JOC The Journal of Organic Chemistry

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Kinetic and Computational Studies on Pd(I) Dimer-Mediated Halogen Exchange of Aryl Iodides

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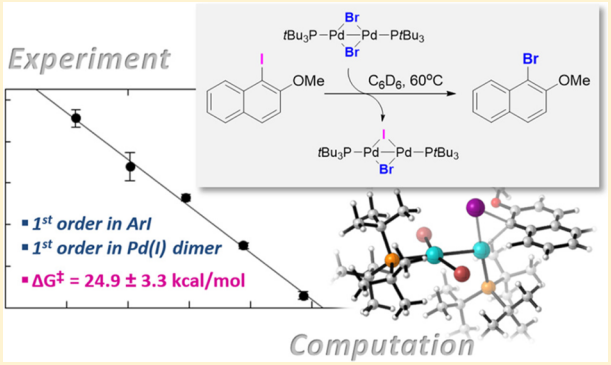
Supporting Information

ABSTRACT: Building on our previous discovery and reactivity explorations of the Pd(I) dimer $[(PtBu_3)PdBr]_2$-mediated halogen exchange of aryl iodides [*Chem. Sci.* **2013**, *4*, 4434], this report presents kinetic studies of this process, giving first-order kinetic dependence in the Pd(I) dimer and aryl iodide. An activation free energy barrier of $\Delta G^{\ddagger}$ = 24.9 ± 3.3 kcal/mol was experimentally determined. Extensive computational studies on the likely reaction pathway were subsequently carried out. A variety of DFT methods were assessed, ranging from dispersion-free methods to those that better account for dispersion (M06L, ωB97XD, D3-DFT). While significant discrepancies in the quantitative prediction of activation barriers were observed, all computational methods consistently predicted the analogous qualitative reactivity that is in agreement with all spectroscopic and reactivity data collected. Overall, these data provide compelling additional support of the direct reactivity of Pd(I)−Pd(I) with aryl iodides.



INTRODUCTION

A vast number of palladium-mediated transformations have been developed for the construction of organic molecules.[1,2] Of particular note are cross-coupling reactions involving Pd(0)/Pd(II) catalytic cycles,[3] for which the Nobel Prize in Chemistry was awarded in 2010.[4]

The chemistry and mechanisms relating to palladium have been most extensively studied for the oxidation states (0) and (+II),[1−5] as well as, to an extent, the higher oxidation state Pd(IV).[6] On the other hand, much less is known about palladium in its odd oxidation states, e.g., (+I).[7] A number of Pd(I)−Pd(I) dimeric complexes have been synthesized[8] and, in some cases, have even been implicated or observed under catalytically relevant conditions.[9,12] Our own work had recently demonstrated that these dimers (**1** and **3**, Scheme 1)[10,11] may form under catalytically relevant, typical Pd(0) conditions.[12] With a view to potentially uncover fundamentally novel organometallic reactivities for the development of catalytic processes,[13] we began to study the chemistry of these dimeric Pd(I) complexes in greater detail.[12,14]

Recently, we reported our discovery and reactivity studies of a halogen exchange between aryl iodides and the bromine-bridged palladium(I) dimer **1** (Scheme 1).[16] It was found that mixing **1** with a slight excess of 9-iodoanthracene (**2**) gave rise to efficient halogen exchange, furnishing the fully iodinated dimer **3** along with 2 equiv of 9-bromoanthracene (**4**) within 3 h at room temperature. The same halogen exchange was also found to be possible with other aryl iodides (e.g., 1-iodonaphthalene, 1-iodo-2-methoxynaphthalene, 9-iodophenanthrene), albeit with lower efficiency than the anthracenyl derivative.

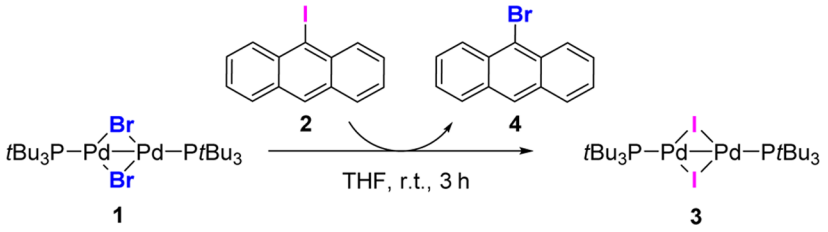
Our control experiments had suggested that radical processes would not be involved in this halogen exchange, as addition of radical traps (9,10-dihydroanthracene) had no marked effect on the process. Also, employment of conditions, which have previously been reported to generate Pd(I) radicals,[15] or those mimicking radical nucleophilic substitution reactions, yielded at best a trace amount of I/Br exchange.[16] Additional experiments also indicated that typical Pd(0)/Pd(II) conditions would not give rise to this halogen exchange.[16] Importantly, the key Pd(II) intermediate $[(PtBu_3)(Br)Pd^{(II)}(anthracene)]$, which would be expected to form in a Pd(0)/Pd(II) mechanism, only resulted in trace elimination to ArBr under analogous reaction conditions (3 h, r.t.). These experiments along with spectroscopic studies, which indicated that dinuclear Pd(I) complexes are the only phosphine-containing intermediates in the halogen exchange process, strongly supported that distinctly different reactivities of Pd(I)−Pd(I) were operating.[16] While these experimental studies had excluded various mechanistic alternatives, our computational data indicated that the direct reactivity of Pd(I)−Pd(I) with aryl iodides may in fact be feasible.

This report describes detailed kinetic investigations on the likeliness of direct reactivity of a Pd(I) dimer with an aryl halide, elucidating the activation parameters and reaction orders

Special Issue: Mechanisms in Metal-Based Organic Chemistry

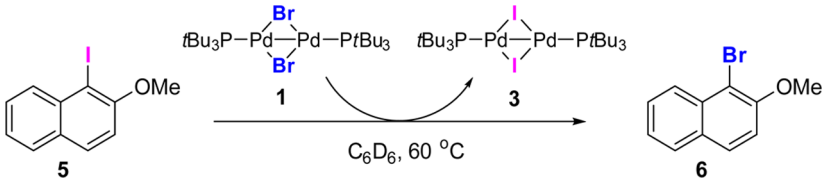
Received: August 15, 2014
Published: September 23, 2014

Scheme 1. Aromatic Halogen Exchange between Pd(I) Dimer 1 and 9-Iodoanthracene 2[a16]



[a]1 equiv of **1**; 10 equiv of **2**: 92% conversion to **4** after 3 h (1.8 equiv relative to **1**).

Scheme 2. Investigated Halogen Exchange between Pd(I) Dimer 1 and Aryl Iodide 5



of the described halogen exchange. The data are correlated with computational studies, including an extensive evaluation of various DFT methods.

RESULTS AND DISCUSSION

Most of our earlier investigations had focused on the reaction between iodoanthracene **2** and Pd(I) dimer **1** (see Scheme 1). However, since the latter reaction proceeds very rapidly at room temperature and, therefore, may potentially impede reliable data acquisition, we shifted our attention to the less reactive 1-iodo-2-methoxynaphthalene (**5**). The latter reacts with **1** at 60 °C in a manner that is suitable to monitor the reaction progress in the context of initial rate kinetic analyses by NMR spectroscopy (Scheme 2).[17] The ^{1}H NMR spectrum of **6** in benzene-d_6 exhibits an aromatic proton signal that resonates at a different chemical shift than those of **5**, allowing unambiguous quantification via ^{1}H NMR spectroscopy (see the Supporting Information for more details).

We studied the stoichiometric halogen exchange between **5** and **1** with the method of initial rates kinetics. To determine the reaction order in aryl iodide, five kinetic runs were performed with varying concentrations of aryl iodide **5**, but a constant concentration of **1**. Each of these was performed for a period of 1 h in a preheated NMR spectrometer (and analyzed to approximately 10% conversion), with spectra being recorded at 5 min intervals. The rate of the formation of **6** was found to increase linearly with increasing aryl iodide concentration. Figure 1 illustrates the logarithmic plot of the rate against the initial concentration of **5**, furnishing a straight line with a slope of 1.02 ± 0.13. These data suggest that the halogen exchange reaction is first-order in aryl iodide.

We subsequently investigated the order in Br–Pd(I) dimer **1**. Studying six different concentrations of **1** in benzene-d_6 (from 4 to 11 mM) in the presence of excess aryl iodide **5** (48 mM solution) revealed that there is also a linear trend for the initial rates. The values for the logarithm of the rate for each experiment were then plotted against the logarithm for the initial concentration of Br dimer **1**. This provided a straight line with a gradient of 1.02 ± 0.24, indicating that the reaction is first-order in Br dimer **1** (Figure 2).

The observed first-order kinetics in both, aryl iodide and Pd(I) dimer, would be consistent with a mechanism involving

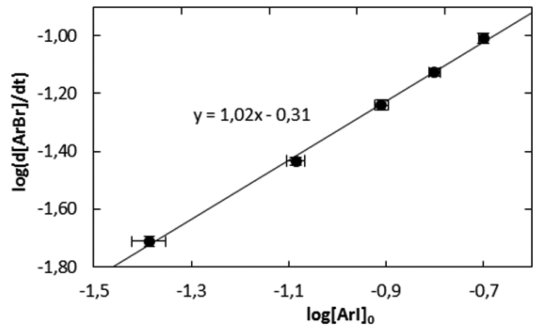


Figure 1. Logarithmic plot of the initial concentration of **5** (mmol/L) against the rate of aryl bromide **6** formation (R^2 = 0.998).

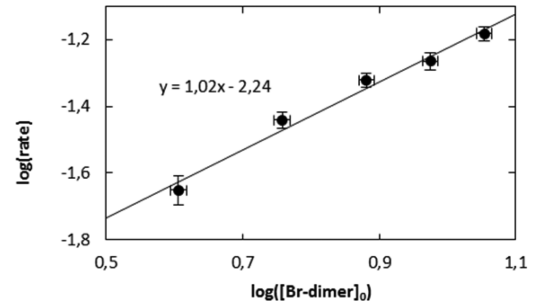


Figure 2. Logarithmic plot of the initial concentration of **1** (mmol/L) against the rate of formation of aryl bromide **6** (R^2 = 0.985).

direct reactivity of the aryl iodide with Pd(I)–Pd(I). An alternative scenario that would also be consistent with these kinetic data is an initial rate-determining and substrate-assisted disproportionation of the Pd(I) dimer complex to Pd(0) and Pd(II), followed by a fast halogen exchange via a Pd(0)/Pd(II) mechanism. However, our earlier studies on the propensity of a Pd(II) intermediate to reductively eliminate ArBr under analogous conditions (see above discussion), showed that Pd(II) furnishes only trace ArBr, suggesting that the rate-determining substrate-assisted disproportionation pathway was less likely than the direct reactivity with Pd(I)–Pd(I). To gain further insight and to also be able to correlate experimentally determined activation barriers with computational studies, we subsequently studied the activation parameters of this halogen

dx.doi.org/10.1021/jo501889j | J. Org. Chem. 2014, 79, 12041–12046

exchange. For that, we measured the reaction rates at five different temperatures (45−65 °C in 5 °C intervals). Following an Eyring analysis,[18] the activation enthalpy, entropy, and free energy were deduced. Figure 3 presents the results. The activation parameters $\Delta G^{\ddagger}$ = 24.9 ± 3.3 kcal/mol, $\Delta H^{\ddagger}$ = 17.8 ± 1.7 kcal/mol, and $\Delta S^{\ddagger}$ = −23.7 ± 5.3 cal/(mol·K) were determined.

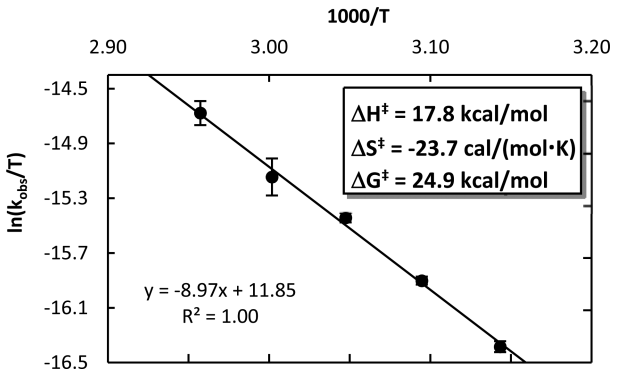


Figure 3. Eyring plot of the reaction of **1** with **5** at T [°C] = 45, 50, 55, 60, 65 with [Br dimer] = 10.4 mM and [ArI] = 50.5 mM.

We subsequently undertook computational studies of the Pd(I) dimer **1**-mediated halogen exchange of aryl iodide **5**.[19] Our previous calculations on this theme had analyzed three different transition-state arrangements for the reaction of iodobenzene with Br−Pd(I) dimer **1**, comparing (i) the direct oxidative addition with (ii) a concerted exchange and (iii) activated substitution mechanism, in which a halide would first be displaced from the dimer that then would undergo substitution on the activated complex (see Figure 4, top). Of the possibilities considered, the direct oxidative addition was approximately 30 kcal/mol favored over the alternatives.[16] An illustration of the calculated[20] transition state (**TS-1**) arising from direct oxidative addition of Pd(I) dimer **1** to the substrate studied herein, 1-iodo-2-methoxynaphthalene (**5**), is shown in Figure 4 (bottom).

The full free energy profile for the halogen exchange was subsequently calculated at the CPCM (benzene) M06L/def2TZVP//B3LYP/6-31G(d) [with LANL2DZ for Pd,I] level of theory and is illustrated in Figure 5. After initial oxidative addition of Pd(I) dimer **1** to aryl iodide **5**, which is endergonic in nature, the resulting dimeric Pd(II) intermediate readily undergoes halogen exchange and subsequent reductive elimination to give the mixed Br/I−Pd(I) dimer **7** and bromoarene **6**. Mixed dimer **7** may then react with another aryl iodide **5**. However, in the context of the initial rates method applied herein, in which a maximum conversion of 10% was studied, it is likely that only the Br−Pd(I) dimer **1** was reactive on the basis of its greater abundance and also higher reactivity than the mixed analogue **7**. The computed profile would be consistent with all of the collected mechanistic data. That is, (i) no stable intermediate other than the Pd(I) dimers could be observed with ^{31}P NMR spectroscopy; (ii) first-order dependence in aryl iodide and Pd(I) dimer was observed, consistent with reductive elimination being the rate-determining step; and (iii) the halogen exchange is overall thermodynamically driven.

We also evaluated the reaction pathway with various additional DFT methods (see Table 1). While those predicted the analogous qualitative reactivity trend, i.e., that oxidative addition is endergonic, the reductive elimination rate-determining and the halogen exchange overall driven by thermodynamics, we observed a significant scatter of the predicted barriers. Those functionals that better account for dispersion (e.g., M06L) or were dispersion-corrected (D3) gave significantly lower activation free energy barriers than the non-dispersion-corrected DFT methods. BP86 showed the most dramatic changes, with the D3 correction leading to unrealistically low values. A considerable effect of basis set was also noted. While potential overestimations of dispersion corrections have recently been noted,[21] other reports described that these methods would show an adequate performance in the quantitative reproduction of kinetic data for the oxidative

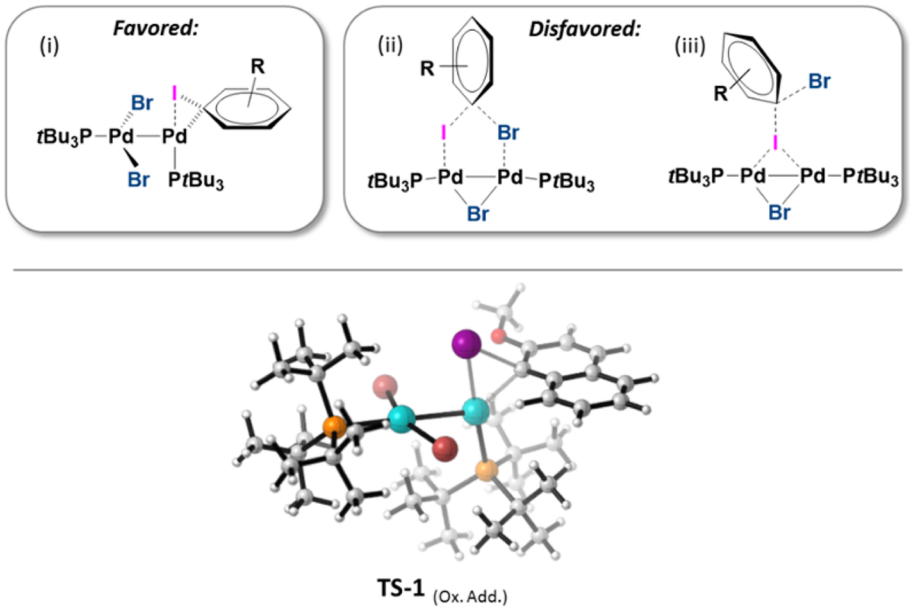


Figure 4. Analysis of potential TS configuration (top)[16] and calculation of direct oxidative addition transition state of Pd(I) dimer **1** to **5** (bottom).

dx.doi.org/10.1021/jo501889j | J. Org. Chem. 2014, 79, 12041−12046

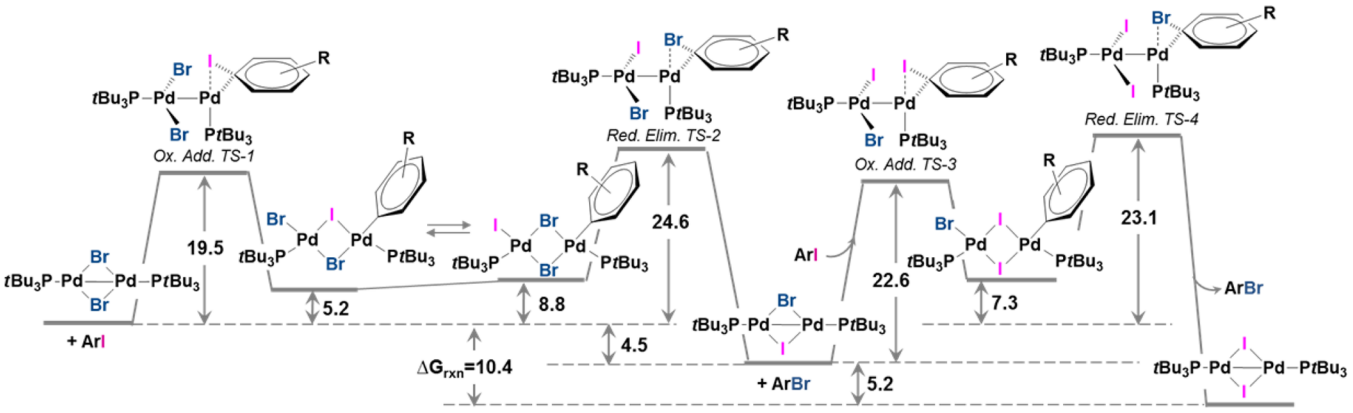


Figure 5. Free energy pathway of the halogen exchange reaction between Br dimer **1** and 1-iodo-2-methoxynaphthalene **5**, calculated at CPCM (benzene) M06L/def2TZVP//B3LYP/6-31G(d) [with LANL2DZ for Pd,I]. Values are reported in kcal/mol.

Table 1. Comparison of Experimentally Obtained Activation Free Energy Barrier with Calculated Activation Free Energies[a]

	$\Delta G^{\ddagger}$	
method	**TS-1**$_{(Ox.\ Add.)}$	**TS-2**$_{(Red.\ Elim.)}$
experiment	24.9 ± 3.3	
M06L/BS1	15.7	18.3
M06L/BS2	19.5	25.6
M06-2X/BS1	19.6	25.0
M06-2X/BS2	23.8	28.3
ωB97XD/BS1	20.7	24.2
ωB97XD/BS2	24.2	29.4
B3LYP/BS1	42.5	44.9
B3LYP/BS2	44.8	48.2
B3LYP-D3/BS1	12.3	16.0
B3LYP-D3/BS2	14.6	19.3
BP86-D3/BS1	1.9	4.9
BP86-D3/BS2	4.4	8.6
BP86/BS1	35.9	37.6
BP86/BS2	38.4	41.2

[a]Different solvation-corrected (CPCM = benzene) single-point energies were calculated with the 6-311++G(d,p) basis set and SDD ECP (BS1) or def2TZVP (BS2) on B3LYP/6-31G(d) [with LANL2DZ for Pd,I] optimized geometries. All values are reported in kcal/mol and are relative to the starting materials **1** and **5**.[23]

addition by Pd(0).[22] Overall, M06L/def2TZVP provided a good match with the experimentally determined activation parameters: $\Delta G^{\ddagger}$ = 24.6 kcal/mol was calculated for the reductive elimination step (**TS-2**), which is in line with the experimental value ($\Delta G^{\ddagger}$ = 24.9 ± 3.3 kcal/mol). However, given the large discrepancies in calculated absolute barriers for the various methods, relative to the experimentally determined value, no confident conclusion can be drawn as to whether the computed reaction free energy pathway (Figure 5) is also the true reaction pathway. However, its characteristics (as discussed above) are consistent with all experimental data.

CONCLUSIONS

In conclusion, this report presented kinetic investigations of the stoichiometric halogen exchange of 1-iodo-2-methoxynaphthalene mediated by the Pd(I) dimer, {Pd(I)Br($PtBu_3$)}$_2$ **1**. First-order kinetics were observed in each reaction partner. The activation parameters $\Delta G^{\ddagger}$ = 24.9 ± 3.3 kcal/mol, $\Delta H^{\ddagger}$ = 17.8 ± 1.7 kcal/mol, and $\Delta S^{\ddagger}$ = −23.7 ± 5.3 cal/(mol·K) were experimentally determined via an Eyring analysis. A likely reaction pathway arising from direct oxidative addition of the Pd(I) dimer to ArI was calculated. A variety of computational methods were assessed. While these data qualitatively agreed with experimental observations, a significant discrepancy of predicted activation barriers were observed. D3-corrected methods resulted in significantly lower activation barriers than traditional DFT methods (with differences of up to 30 kcal/mol). M06L and ωB97XD, on the contrary, predicted barriers in good agreement with the experimentally determined values, in line with previously observed deviations of D3-corrected data.[21] Overall, the various reactivity explorations and spectroscopic, kinetic, and computational data provide compelling support of a halogen exchange mechanism that involves the direct reactivity of the Pd(I) dimer with ArI.

EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR spectra for the kinetic studies were recorded at 400 MHz. Samples were prepared under an inert atmosphere in a glovebox and then stored at −20 °C until required. NMR samples were allowed 3−5 min to heat to the corresponding temperature before any data were acquired, and then spectra were recorded at 5 min intervals and at 50 °C for the aryl iodide study, and at 60 °C for the Br dimer study, over a period of 40−60 min. Spectrometer parameters: relaxation delay, 1.000 s; pulse angle, 45°; acquisition time, 3.041 s; repetitions, 16 (aryl iodide study) or 64 (Br dimer study and activation barrier study). Measurement errors (weighing and volumetric) and standard deviations of integrated data and slopes were considered in uncertainty analysis (error bars).

All reagents were purchased from commercial sources and used as received. Solvents were either purified by a solvent drying system (THF, toluene, *n*-hexane), purchased dry and oxygen-free (DMF, methanol, benzene-d_6), or were distilled from a technical grade solvent (dichloromethane, ethyl acetate). Chemical shifts (δ/ppm) were referenced to the residual solvent peak (77.0 ppm in ^{13}C for $CDCl_3$ and 7.16 ppm in ^{1}H and 128.1 ppm in ^{13}C for benzene-d_6), and a known quantity of $P(O)(OEt)_3$ was added to act as an internal standard for determining concentrations of product (as well as being a convenient internal standard with which to inspect the ^{31}P NMR spectrum after the kinetic study for selected cases; δ = −0.8 ppm).

Procedure for Determining the Reaction Order in 1. A 227 mM stock solution of **5** was prepared by dissolving **5** (60 mg, 211 μmol) in benzene-d_6 (850 μL) and adding 80 μL of stock solution of triethyl phosphate (27 mg in 1.2 mL of benzene-d_6). A 15 mM stock solution of **1** was prepared by dissolving 23 mg of **1** in 1.95 mL of benzene-d_6. A 140 μL aliquot of the stock solution of **5** was added to 5 vials and weighed, followed by five different volumes of stock solution

dx.doi.org/10.1021/jo501889j | J. Org. Chem. 2014, 79, 12041−12046

of **1** and benzene-d_6, which were also weighed to reach final concentrations of 3.8, 5.7, 7.6, 9.4, and 11.3 mM. The obtained reaction mixtures were transferred to NMR tubes that were subsequently sealed with parafilm and stored at −20 °C until required. Kinetic studies using NMR spectroscopy were then carried out with each of the five samples, as described in the General Procedures.

Procedure for Determining the Reaction Order in 5. A 20 mM stock solution of **1** was prepared by dissolving **1** (47 mg, 60 μmol) in benzene-d_6 (3.0 mL). To this stock solution was added triethyl phosphate (25 mg, 137 μmol). Quantities of **5** were separately weighed into five different vials (7, 14, 21, 27, and 34 mg), and to each of these was added 0.6 mL of the stock solution of **1**, to provide different concentrations of **5** (41, 82, 123, 158, and 200 mM, respectively). These solutions were transferred to five different NMR tubes, which were sealed with parafilm and stored at −20 °C until required. Kinetic studies using NMR spectroscopy were then carried out with each of the five samples, as described in the General Procedures.

Procedure for Determining the Activation Barrier. A reaction mixture was prepared by weighing 28 mg of **1** and 50 mg of **5** and dissolving them in 3.6 mL of benzene-d_6. Lastly, 50 mg of a solution of internal standard (35 mg of triethyl phosphate in 1.2 mL of benzene-d_6) was added. Then, 0.7 mL aliquots of that mixture were transferred to five different NMR tubes, sealed with parafilm, and were then stored at −20 °C until required. Kinetic studies using NMR spectroscopy were then carried out with each of the five samples, as described in the General Procedures. The linear form of the Eyring−Polany eq 1 was used to obtain the activation enthalpy and entropy values from the average of two measurement series.

$$\ln\frac{k}{T} = \frac{-\Delta H^{\ddagger}}{R}\cdot\frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R} \quad (1)$$

Preparation of [Tris(*tert*-butyl)phosphino]palladium(I) Bromide Dimer 1. A solution of Pd_2dba_3 (227 mg, 0.25 mmol) and P^tBu_3 (202 mg, 1.04 mmol) in 10 mL of THF was stirred in a 25 mL round-bottom flask for 80 min at r.t. $PdBr_2$ (132 mg, 0.50 mmol) was added to a filtered solution and stirred for an additional 90 min. Upon filtration, the solution was layered with acetone and stored in the freezer (−30 °C) for 18 h. Filtration and drying in vacuo yielded 177 mg of shiny green-blue crystals in 46% yield. ^{1}H NMR (400 MHz, C_6D_6) δ 1.32 (m). ^{13}C NMR (101 MHz, C_6D_6) δ 36.2, 32.5. ^{31}P NMR (121 MHz, toluene) δ 85.7.

Synthesis of 1-Iodo-2-methoxynaphthalene 5. Prepared from 2-methoxynaphthalene according to the literature procedure.[24] Yield 1.96 g, 60%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.35 (m, 1H), 7.48 (m, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.27 (m, 1H), 7.11 (m, 1H), 6.60 (d, J = 8.9 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.6, 135.6, 131.1, 130.3, 129.9, 128.2, 128.1, 124.3, 112.9, 87.7, 57.2; MS (EI) m/z 284.0 (M^+, 100%); ν IR (ATR)/cm^{-1} 2985, 2928, 1682, 1288, 1184, 866, 760.

Synthesis of 1-Bromo-2-methoxynaphthalene 6. Prepared from 1-bromo-2-naphthol according to the literature procedure.[25] Yield 3.39 g, 64%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.39 (m, 1H), 7.52 (m, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.30 (m, 1H), 7.13 (m, 1H), 6.68 (d, J = 9.0 Hz, 1H), 3.31 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.7, 133.1, 129.8, 128.9, 128.0, 127.7, 126.1, 124.3, 113.6, 108.7, 57.1; MS (EI) m/z 236.0 (M^+, 100%), 238.0 (M^+, 99%); ν IR (ATR)/cm^{-1} 3041, 2958, 1598, 1252, 1057, 799, 744.

Computational Methods. All calculations were performed with the Gaussian 09 program package.[19] Structural optimizations and frequency calculations were performed with B3LYP and ωB97XD functionals along with the 6-31G(d) basis set on lighter atoms and the ECP LanL2DZ on Pd and I atoms. Single-point energy calculations were performed with alternative DFT methods and the 6-311++G(d,p) basis set on lighter and Stuttgart-Dresden ECP on Pd and I atoms (BS1) or def2-TZVP on all atoms (BS2). Benzene solvation was taken into account using the CPCM solvation model. Frequency analysis was used to confirm whether the structure is a minimum (NImag = 0) or a transition state (NImag = 1). Intrinsic reaction coordinate (IRC) analysis was used to confirm that the obtained transition states connect the correct minima. D3 corrections have been calculated using the Becke−Johnson damping function.[26] All energies were corrected to the 1 M standard state.[27]

■ ASSOCIATED CONTENT

Supporting Information

Kinetic data, general information on computation, Cartesian coordinates of calculated structures, and NMR data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

■ ACKNOWLEDGMENTS

We thank the RWTH Aachen University and the NRW Returning Scholars Program for financial support. We also thank Shannon Stahl for helpful discussions. The authors gratefully acknowledge the computing time granted by the JARA-HPC Vergabegremium and provided on the JARA-HPC partition's part of the RWTH Bull Cluster in Aachen (grant number JARA0091).

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