aryl chlorides were synthesized by Br/Cl-exchange with stoichiometric amounts of CuCl in refluxing DMF.

General Procedure for the Synthesis of the Imidazolium Triflates. To a suspension of AgOTf (1.45 equiv) in CH_2Cl_2 (0.3 M) was added chloromethyl pivalate (1.45 equiv), and the resulting suspension was stirred for 45 min. The supernatant was transferred via syringe to the bioxazoline (1 equiv), and the resulting solution was stirred in a sealed tube in the dark at 40 °C for 20 h. After the solution was cooled to room temperature, the reaction was quenched with methanol and the solvent evaporated in vacuo. The resulting oil was chromatographed on silica gel (CH_2Cl_2/MeOH). Subsequent crystallization from CH_2Cl_2/diethyl ether gave the imidazolium triflate as colorless crystals.

IBiox12·HOTf. Following the general procedure gave IBiox12·HOTf (4.5 g, 60%) as colorless crystals after chromatography on silica (CH_2Cl_2 to CH_2Cl_2/MeOH = 100/12) and crystallization.

R_f = 0.53 (EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.71 (s, 1H, NCHN), 4.73 (s, 4H, CCH_2O), 2.29−2.17 (m, 4H, CH_2), 1.92−1.70 (m, 4H, CH_2), 1.69−1.55 (m, 4H, CH_2), 1.55−1.23 (m, 34H, CH_2); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 125.2 (ONC), 121.0 (q, J^1_{CF} = 324 Hz), 114.5 (NCHN), 87.3 (OCH_2), 70.9 ($C(CH_2)_2$), 30.8 (CH_2), 25.9 (CH_2), 22.3 (CH_2), 21.9 (CH_2), 19.5 (CH_2); ^{19}F NMR (282 MHz, CD_2Cl_2) δ −78.8; IR (KBr) 3094, 2934, 2862, 1773, 1516, 1472, 1447, 1333, 1262, 1224, 1154, 1031, 1000, 965, 943, 903, 828, 748, 726, 637, 572, 517 cm^{-1}. MS (EI), *m*/*z* (%) 457 (100), 278 (12), 206 (62), 100 (5), 97 (6), 95 (7), 83 (6), 81 (9), 69 (9), 55 (12), 41 (5); HRMS (EI) calcd for $C_{29}H_{49}N_2O_2$ 457.3794, found 457.3785. Crystal data for IBiox12·HOTf: $[C_{29}H_{49}N_2O_2]^+[CF_3O_3S]^-\cdot CH_2Cl_2$, from dichloromethane/heptane, M_r = 691.70, crystal size: 0.05 × 0.05 × 0.06 mm; a = 14.6777(4), b = 25.7698(7), c = 9.1906(2) Å, V = 3476.3(2) Å^3, T = 150 K, orthorhombic, space group *Pnma* (No. 62), Z = 4, ρ_{calcd} = 1.322 g cm^{-3}, $F(000)$ = 1472, Nonius KappaCCD diffractometer, λ(Mo Kα) = 0.71073 Å, μ = 0.30 mm^{-1}, 51 282 measured and 3038 independent reflections (R_{int} = 0.099), 1890 with $I > 2\sigma(I)$, θ_{max} = 24.81°, T_{min} = 0.998, T_{max} = 1.00 (multiscan absorption correction), direct methods (SHELXS-97) and least-squares refinement (SHELXl-97) on F_o^2, both programs from G. Sheldrick, University of Göttingen, 1997; 388 parameters. The structure is twinned (*Pna*2$_1$ emulating *Pnma*, twinning law: [1 0 0, 0−1 0, 0 0 1]); two crystals were investigated, and both were similarly twinned. The structure was refined in the centrosymmetric space group *Pnma*, with 50:50 disorder about the psuedo mirror plane perpendicular to the *b* axis. Dichloromethane solute in crystal, H atoms riding except on solute, Chebyshev weights, R_1 = 0.0640 ($I > 2\sigma(I)$), wR_2 = 0.1701 (all data), $\Delta\rho_{max/min}$ = 0.220/−0.203 e Å^{-3}.

General Procedure for the Suzuki−Miyaura Cross-Coupling Reactions. Preparation of the catalyst solution: In a glovebox, a mixture

of IBiox12·HOTf (109 mg, 0.18 mmol), KH (10 mg, 0.25 mmol), and KO*t*Bu (3 mg, 0.03 mmol) was stirred in THF (0.5 mL) until hydrogen evolution ceased. The resulting suspension was filtered through a short pad of sand, and the vial was washed with THF to give 2 mL of filtrate. Finally, the filtrate was mixed with $Pd(OAc)_2$ (27 mg, 0.12 mmol) to give the catalyst solution.

Aryl boronic acid (1.5 mmol) and K_3PO_4 (3.0 mmol) were dissolved in 2.5 mL of solvent and were stirred vigorously for 5 min. Aryl halide (1.0 mmol) was added, followed by the addition of 0.5 mL of a previously prepared catalyst solution. After 16 h at 110 °C, the solvent was removed in vacuo and the residue was chromatographed on silica gel giving the corresponding biaryl products.

General Procedure for the Formation of (IBiox)Ir(CO)$_2$Cl. CO gas was passed through an ice-cold solution of (IBiox)Ir(COD)Cl in CH_2Cl_2 (5 mL) for 15 min. Solvent was evaporated at 0 °C, and the residue was washed several times with cold pentane to give (IBiox)-Ir(CO)$_2$Cl as a light yellow solid.

(IBiox6)Ir(CO)$_2$Cl. Light yellow solid (54 mg, 95%). IR (CH_2Cl_2) ν(CO) 2065, 1982; IR (KBr) 2940, 2061, 1965, 1754, 1455, 1430, 1358, 1340, 1218, 986, 924, 859, 684, 653, 618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (ABq, υ_A = 4.64, υ_B = 4.62, J = 8.7 Hz, 4H, OCH_2), 2.71−2.54 (m, 4H, $(CH_2)_{cyclohexyl}$), 1.98−1.84 (m, 8H, $(CH_2)_{cyclohexyl}$), 1.69 (m, 2H, $(CH_2)_{cyclohexyl}$), 1.43−1.10 (m, 6H, $(CH_2)_{cyclohexyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 168.2, 149.5, 124.9 (ONC), 84.1 (OCH_2), 64.9 ($C(CH_3)_2$), 36.0, 35.1, 24.3, 23.8 ($(CH_2)_{cyclohexyl}$); MS (EI), *m*/*z* (%) 572 (28), 570 (14), 544 (13), 542 (11), 516 (26), 514 (88), 512 (100), 510 (34), 476 (38), 474 (28), 95 (16), 91 (6), 67 (14), 55 (10), 41 (9); HRMS (EI) calcd for $C_{19}H_{24}ClIrN_2O_4$ 572.1057, found 572.1055. Crystal data for (IBiox6)Ir(CO)$_2$Cl: [$C_{19}H_{24}ClIrN_2O_4$], from d_6-benzene, M_r = 572.05, crystal size: 0.05 × 0.10 × 0.18 mm; a = 13.1029(2), b = 9.5315(1), c = 16.4726(2) Å, β = 105.399(1), V = 1983.41(4) Å^3, T = 100 K, monoclinic, space group $P2_1/n$ (No. 14), Z = 4, ρ_{calcd} = 1.916 g cm^{-3}, F(000) = 1112, Nonius KappaCCD diffractometer, λ(Mo Kα) = 0.71073 Å, μ = 6.89 mm^{-1}, 32 725 measured and 6221 independent reflections (R_{int} = 0.041), 5445 with $I > 2\sigma(I)$, θ_{max} = 30.97°, T_{min} = 0.335, T_{max} = 0.720, direct methods (SHELXS-97) and least-squares refinement (SHELXl-97) on F_o^2, both programs from G. Sheldrick, University of Göttingen, 1997; 244 parameters, H atoms riding, Chebyshev weights, R_1 = 0.0226 ($I > 2\sigma(I)$), wR_2 = 0.0685 (all data), $\Delta\rho_{max/min}$ = 1.277/−1.165 e Å^{-3}.

[(IBiox7)PdCl$_2$]$_2$. IBiox7·HOTf (1.12 g, 24.0 mmol), $Pd(OAc)_2$ (537 mg, 24.0 mmol), and LiCl (2.0 g) were suspended in THF (10 mL) and stirred at 100 °C in a sealed tube. Within 16 h, the color of the suspension changed from brown to yellow. The solvent was removed, and the residue was extracted with DCM/water. Concentration of the organic layer and drying in vacuo gave the complex as an orange solid (1.10 g, 92%).

IR (KBr) 2923, 2853, 1752, 1495, 1421, 1280, 1212, 998, 946, 917, 856, 804, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (AB$_q$, υ_A = 4.52, υ_B = 4.49, J = 8.2 Hz, 8H, OCH_2), 3.14−2.71 (m, 12H, $(CH_2)_{cycloheptyl}$), 2.71−2.48 (m, 4H, $(CH_2)_{cycloheptyl}$), 2.03−1.84 (m, 16H, $(CH_2)_{cycloheptyl}$), 1.84−1.49 (m, 16H, $(CH_2)_{cycloheptyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.4, 112.0, 84.8 (OCH_2), 69.4 ($C(CH_3)_2$), 37.6, 37.0, 30.1, 29.8, 24.3, 24.1 ($(CH_2)_{cycloheptyl}$); MS (ESIpos/MeCN) 500 ((IBiox7)PdCl+MeCN), 412 ((IBiox7)PdCl−HCl), 315 (IBiox7). Crystal data for [(IBiox7)PdCl$_2$]$_2$: [$C_{38}H_{56}Cl_4N_4O_4Pd_2$], from dichloromethane/hexane/ethyl acetate, M_r = 987.47, crystal size: 0.16 × 0.33 × 0.40 mm; a = 13.2368(2), b = 11.6748(1), c = 13.6306(1) Å, β = 97.3395(4), V = 2089.17(4) Å^3, T = 100 K, monoclinic, space group $P2_1/n$ (No. 14), Z = 2, ρ_{calcd} = 1.570 g cm^{-3}, F(000) = 1008, Nonius KappaCCD diffractometer, λ(Mo Kα) = 0.71073 Å, μ = 1.16 mm^{-1}, 35 433 measured and 6612 independent reflections (R_{int} = 0.039), 6088 with $I > 2\sigma(I)$, θ_{max} = 31.01°, T_{min} = 0.678, T_{max} = 0.804, direct methods (SHELXS-97) and least-squares refinement (SHELXl-97) on F_o^2, both programs from G. Sheldrick, University of Göttingen, 1997; 235 parameters, H atoms riding, Chebyshev weights, R_1 = 0.0282 ($I > 2\sigma(I)$), wR_2 = 0.0687 (all data), $\Delta\rho_{max/min}$ = 1.371 [0.77 Å from Pd]/−0.692 e Å^{-3}.

[(IBiox12)PdCl$_2$]$_2$. IBiox12·HOTf (50 mg, 0.08 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), LiCl (100 mg, 2.38 mmol), and Cs_2CO_3 (26 mg, 0.08 mmol) were suspended in dioxane (3 mL) and stirred for 24 h at 100 °C. The solvent was removed, and the residue was extracted with DCM/water. Concentration of the organic layer and drying in high vacuum gave the complex as an orange solid (23 mg, 45%).

IR (KBr) 2928, 2861, 1759, 1470, 1444, 1422, 1364, 1292, 1210, 954, 860, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (bs, 8H, OCH_2), 3.01−2.50 (bs, 8H, $(CH_2)_{cylcododecyl}$), 2.30 (bs, 8H, $(CH_2)_{cylcododecyl}$), 1.92−1.11 (m, 72H, $(CH_2)_{cyclododecyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.7, 113.2, 84.6 (OCH_2), 69.7 ($C(CH_3)_2$), 35.2 (bs), 26.2 (bs), 24.6, 24.4 (bs), 23.9 (bs), 21.9 (bs)($(CH_2)_{cyclododecyl}$); MS (ESIpos/MeCN) 638 ((IBiox12)PdCl+MeCN), 561 ((IBiox12)PdCl−HCl), 457 (IBiox12).

Crystal data for [(IBiox12)PdCl$_2$]$_2$·1.3(C_6H_{14}): [$C_{58}H_{96}Cl_4N_4O_4Pd_2$]·1.3[$C_6H_{14}$], from dichloromethane/hexane, M_r = 1382.97, crystal size: 0.08 × 0.06 × 0.08 mm; a = 31.189(2), b = 8.7086(4), c = 23.904(1) Å, β = 94.711(2), V = 6470.7(5) Å^3, T = 100 K, monoclinic, space group $C2/c$ (No. 15), Z = 4, ρ_{calcd} = 1.420 g cm^{-3}, F(000) = 2923, Nonius KappaCCD diffractometer, λ(Mo Kα) = 0.71073 Å, μ = 0.771 mm^{-1}, 30 015 measured and 10 693 independent reflections (R_{int} = 0.053), 6676 with $I > 2\sigma(I)$, θ_{max} = 31.50°, T_{min} = 0.842, T_{max} = 1.00 (multiscan absorption correction), direct methods (SHELXS-97) and least-squares refinement (SHELXl-97) on F_o^2, both programs from G. Sheldrick, University of Göttingen, 1997; 340 parameters. The two cyclododecyl rings of the ligand are disordered and were modeled by C atoms with isotropic displacement parameters. The crystal also contains disordered hexane solute, which was similarly treated. Due to the extent of the disorder, no H atoms were included in the refinement. Chebyshev weights, R_1 = 0.0820 ($I > 2\sigma(I)$), wR_2 = 0.2211 (all data), $\Delta\rho_{max/min}$ = 3.343 [1.0 Å from Pd]/−0.961 e Å^{-3}.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. Crystallographic information files (CIF) are available for IBioxMe$_4$·HOTf, IBioxn·HOTf (n = 5,7,8,12), (IBiox6)Ir(CO)$_2$Cl, [(IBiox7)-PdCl$_2$]$_2$, and [(IBiox12)PdCl$_2$]$_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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