Aryl to Aryl Palladium Migration in the Heck and Suzuki Coupling of *o*-Halobiaryls

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Abstract: A novel 1,4-palladium migration between the *o*- and *o′*-positions of biaryls has been observed in organopalladium intermediates derived from *o*-halobiaryls. The organopalladium intermediates generated by this migration have been trapped either by a Heck reaction employing ethyl acrylate or by Suzuki cross-coupling using arylboronic acids. This palladium migration can be activated or deactivated by choosing the appropriate reaction conditions. Chemical and computational evidence supports the presence of an equilibrium that correlates with the C−H acidity of the available arene positions.

Introduction

The Heck[1−7] and Suzuki[8−11] cross-coupling reactions are probably the two most important Pd-catalyzed C−C bond forming methodologies, having found numerous applications in synthetic organic chemistry. The key organopalladium intermediates are generally prepared *in situ* by the oxidative addition of organic halides or triflates to Pd(0), and subsequent C−C bond formation usually occurs at the position originally occupied by the halide or triflate. For instance, Heck reactions employing *o*-bromobiaryls[12−14] and Suzuki cross-couplings with *o*-halobiphenyls[15] have been reported to give only the corresponding *ortho* substitution products. Thus, it was a great surprise to find that, upon carrying out Heck[16] reactions and Suzuki cross-couplings with *o*-halobiaryls under various reaction conditions, we obtained mixtures of the expected *o*- as well as the unexpected *o′*-derived Heck and Suzuki products. These observations suggest the presence of a 1,4-rearrangement of the palladium moiety between the *o*- and *o′*-positions of these biaryls. Scheme 1 illustrates how the palladium migration generates two different arylpalladium intermediates from a single *o*-halobiaryl substrate. Subsequent trapping of these two intermediates with either ethyl acrylate or arylboronic acids gives

Scheme 1
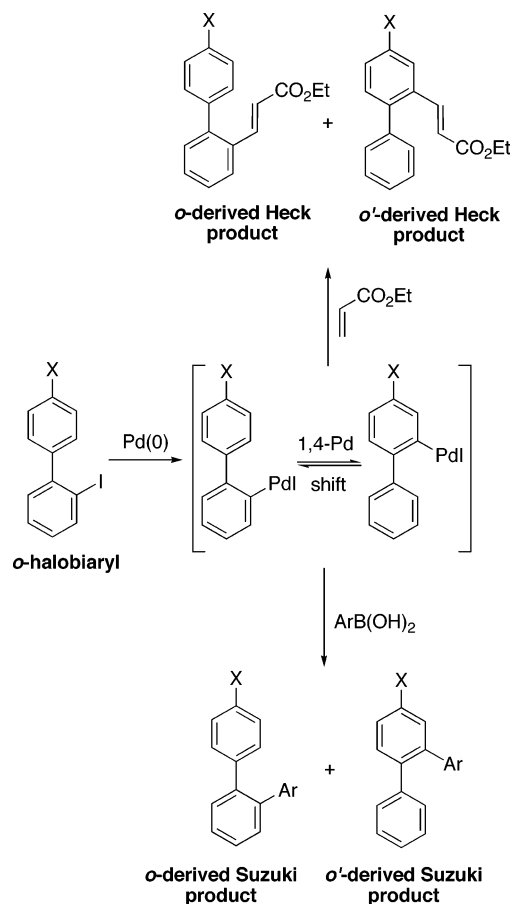
mixtures of *o*- and *o′*-derived Heck and Suzuki products, respectively.

We have previously communicated the 1,4-palladium migration in organopalladium intermediates derived from *o*-halobiaryls under Heck reaction conditions[16] and now wish to disclose the full details of our investigation on this fascinating process.

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Table 1. Pd-Catalyzed Reaction of 2-Iodo-4′-methylbiphenyl (**1a**) and Ethyl Acrylate (EA)[a]

|				mole ratio	
entry	equiv EA	conditions	time (d)	**2a:3a**[b]	% yield
1	4	TBAC, NaHCO$_3$[c]	1.0	100:0	100
2	4	TBAC, NaHCO$_3$	1.0	95:5	100
3	1	TBAC, NaHCO$_3$	1.0	77:23	92
4	1	TBAC, CsPiv	1.5	55:45	89
5	1	CsPiv	1.5	54:46	93
6	1	5% dppm, CsPiv	1.5	50:50	88
7	1	10% PPh$_3$, CsPiv	1.5	50:50	87
8	1	5% dppm, CsOAc	1.5	55:45	90
9	1	5% dppm, NaOAc	1.0	69:31	75
10	1	5% dppm, CsPiv[d]	1.0	75:25	94
11	1	5% dppm, Et$_3$N	1.0	100:0	90

[a] The reaction was run using 0.25 mmol of the iodobiaryl, ethyl acrylate (EA), 2 equiv of an appropriate base, and 1 equiv of *n*-Bu$_4$NCl (TBAC) where indicated in 4 mL of DMF at 100 °C unless otherwise indicated. [b] The mole ratio was determined by ^{1}H NMR spectroscopic analysis. [c] DMF (1 mL) as solvent. [d] Toluene (4 mL) as solvent.

Similar palladium migration side products were reported simultaneously by Gallagher during his study of the Heck olefination of halophenylpyridines.[17] In order to better understand the parameters governing palladium migration, we have also carried out a series of experiments under Suzuki cross-coupling reaction conditions, which have provided useful information on the basic reactivity of these biarylpalladium intermediates, as well as the overall kinetics of the system. Furthermore, we have used computational methods to model the migration tendencies of the palladium moiety within the biaryl and obtained results that are in good agreement with isolated product ratios.

Results and Discussion

Palladium Migration in Heck Reactions. In order to obtain a clear picture of how the reaction variables affect the palladium biaryl migration, we studied the behavior of 2-iodo-4′-methyl-biphenyl (**1a**, X = CH$_3$) and ethyl acrylate under various reaction conditions (Table 1). Under the classical reaction conditions described by Jeffrey[18] (procedure A), the expected ethyl *E*-3-(4′-methylbiphen-2-yl)acrylate (**2a**, X = CH$_3$) was obtained exclusively and in a quantitative yield (Table 1, entry 1). By diluting the reaction mixture 4-fold, we observed formation of small amounts of the migration product, ethyl *E*-3-(4-methylbiphen-2-yl)acrylate (**3a**, X = CH$_3$, entry 2), retaining the overall quantitative yield.
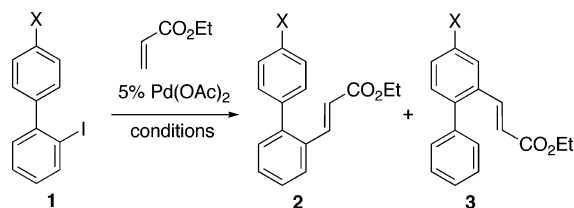
Reducing the number of equivalents of ethyl acrylate from 4 to 1 reduces the overall yield of Heck product to about 92% (entry 3) but gives a 77:23 mixture of **2a:3a**.[19] These observations suggest an underlying palladium migration reaction whose
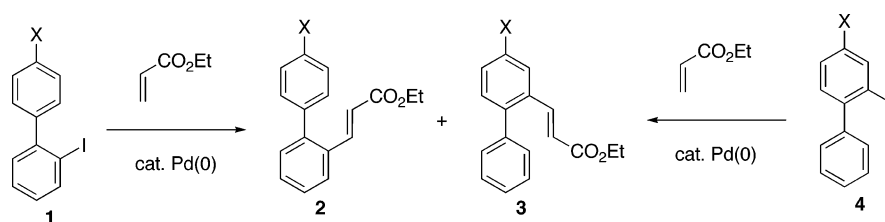
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(19) All stated yields are relative to the total amount of starting material, with reactions run until the starting material was completely consumed, unless stated otherwise.

Table 2. Heck Reaction of Substituted *o*-Halobiphenyls with Ethyl Acrylate

						mole ratio
entry	substrate	X	procedure[a]	time (d)	% yield	**2:3**[b]
1	**1a**	Me	A	1.0	100	100:0
2			C	1.5	88	50:50
3	**4a**	Me	A	1.0	93	0:100
4			C	1.5	86	49:51
5	**1b**	NMe$_2$	A	1.0	80	100:0
6			C	1.0	90	55:45
7	**4b**	NMe$_2$	A	1.0	100	0:100
8			C	1.5	93	49:51
9	**1c**	OMe	A	2.0	100	100:0
10			C	2.0	93	52:48
11	**4c**	OMe	A	2.0	99	0:100
12			C	2.0	92	48:52
13	**1d**	CO$_2$Et	A	2.0	72	100:0
14			D	1.0	86	48:52
15	**4d**	CO$_2$Et	A	1.0	99	0:100
16			D	1.0	83	42:58
17	**1e**	NO$_2$	B	1.0	85	100:0
18			D	2.5	46 (40)[c]	39:61
19	**4e**	NO$_2$	B	1.0	89	0:100
20			D	2.5	37 (50)[c]	33:67

[a] Procedure A: 0.25 mmol of the *o*-iodobiphenyl, 5 mol % Pd(OAc)$_2$, 1.0 equiv of *n*-Bu$_4$NCl, 2.0 equiv of NaHCO$_3$, and 4.0 equiv of ethyl acrylate in 1 mL of DMF at 100 °C. Procedure B: same as procedure A, except using 2.0 equiv of Et$_3$N as the base. Procedure C: 0.25 mmol of the *o*-iodobiphenyl, 1.0 equiv of ethyl acrylate, 5 mol % Pd(OAc)$_2$, 5 mol % dppm, and 2.0 equiv of CsPiv in 4 mL of DMF at 100 °C. Procedure D: same as procedure C, except using DMF (3.8 mL) and H$_2$O (0.2 mL) as the solvent. [b] The mole ratio was determined by ^{1}H NMR spectroscopic analysis. [c] The yield in parentheses is for the reduced biphenyl.

observation or suppression might be effected by manipulation of the kinetics through adjustment of the reaction conditions.

For example, replacing the NaHCO$_3$ with CsO$_2$CCMe$_3$ (CsPiv), we observed almost equal amounts of the direct olefination product **2a** and the rearranged product **3a** (entry 4). Furthermore, the addition of *n*-Bu$_4$NCl (TBAC) was unnecessary to achieve virtually the same results (entry 5). The use of phosphine ligands, such as 1,1-*bis*(diphenylphosphino)methane (dppm) and PPh$_3$, further changed the isomer distribution to 50:50 (entries 6 and 7).

The choice of carboxylate bases in the reaction mixture plays a critical role in the isomer distribution. Solubility may play an important role, but Fagnou has recently pointed out that pivalate is superior to acetate, methylpropionate, and adamantanecarboxylate under conditions where all of them were soluble in a closely related reaction.[20] Computational modeling by Fagnou demonstrated that pivalate lowered the transition state for Pd-catalyzed arylation of benzene over bicarbonate by 1.3 kcal/mol. In our experiments, under otherwise identical conditions, CsPiv, CsOAc, and NaOAc (which have decreasing solubilities in DMF) gave decreasing amounts of isomer **3a**, as shown in entries 6, 8, and 9. We also carried out the reaction under our standard migration conditions but used a less polar solvent, toluene, in which CsPiv has a much lower solubility than in DMF, and only one-fourth of the Heck product mixture was **3a** (94% overall, entry 10 versus entry 6). Indicating that solubility is certainly not the only consideration, the use of Et$_3$N as a base completely suppressed formation of the migration product. Using Et$_3$N instead of CsPiv under conditions otherwise identical to those of entry 6 (procedure B), we

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Scheme 2

obtained isomer **2a** exclusively in 90% yield (entry 11). The nature of carboxylates as bidentate ligands/bases may also play a mechanistic role.[20] However, beyond the phenomenological optimizations discussed here, we have not conducted further experiments to determine why pivalate appears to be optimal for migration.

It is important to note that by manipulating the reaction conditions, we can switch the palladium migration "on" or "off" in this biphenyl system.[21] Relating again to the recent work of Fagnou,[20] a reasonable hypothesis is that the pivalate is an optimum ligand and/or proton shuttle for enhancing the rate of the palladium migration. With other bases, the rate of migration is much slower than the rate at which the intermediate in the Heck reaction is captured. Beyond this association, though, our work remains simply phenomenological on this point.

Our optimal migration conditions for observing palladium migration are those described in entry 6 of Table 1 (procedure C), and the conditions employed to prevent palladium migration are those described in entry 1 (procedure A). Furthermore, it turned out that ethyl acrylate was superior to other olefins as a Heck trap. For instance, the reaction of **1a** with either methyl vinyl ketone or styrene using procedure C gave complex mixtures, and none of the desired Heck products were isolated.

In principle, the palladium migration ought also to occur with less reactive *o*-bromobiphenyls, assuming that the initial palladium-bearing intermediate can be generated and that the substitution of bromide for iodide as a possible ligand on the Pd has little effect on the reactivity. Thus, we attempted the Heck reaction of 2-bromo-4′-methylbiphenyl (**1a′**) and ethyl acrylate using procedure C but failed to observe any significant amount of Heck products after 3 d. When the same reaction was carried out using wet DMF (5% H_2O by volume) as the reaction solvent, compound **1a′** produced a 50:50 mixture of **2a** and **3a** in 49% yield, along with 45% of 4-methylbiphenyl, the product of reduction of the C−Br bond. The iodo-bearing analogue, 2-iodo-4′-methylbiphenyl (**1a**), and ethyl acrylate also reacted under the latter reaction conditions to produce a 50:50 mixture of **2a** and **3a** in 85% yield, verifying that **1a** and **1a′** generate identical mixtures of **2a** and **3a** under the same reaction conditions. Thus, two different palladium migration procedures have been developed, namely procedure C, which is described in entry 6 of Table 1, and procedure D, where 5% of the DMF is replaced by water.

Having observed these 50:50 product distributions, an obvious question is whether, under such conditions, 2-iodo-4-methyl-biphenyl (**4a**) and ethyl acrylate would generate the same distribution of isomers **2a** and **3a** as previously obtained from **1a** and ethyl acrylate (Scheme 2). Indeed, substrate **4a** generated

a 49:51 mixture of isomers **2a** and **3a** in 86% yield using our optimized palladium migration procedure C (entry 4, Table 2). This result seems to indicate that, under our optimal palladium migration reaction conditions, the arylpalladium intermediates, generated from either **1a** or **4a**, undergo apparent equilibration prior to olefin trapping and, thus, generate essentially identical mixtures of **2a** and **3a**. (Compare entries 2 and 4 of Table 2.) As with **1a**, we were able to suppress the palladium migration by carrying the reaction out under the conditions described by Jeffrey (procedure A). Thus, **4a** produced **3a** exclusively, in 93% yield, under the Jeffrey conditions (entry 3, Table 2).

To explore the relationship between electronic effects in the *o*-iodobiphenyls and the ratio of Heck products, we studied the reaction of various substituted *o*-iodobiphenyls with ethyl acrylate under our standard palladium migration conditions; the data are presented in Table 2. Two groups classically thought of as π-electron donating were chosen: 4′-methoxy and 4′-dimethylamino. The use of Jeffrey's conditions led to formation of only the "expected" Heck product; upon reaction with ethyl acrylate, **1b** and **4b** produced **2b** and **3b**, respectively, in 80 and 100% yields (entries 5 and 7). Correspondingly, under Jeffrey's conditions, **1c** and **4c** produced **2c** and **3c** in quantitative and 99% yields, respectively (entries 9 and 11).

Reactions of the methoxy- and dimethylamino- substrates using procedure C produced near, but apparently not quite complete, equilibration of the Pd before trapping. In each instance, there was a slight preference for trapping the initial Pd intermediate. Thus, reaction of **1b** produced a 55:45 mixture of isomers **2b** and **3b** in 90% overall yield, while a 49:51 mixture of **2b** and **3b** was obtained in 93% yield from **4b** (entries 6 and 8). Compound **1c** produced a 52:48 mixture of **2c** and **3c** in 93% total yield (entry 10), and compound **4c** gave a 48:52 distribution in 92% yield (entry 12). This observation of "near-equilibration" is important mechanistically, because it indicates that the product distribution is not likely dominated by differential trapping rates after full and relatively rapid equilibration. Instead, it implies that the equilibration and trapping occur on comparable timescales and that the product distributions are at least qualitative indicators of the equilibrium distribution of the Pd among the available sites.

Next, we switched our attention to the Heck reactions of biphenyls bearing electron-withdrawing substituents, choosing CO_2Et and NO_2 as representative groups. Although the Pd-catalyzed reactions of **1d** and **4d** with ethyl acrylate were unsuccessful using procedure C, the reaction proceeded smoothly using procedure D. Thus, **1d** produced a 48:52 mixture of **2d** and **3d** in 86% yield (entry 14), while **4d** produced a 42:58 mixture of **2d** and **3d** in 83% yield (entry 16). Again, the small difference in distribution is attributed to near-equilibration of the corresponding arylpalladium intermediates. The average ratio of **2d** to **3d** is 45:55, which indicates that there is a slight

(21) To be more precise, we can switch on or off the formation of the migration product. The present evidence does not directly speak to whether the migration is slowed or whether the coupling reactions are accelerated.
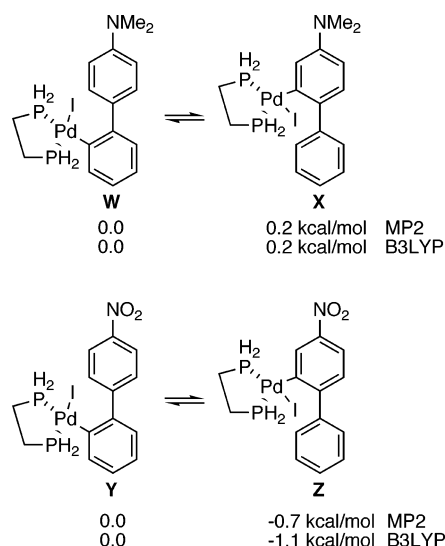
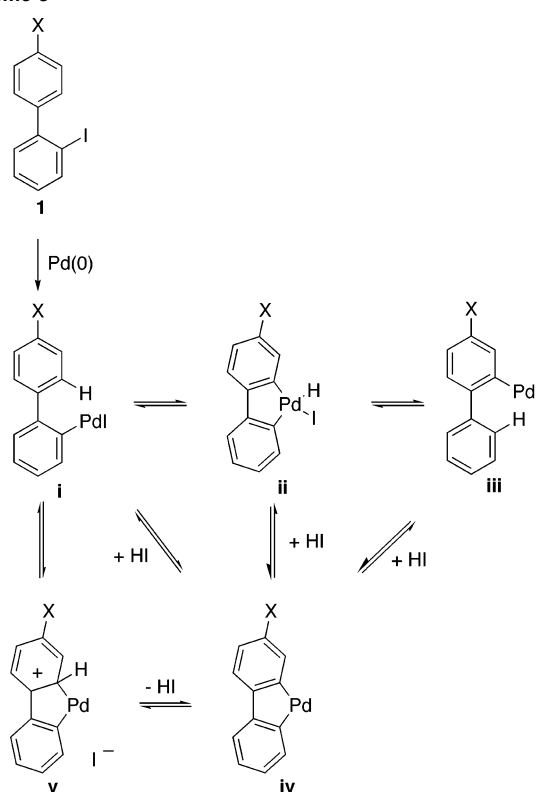**Figure 1.** Computed enthalpy differences for isomerization of W and Y.

tendency for these iodobiphenyls to form isomer **3d**. The Heck reactions of the strong electron-withdrawing nitro-substituted biphenyls **1e** and **4e** exhibit a pattern like that observed previously with the ester-substituted biphenyls. Using procedure D, **1e** generated a 39:61 mixture of **2e** and **3e** respectively in 46% yield, plus a 40% yield of reduction product (entry 18). Under the same conditions, aryl iodide **4e** produced a 33:67 mixture of **2e** and **3e** in 37% yield, plus a 50% yield of the reduction product (entry 20). The average ratio of **2e** to **3e** is 36:64, again showing a preference for forming the isomer in which the Heck coupling occurs on the ring that bears the electron-withdrawing substituent. Entries 13, 15, 17, and 19 show the controls, in which each starting material is converted exclusively to the conventional Heck product. Use of Et₃N was necessary in the case of compounds **1e** and **4e** in order to eliminate small amounts of migration products that were observed under the usual Jeffrey NaHCO₃ conditions (procedure A).

Computational Evidence of Equilibrium Distributions. In order to test the hypothesis that the equilibrium mixtures of the key arylpalladium intermediates are reflected in the product mixtures obtained under equilibrating conditions, calculations were carried out on two selected systems, one with a strong electron-donating substituent and the other with a strong electron-withdrawing group. Thus, the energies[22] of the four species W−Z were calculated at both the MP2 and B3LYP levels of theory with basis sets chosen to be as accurate as reasonable without making the calculation unreasonably time- and resource-consuming. As shown in Figure 1, the energy differences between the 2- and 2′-palladated isomers of both 4-(dimethylamino)biphenyl and 4-nitrobiphenyl are small and correspond to the direction of the apparent equilibria derived from the products.

Given the uncertainties involved in computational chemistry, including the slight simplification of the molecules and the lack of solvent treatment, the energy differences cannot be taken literally. However, the fact that they are very small is quite

Scheme 3

consistent with the near 50:50 mixtures of Heck products obtained under equilibrating conditions. Moreover, compound Z corresponds to the precursor to **3e** (entries 17−20, Table 2), and the slight preference for the 2-isomer is correctly predicted; the trend slightly in the other direction for electron-donating substituents (e.g., **2a-c** vs **3a-c**) is also predicted.

Mechanistic Considerations. Taking all these data into account, the migration of Pd in intermediates represented by **W** and **X** seems well, if indirectly, established. However, the precise mechanism by which migration occurs is not. In Scheme 3, we consider potential pathways for the palladium migration. (For simplicity, not all ligands on the Pd are shown.) After oxidative addition of the aryl halide to Pd(0) to generate intermediate **i**, three mechanistic possibilities are imagined. The initial intermediate may undergo oxidative addition of a neighboring C−H bond to produce hydridopalla(IV)cycle (**ii**), followed by reductive elimination of C−H to generate either **iii** or **i**. Alternatively, **i**, **ii**, and **iii**, might interconvert via pallada-(II)cycle **iv**.

Finally, **iv** might be formed by an electrophilic reaction step via **v**, as illustrated for **i**.[23,24−27] The current data in Table 2 and elsewhere are inconsistent with the selectivity expected with such a mechanism. Moreover, selectivity studies on intramolecular arylation, similar to the chemistry of Fagnou, by Maseras and Echavarren,[28] and others[29] do not support an electrophilic

(22) Energies are for gas phase calculations, including zero-point energies. Basis sets are as follows: C and H, 6-31G(d); N and O, 6-311+G(2d); P, 6-311+G(3df); I, LANL2DZ + s and p diffuse functions and d and f polarization functions; Pd, LANL2DZ with f polarization functions.

(23) For leading mechanistic studies suggesting electrophilic species in intramolecular C−H activation by palladium, see refs 24−27.
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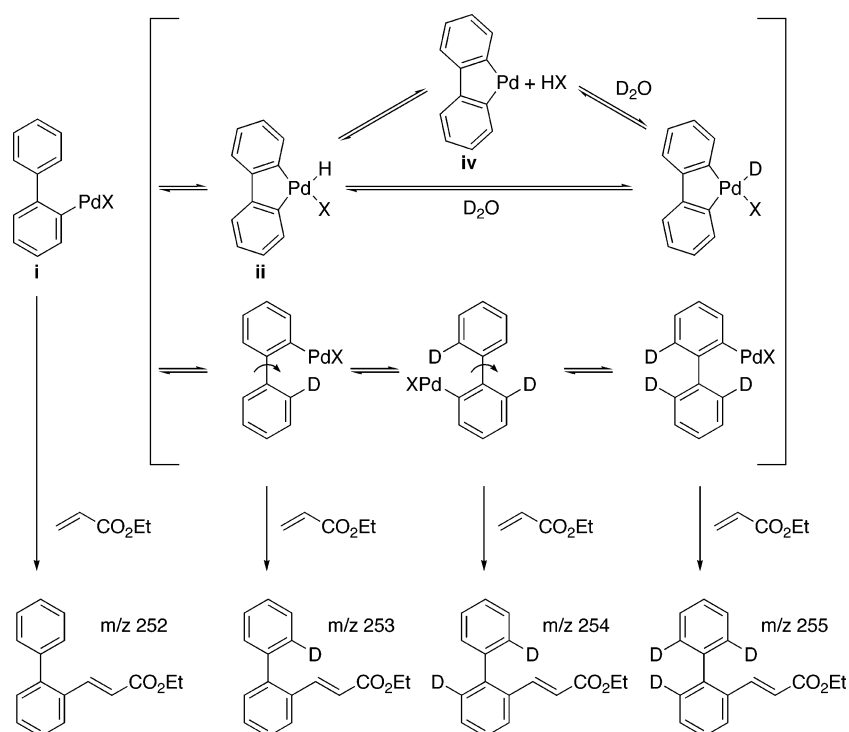(25) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *425*, 151−4.
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(28) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066−1067.

Scheme 4

mechanism. Simply put, the pattern of reactivity for electron-donating and -withdrawing groups is inconsistent with formation of **v**, and we will not consider an electrophilic palladation mechanism further.

Although recent computational evidence in a related reaction favored an analogue of **iv** over the analogue of **ii**,[30] we wished to consider the intermediacy of **ii** for two reasons. First, it seems improbable that intermediate **iv** could react with HI under the basic reaction conditions we have employed. Second, Catellani and Chiusoli have suggested that pallada(II)cycles analogous to intermediate **iv** easily undergo oxidative addition of aryl and alkyl halides to generate palladium(IV) intermediates generating characteristic polycyclic compounds,[31-37] which have not been observed under our reaction conditions.

Organopalladium(IV) species are well-known,[38] although no such hydride-containing species have ever been isolated.[39-41] As a result, we sought evidence for the reversible interconversion between **i** and **iii** via hydridopallada(IV)cycle **ii**. We report two sets of experiments carried out to test whether the intermediacy of **ii** could be disproved or supported. Neither has allowed us to distinguish between **ii** and **iv** definitively.

Nonetheless, as they are directly consistent with both possibilities, they merit discussion.

The first measurements involve the incorporation of deuterium into the product when employing an overwhelming excess of D$_2$O. In the presence of D$_2$O, deuterium incorporation in the *ortho* positions would be expected if the migration proceeds through formation of **iv**. If equilibration of the Pd substituent among the *ortho* positions is substantially faster than the coupling step, then virtually complete D incorporation would be expected in the three available positions, as shown in Scheme 4. Lack of deuterium incorporation would, of course, imply that no intermediate with exchangeable H was involved and, thus, eliminate **iv** as an intermediate. The rate of hydrogen exchange in **ii** is unknown. However, if it were slow enough, migration could occur without incorporation of deuterium.

We first treated 2-iodobiphenyl and 4 equiv of ethyl acrylate with 5 mol % Pd(OAc)$_2$, 5 mol % dppm, 1 equiv of TBAC, 2 equiv of NaHCO$_3$ in 1 mL of DMF, and 0.05 mL of D$_2$O (procedure A), conditions under which migration is not observed. No deuterium incorporation in the *ortho* positions of the coupled product is expected, because only the original position of the I-substituent is ever activated. This expectation was met for the ester product, as analyzed by ^{1}H NMR and GC–MS.

However, for this reaction, when conducted using procedure D, but employing 0.2 mL of D$_2$O, instead of 0.2 mL of H$_2$O, an overall average of approximately two hydrogens were substituted by deuterium, as indicated by the ^{1}H NMR spectrum of the ester product obtained. A broad peak in the ^{2}H NMR spectrum at 7.4 ppm was also observed, consistent with deuterium incorporation occurring at more than one carbon atom. Mass spectral data indicated that comparable amounts of

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the nondeuterated (m/z 252), monodeuterated (m/z 253), dideuterated (m/z 254), and trideuterated (m/z 255) esters were observed.

The observed incomplete deuteration indicates that our "equilibrating" conditions are not such that migration of the Pd species is orders of magnitude faster than the coupling step, just as the product distributions from **1** and **4** also indictate. However, this result does not clearly distinguish between the intermediacy of **ii** and **iv**, because, while it is obvious that H exchange would occur with formation of **iv**, it is also reasonable that H exchange could occur with **ii** as the key intermediate, even if **iv** were never formed.

To explore this further, an equivalent experiment using the substituted starting material **1d** in the presence of excess D_2O was run. For **1d** to yield **3d**, it is required that palladium migration occurs as part of the sequence. Thus, if **iv** is an intermediate, then at least one deuterium *must* be incorporated. However, if **iv** is not an intermediate and Pd–H exchange from intermediates like **ii** is sufficiently slow, some **3d** might be formed without any deuteria. In the event, all of the isolated **3d** contained at least one deuterium, as determined by mass spectrometry. Again, this result is necessary, but not sufficient, to prove the involvement of **iv**.

A second experiment involved the formation of **iv** via an alternate synthetic pathway. Biphenylene has been reported to react under some conditions with Pd(0) to generate **iv** (X = H),[42] which can also undergo Heck and Suzuki couplings.[43] If this were to occur under our optimal equilibration reaction conditions, the same ester products should be observed from biphenylene as from 2-iodobiphenyl. Thus, use of a substituted biphenylene derivative should give very similar product ratios to the other precursors generated under equilibrating conditions (see Table 2) and might give a distinct product distribution under our nonequilibrating conditions.

However, biphenylene was not an effective precursor to the Heck product under our conditions. When biphenylene was allowed to react with 1 equiv of ethyl acrylate (0.25 mmol) in the presence of 5 mol % Pd(OAc)$_2$, 5 mol % dppm, 2 equiv of CsPiv in 3.8 mL of DMF, and 0.2 mL of D_2O, GC–MS spectral analysis indicated that, after reaction for 1 d, none of the anticipated ester product was obtained and only the starting biphenylene was present. Since 1 equiv of HI acid is usually generated in our Heck palladium migration reactions, this reaction was repeated in the presence of 1 equiv of DCl. Again, none of the anticipated Heck product was obtained. This reaction was also conducted using 1 equiv of Pd(OAc)$_2$. After reaction for 1 d, only biphenylene was evident by GC–MS spectral analysis.
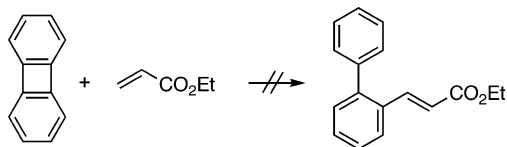
This result is, again, mechanistically ambiguous regarding the Pd migration. The most likely cause of the problem may be that the conditions were not conducive to Pd insertion into the

biphenylene C–C bond. Indeed, Gallagher has demonstrated directly a kinetic preference for Pd insertion into aryl bromides over biphenylene.[44] Alternatively, it could be that **iv** is reversibly formed but unreactive under the conditions (and thus excluded mechanistically from the palladium migration chemistry). However, without any other evidence for the formation of **iv**, such a conclusion cannot be drawn.

Other workers have considered this question as well. The computational results of Dedieu[30] and Fagnou[45] on couplings
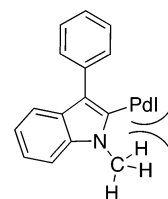
closely related to the chemistry described here are consistent with a concerted four-centered transition state for activation of the arene. Dedieu argues that a Pd-hydride species analogous to **ii** is several kcal/mol above the low-energy pathway, in which a Pd(II) intermediate is formed directly. Fagnou's computations show a low-energy pathway that directly produces a Pd(II) intermediate and HBr (by proton transfer to a Br ligand on the catalyst.) We recognize that the analogous intermediate in both cases is **iv**, rather than **ii**, and we have no direct evidence supporting the formation of **ii**, although the previously outlined chemical arguments for **ii** remain.

Effects of Other Substituents. For a more general understanding of the scope and generality of the Pd migration in the Heck reaction, several other substituted biaryls have been investigated, as illustrated in Scheme 5. The reaction of 2-iodo-3-phenylbenzofuran (**5**) and ethyl acrylate using procedure C gives exclusively ethyl *E*-3-(3-phenylbenzofuran-2-yl)acrylate (**6**) in 85% yield in 24 h. This result, showing no apparent 1,4-Pd shift, suggested that palladium has a strong preference for the 2-position of the benzofuran moiety. To test this hypothesis, 3-(2-iodophenyl)benzofuran (**8**) was used as a substrate under the same conditions. Acrylate **6** was produced in 24 h in 78% yield, alongside only ~5% of isomer **7**, indicating a strong preference for palladium to migrate from the phenyl to the benzofuran ring.[46,47] As before, however, from the product distributions alone, we cannot specifically rule out the possibility that very different reactivities of the two arylpalladium intermediates toward ethyl acrylate could be favoring the formation of **6**, although this seems unlikely, given the preponderance of evidence. Once again, as a control experiment, compound **7** was prepared as the sole product from **8** in 75% yield in 24 h by carrying out the Heck reaction with ethyl acrylate under Jeffrey's reaction conditions (procedure A).

Similarly, the *N*-methylindole analogues of **5** and **8** were reacted with ethyl acrylate (Scheme 5). Using procedure C, **9** produced exclusively *E*-3-(1-methyl-3-phenylindol-2-yl)acrylate (**10**) in 94% yield in 24 h; a mixture of 77% **10** and 13% **11**

(42) Edelbach, B. L.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2843–2853.
(43) Satoh, T.; Jones, W. D. *Organometallics* **2001**, *20*, 2916–2919.

(44) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694–695.
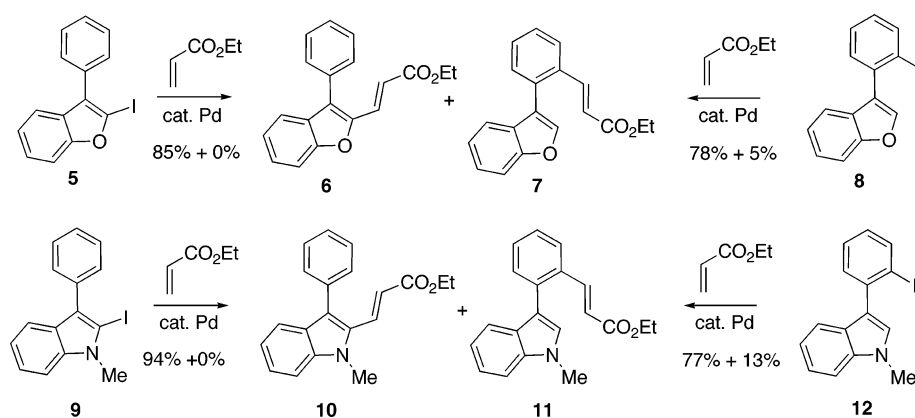(45) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756.
(46) The 2-position of benzofuran can readily be palladated catalytically via C–H activation. See ref 47 for a leading reference.
(47) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097–2100.

Scheme 5

was obtained from 3-(2-iodophenyl)-1-methylindole (**12**). Using procedure A as the nonmigration control again, an 85% yield of **11** was obtained from **12**.

We believed that the 13 mol % of indole acrylate **11**, generated from **12** through procedure C, is a result of slow palladium equilibration, which might be due to unfavorable steric interactions imposed on the palladium when migrating to the relatively more hindered 2-position of the *N*-methylindole. Therefore, we postulated that steric hindrance might be a significant factor in this palladium migration chemistry disfavoring sterically congested arylpalladium intermediates.

In order to study the effect of steric hindrance on the palladium migration, we prepared 2-iodo-3′,5′-dimethylbiphenyl (**13**). The methyl substituent is not likely to chelate palladium, and it appears to be essentially electronically neutral in the palladium migration, based on the data reported in Table 2. Using procedure A as the control, **14** was obtained in a 97% yield, without formation of **15**, as expected. Using the equilibrating procedure C, **14** was still the exclusive Heck product, formed in 94% yield. We thus conclude that the steric bulk of an adjacent methyl group is sufficient to strongly inhibit palladium migration. Unfortunately, we have been unable to prepare 2-iodo-3,5-dimethylbiphenyl to examine its palladium migration chemistry.
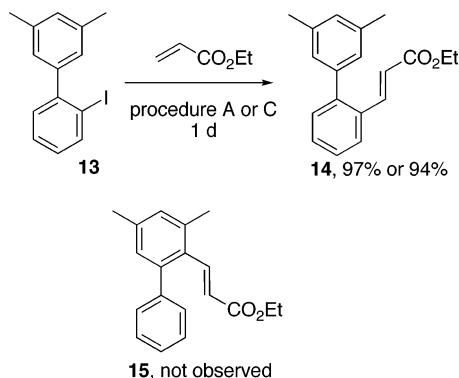
A related example of palladium migration involves the Heck reaction of 2-iodo-2′-methylbiphenyl (**16**). Steric congestion is not reduced by migration of the Pd because the methyl and iodo/Pd substituents are not in the same plane. (We presume the two phenyl planes are nearly perpendicular in the low energy conformation.) Thus, while procedure A results in the formation of **17** in a 92% yield as the only Heck product, procedure C

results in the formation of a 65:35 mixture of isomers **17** and **18** (in 91% overall yield), within experimental error of the statistical 2:1 ratio.
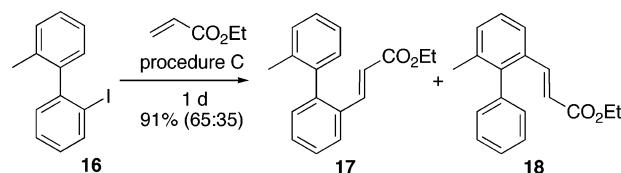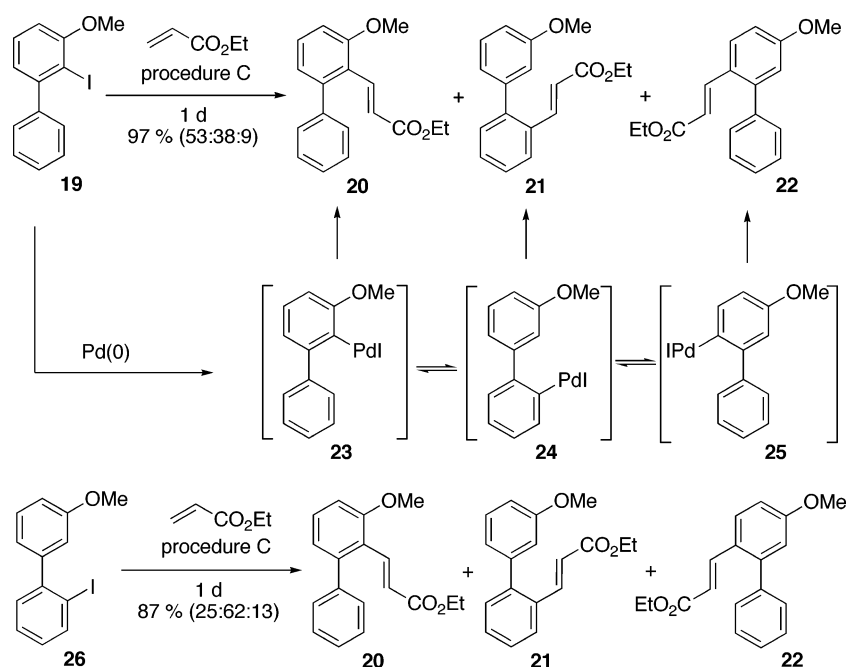

The multiply deuterated products discussed previously (Scheme 4) clearly indicate that multiple migrations can occur before the key coupling step. This can be dramatically demonstrated in another way by employing a substituent in the *meta* position, as illustrated in Scheme 6. Thus 2-iodo-3-methoxybiphenyl (**19**) produces isomers **20**−**22** (53:38:9 respectively, in 97% overall yield) using equilibrating procedure C. The presence of the key intermediate **25**, generated after a minimum of two 1,4-Pd shifts between the 2-, 2′-, and 6-positions of the biphenyl, explains the formation of isomer **22**.

Interestingly, the reaction of 2-iodo-3′-methoxybiphenyl (**26**) and ethyl acrylate using procedure C produced a 25:62:13 mixture of compounds **20**, **21**, and **22**, respectively, in 87% overall yield (Scheme 6). The wide discrepancy in the Heck product distributions obtained from the reaction of **19** versus **26** indicates that palladium is unable to achieve equilibrium between the three different positions of the biphenyl prior to olefin trapping under the reaction conditions employed. This result is consistent with the deuterium exchange results and some of the entries in Table 2, both of which imply that a true equilibrium is not quite achieved before the carbon−carbon coupling step.

Another factor that may add to the complexity of this particular system is the possibility of intramolecular oxygen chelation in the arylpalladium intermediate **23**. Such chelation would obviously affect both the rates and equilibrium, presumably in a manner opposite to that expected due to the steric hindrance of the methoxy group.

Palladium Migration in Suzuki Reactions. After exploring the Heck reaction, we proceeded to examine the Suzuki cross-coupling[2] of the same *o*-halobiaryls with arylboronic acids. Because the conditions for the Suzuki and Heck reactions differ, we cannot assume that the rate of palladium migration will be identical in both processes. However, understanding the relative rates of migration vs coupling in the Suzuki reaction and the

Scheme 6

19 → **20** + **21** + **22**

procedure C, 1 d, 97 % (53:38:9)

Pd(0) → **23** ⇌ **24** ⇌ **25**

26 → **20** + **21** + **22**

procedure C, 1 d, 87 % (25:62:13)

Table 3. Pd-Catalyzed Reaction of 2-Iodo-4′-methylbiphenyl (**1a**) and 4-(Methoxycarbonyl)phenylboronic Acid (**27a**)

entry	23a, equiv	procedure[a]	time, h	mole ratio 28a:29a[b]	% yield
1	1.2	E	8	100:0	62
2	1.0	F	72		trace
3	1.0	F + 20 H$_2$O	8	57:43	55
4	1.0	F + 20 H$_2$O + 2 PA[c]	24	50:50	57
5	1.4	F + 20 H$_2$O + 2 PA[c]	4	51:49	78

[a] All reactions were run using 0.25 mmol of **1a**, 5 mol % Pd(OAc)$_2$, and appropriate equivalents of boronic acid **27a** and base. Procedure E: 10 mol % PPh$_3$, 2.2 equiv of CsF in 1 mL of DME at 90 °C. Procedure F: 5 mol % (Ph$_2$P)$_2$CH$_2$ (dppm) and 2.0 equiv of CsPiv in 4 mL of DMF at 100 °C. [b] The mole ratio was determined by ^{1}H NMR spectroscopic analysis. [c] PA = pivalic acid (Me$_3$CCO$_2$H).

compatibility of the Suzuki reaction with palladium migration for synthetic purposes was of interest. To establish what reaction conditions best promote palladium migration, we first studied the Suzuki coupling of 2-iodo-4′-methylbiphenyl (**1a**) and 4-(methoxycarbonyl)phenylboronic acid (**27a**) under various reaction conditions (Table 3).

1a + ArB(OH)$_2$, cat. Pd → [1,4-Pd shift] → **28a** + **29a**

Ar = *p*-MeO$_2$CC$_6$H$_4$ (**27a**)
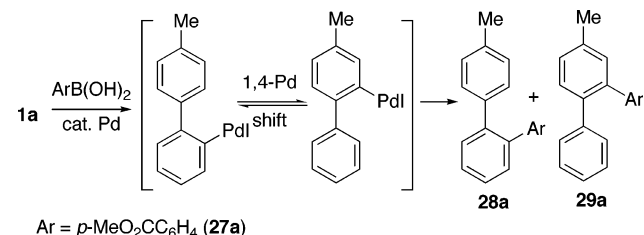
The Pd-catalyzed Suzuki coupling of **1a** and **27a** under conditions described by Wright et al.[48] [0.25 mmol **1a**, 5 mol % Pd(OAc)$_2$, 10 mol % PPh$_3$, 1.2 equiv of boronic acid and 2.2 equiv of CsF in 1 mL of DME at 90 °C, procedure E] produced methyl 4′-methyl-*o*-terphenyl-4-carboxylate (**28a**) in 62% yield (entry 1, Table 3), with no other Suzuki product. In

an attempt to promote palladium migration, the coupling reaction of **1a** and **27a** was then carried out under migration conditions similar to those employed in procedure C for the Heck reaction (entry 2). However, only trace amounts of coupling products were observed. It has been reported that the addition of water facilitates Suzuki coupling reactions.[14] Therefore, we carried out the coupling reaction of **1a** and **27a** in the presence of 20 equiv of H$_2$O and obtained a 57:43 mixture of Suzuki product **28a** and palladium migration product **29a** in 55% overall yield (entry 3). Based on previous experience with the Heck reaction, it was assumed that the true "equilibrium" distribution of the two products should be approximately 1:1, so conditions were sought which would approach that ratio.

Realizing that the presence of base probably activates the arylboronic acid toward direct Suzuki coupling prior to palladium migration, we buffered the reaction mixture using a combination of 2 equiv of cesium pivalate (CsPiv) and 2 equiv of pivalic acid (PA). To our satisfaction, the reaction of **1a** and **27a** under these buffered conditions produced a 50:50 mixture of **28a** and **29a** in 57% overall yield (entry 4). An even higher overall yield (78%) of a 51:49 mixture of **28a** and **29a** could be obtained by employing 1.4 equiv of the arylboronic acid **27a** (entry 5, also entry 1 in Table 4).

An identical distribution of Suzuki products, in 83% overall yield, was obtained from **4a** (X = Me, Scheme 7). Thus, we chose this latter set of reaction conditions, described in entry 5, Table 3, as our standard palladium migration conditions for the Suzuki coupling of *o*-iodobiphenyls with other arylboronic acids (Scheme 7, Table 4). The iodobiaryls **1a** and **4a** gave similar distributions of Suzuki products **28a** and **29a** when coupled with either phenylboronic acid (**27b**) or 4-methoxyphenylboronic acid (**27c**) using our standard Suzuki migration procedure (Table 4, entries 3−6). The insensitivity of the product ratio to the electron demand of the boronic acids implies that the product distribution is determined by the equilibrium position of the palladated intermediate before transmetallation.

(48) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

Table 4. Pd-Catalyzed Reaction of *o*-Iodobiphenyls (**1** and **4**) and Arylboronic Acids (**27**) Using the Standard Suzuki Migration Procedure[a]

entry	biphenyl, X =	ArB(OH)$_2$, Ar =	time (h)	mole ratio 28:29[b]	% yield
1	**1a**, Me	*p*-MeO$_2$CC$_6$H$_4$ (**27a**)	4	51:49	78
2	**4a**, Me	(**27a**)	6	49:51	83
3	**1a**, Me	Ph (**27b**)	3	52:48	79
4	**4a**, Me	(**27b**)	10	50:50	69
5	**1a**, Me	*p*-MeOC$_6$H$_4$ (**27c**)	3	52:48	93
6	**4a**, Me	(**27c**)	6	49:51	90
7	**1b**, MeO	(**27a**)	4	42:58	85
8	**4b**, MeO	(**27a**)	9	39:61	75
9	**1c**, CO$_2$Et	(**27a**)	10	40:60	84
10	**4c**, CO$_2$Et	(**27a**)	10	34:66	68
11	**1d**, NO$_2$	(**27a**)	25	23:77	61
12	**4d**, NO$_2$	(**27a**)	10	16:84	75

[a] All reactions were run using 0.25 mmol of the *o*-iodobiphenyl, 1.4 equiv of arylboronic acid, 5 mol % Pd(OAc)$_2$, 5 mol % dppm, 2.0 equiv of CsPiv, 2.0 equiv of PA, and 20 equiv of H$_2$O in 4 mL of DMF at 100 °C. [b] The mole ratio was determined by ^{1}H NMR spectroscopic analysis.

Scheme 7
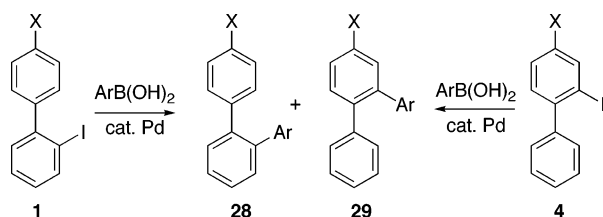
Interestingly, the Pd-catalyzed reactions of the methoxy, carbethoxy, and nitro-substituted *o*-iodobiphenyls **1b**−**d** and **4b**−**d** (X=MeO, CO$_2$Et, NO$_2$) with boronic acid **27a** using our standard Suzuki migration procedure show a consistent trend in the distribution of Suzuki products (entries 7−12), slightly favoring coupling on the substituted phenyl ring. (Control reactions under the Wright conditions provide **4a**−**d** as the only Suzuki products in 62−98% yields.) If these product distributions, along with estimates based on averages from the corresponding Heck reactions, can be taken as qualitative indicators of the equilibrium position of the Pd in the substituted biphenyls, the most sensible correlation consistent with the order NO$_2$ > CO$_2$Et > OCH$_3$ > H is that of *inductive* electron withdrawal by the substituent, i.e., through the sigma framework, rather than through the pi system.

Similar to previous observations on the Heck reaction, an even more marked effect on the product distribution was observed in the reaction of 2-iodo-3-phenylbenzofuran (**5**) with 4-(methoxycarbonyl)phenylboronic acid (**27a**), which under our Suzuki migration conditions gave exclusively 2-[4-(methoxy-carbonyl)phenyl]-3-phenylbenzofuran (**30**) in 79% yield after 3 h (Scheme 8). Obviously, no palladium migration has occurred in this biaryl system. On the other hand, when 3-(2-iodophenyl)-benzofuran (**8**) was allowed to react with boronic acid **27a** under our standard Suzuki palladium migration conditions, **30** was produced in 78% yield in 3 h, along with only ∼5% of isomer **31**. These results again clearly show a preference for palladium migration from the phenyl ring to the benzofuran ring.[47] Furthermore, a 75% yield of **31**, along with only ∼7% of benzofuran **30**, was formed from **8** when employing the reaction conditions described by Wright et al.[48]

Again, the indole analogue was examined. Reaction of 2-iodo-1-methyl-3-phenylindole (**9**) and boronic acid **27a** under our

standard Suzuki palladium migration conditions gave only **32** in 67% yield in 3 h (Scheme 9). When 3-(2-iodophenyl)-1-methylindole (**12**) was allowed to react with **27a**, the migration product **32** was produced in a 57% yield in 6 h, along with a trace amount of isomer **33**, which clearly indicates a preference for palladium migration from the phenyl ring to the indole ring.[15] Adduct **33** can be obtained exclusively in 79% yield when **12** is allowed to react with boronic acid **27a** under the nonmigration conditions described by Wright et al.[48]

Basis for Selectivity. It is our working hypothesis that the mixtures obtained under "equilibrating" conditions qualitatively reflect the preferred position of the Pd, rather than differing rates of reactivity of the arylpalladium complexes. Clearly, the reactivity patterns are not consistent with the pi system of the benzene ring acting as a nucleophile, as in electrophilic aromatic substitution. Rather, as noted, there appears to be a correlation between inductive electron withdrawal or C−H acidity and the favored position.[49]

Fagnou recently showed that haloarenes can be coupled to various fluoroarenes with Pd catalysts by C−H activation of the fluoroarene.[45] Selectivity studies showed a clear correlation between C−H acidity and regiochemistry of C−H activation/coupling in the Fagnou chemistry, indicating at least a kinetic selectivity, and presumably a thermodynamic one as well. The current palladium migration chemistry might be viewed as entropically activated C−H activation, the lower requirements of inherent C−H acidity being overcome by the preorganization aspect of the intramolecular reaction. In fact, intramolecular coupling to form biaryls using arenes bearing no electron-withdrawing groups (and even methoxy groups) have been reported by Fagnou as well.[50]

Conclusions

We have observed a number of palladium-catalyzed reactions that proceed by 1,4-palladium migration in organopalladium intermediates derived from *o*-halobiaryls. These arylpalladium intermediates have been generated under relatively mild reaction conditions compatible with the Heck and Suzuki reactions. We have developed standard migration reaction conditions, which allow arylpalladium intermediates to approach equilibrium prior to the trapping step. The palladium migration can be activated or suppressed at will by simple manipulation of the reaction conditions, and the selectivities for the equilibrated position appear to correlate most strongly with anticipated C−H acidity.

Experimental Section

General Procedure for the Heck Coupling of *o*-Iodobiaryls with Ethyl Acrylate under the Conditions Described by Jeffrey et al. (Procedures A and B).[18] 2-Iodo-4′-methylbiphenyl (73.5 mg, 0.25 mmol), Pd(OAc)$_2$ (2.8 mg, 0.0125 mmol), *n*-Bu$_4$NCl (0.0694 g, 0.25 mmol), NaHCO$_3$ (0.042 g, 0.5 mmol), and ethyl acrylate (0.10 g, 1.0 mmol) in DMF (1 mL) under Ar at 100 °C were stirred for 1 d (procedure A). The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL), and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried (MgSO$_4$), and filtered, and

(49) Computations on the enthalpies of the corresponding naked anions of model biaryls are qualitatively consistent with the product distributions, although the energy differences are much larger than our observed product distributions justify. See the Supporting Information for these data and a brief discussion.

(50) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186−9187.

Scheme 8
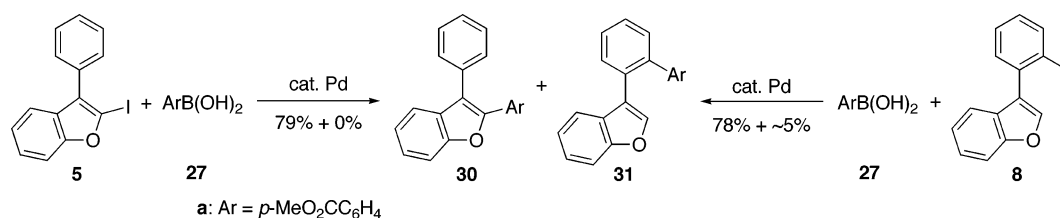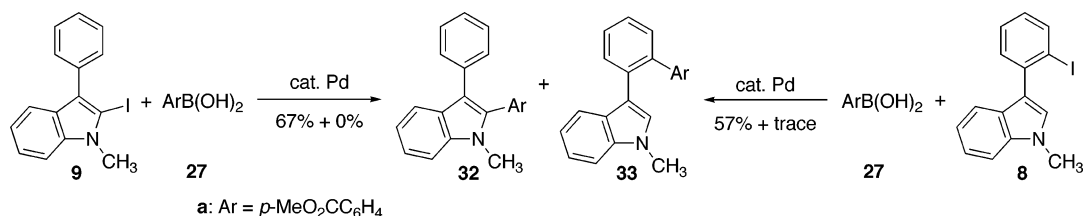
a: Ar = *p*-MeO₂CC₆H₄

Scheme 9

a: Ar = *p*-MeO₂CC₆H₄

the solvent was removed under reduced pressure. The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 66.6 mg (100%) of ethyl *E*-3-(4′-methylbiphen-2-yl)acrylate (**2a**) as a clear oil.[16] In procedure B, the NaHCO₃ was replaced by Et₃N (0.051 g, 0.5 mmol).

General Procedure for the Heck Coupling of *o*-Iodobiaryls with Ethyl Acrylate Using Palladium Migration Procedures C and D. 2-Iodo-4′-methylbiphenyl (73.5 mg, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), (Ph₂P)₂CH₂ (dppm, 4.8 mg, 0.0125 mmol), CsO₂CCMe₃ (CsPiv) (0.117 g, 0.5 mmol), and ethyl acrylate (0.025 g, 0.25 mmol) in DMF (4.0 mL) under Ar at 100 °C were stirred for 1.5 d. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL), and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried (MgSO₄), and filtered, and the solvent was removed under reduced pressure. The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 58.6 mg (88%) of ethyl *E*-3-(4′-methylbiphen-2-yl)acrylate (**2a**) and ethyl *E*-3-(4-methylbiphen-2-yl)acrylate (**3a**) as a clear oil in a 50:50 molar ratio as determined by ¹H NMR spectroscopic analysis.[16] In procedure D, the DMF solvent was replaced by a 95:5 DMF/H₂O mixture.

General Procedure for the Suzuki Coupling of *o*-Iodobiaryls with Arylboronic Acids under Palladium Migration Conditions. To a 2-dram vial was added the *o*-iodobiaryl (0.25 mmol), the arylboronic acid (0.35 mmol, 1.4 equiv), Pd(OAc)₂ (2.8 mg, 5 mol %), (Ph₂P)₂-CH₂ (dppm, 4.8 mg, 5 mol %), CsO₂CCMe₃ (CsPiv, 117 mg, 2.0 equiv), Me₃CCO₂H (PA, 51 mg, 2 equiv), H₂O (90 mg, 20 equiv), and DMF (4.0 mL). The mixture was flushed with Ar and stirred at 100 °C in an oil bath. The completion of the reaction was determined by the observation of palladium black. The reaction mixture was cooled, diluted with ether, and washed with satd aq NaHCO₃. The organic layer was dried (Na₂SO₄), filtered, and evaporated. The residue was purified by column chromatography on a silica gel column, and the molar ratio of the products was determined by ¹H NMR spectroscopic analysis.

General Procedure for the Suzuki Coupling of *o*-Iodobiaryls with Arylboronic Acids under the Conditions Described by Wright et al. (Nonmigration Conditions).[48] To a 2-dram vial was added the *o*-iodobiaryl (0.25 mmol), the arylboronic acid (0.30 mmol, 1.2 equiv), Pd(OAc)₂ (2.8 mg, 5 mol %), PPh₃ (6.5 mg, 10 mol %), CsF (84.0 mg, 2.2 equiv), and DME (1.0 mL). The mixture was flushed with Ar and stirred at 90 °C in an oil bath. The completion of the reaction was determined by the observation of palladium black. The reaction mixture was cooled and purified directly by column chromatography on a silica gel column.

Computational Methods. To find the lowest energy conformations for subsequent *ab initio* optimizations, semiempirical conformational searches were performed, as implemented in MacSpartan.[51] All other

optimization, Hessian, and energy runs were performed with the GAMESS suite of programs.[52] Results were visualized using MacMol-Plt.[53] All structures were found to have all positive definite vibrational frequencies, verifying them as minima.

For Pd-containing compounds, a two-stage procedure was used. After a semiempirical conformational search was used to establish the lowest energy conformation and starting geometry, optimizations were carried out at the RHF and B3LYP[54−57] levels of theory using a mixed group of basis sets. The 6-31G(d) basis set was used for carbon, hydrogen, nitrogen, and phosphorus. For iodine, the LANL2DV effective core potential, supplemented with p-diffuse functions and d-polarization functions, was used. For palladium, the LANL2DV effective core potential was supplemented with f functions.

Single-point energies with larger basis sets were then obtained at the MP2 and B3LYP levels of theory, using the RHF and B3LYP optimized geometries, respectively. For C and H, the basis set was 6-31G(d). For N and O, the basis set was 6-311+G(2d). For P, 6-311+G(3df) was used. For I, the LANL2DZ effective core potential was supplemented with s and p diffuse functions and d and f polarization functions. For Pd, LANL2DZ was supplemented with f polarization functions. Computations on biphenyl anions and their derivatives are described in the Supporting Information.

Supporting Information Available: Preparation and characterization of the starting materials and all new compounds, mass spectral data for the deuteration experiments, and structures and energies for all computational structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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