Formate-Mediated Aryl Halide Reductive Cross-Coupling Catalyzed by Iodide-Bridged Palladium(I) Dimers: Experimental and Computational Studies

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Supporting Information Placeholder

ABSTRACT: The first efficient reductive cross-couplings of aryl halides mediated by an abundant feedstock, sodium formate, are described. These processes, which exploit air-stable Pd(I) iodide dimers, are especially effective for challenging 2-pyridyl systems due to intervention of chelated intermediates. Furthermore, orthogonality with respect to Suzuki and Buchwald-Hartwig coupling processes is displayed, as pinacol boronates and anilines are tolerated. Although palladium-catalyzed transfer hydrogenolyses of aryl halides mediated by formate are longstanding, it is not a major competing pathway under the present conditions. Experimental and computational studies corroborate a novel catalytic cycle for cross-coupling where the Pd(I) precatalyst, $[Pd(I)(P^tBu_3)]_2$, is converted to the active dianionic catalyst, $[Pd_2I_4][NBu_4]_2$, from which aryl halide oxidative addition is more facile. Rapid, reversible Pd-to-Pd transmetalation delivers iodide-bridged diarylpalladium dimers. The hetero-diarylpalladium dimers are more stable than the homodimers and have lower barriers to reductive elimination, resulting in high cross-selectivity.

Introduction

Metal-catalyzed cross-couplings of arylmetal reagents are among the most broadly utilized methods in the discovery and manufacture of small-molecule drugs.[1,2] As conventional cross-couplings require premetalated reagents, which most often derive from halides, efforts to develop direct reductive cross-couplings of halide partners have been put forth.[3,4] The majority of such cross-electrophile reductive couplings exploit metallic reductants (Zn, Mn). Non-metallic reductants have been explored and include tetrakis(dimethylamino)ethylene (TDAE),[5] bis(pinacolato)diboron (B_2Pin_2),[6] tertiary amines (photochemically promoted),[4h,7] and strained diols.[8] Electrochemical[4g,h,i] methods for reductive cross-coupling also show great promise.[4f] Although reductive cross-coupling mediated by low molecular weight feedstock reductants (H_2, 2-propanol or NaO_2CH) would be more ideal, their development remains an unmet challenge (Figure 1).[9,10]

Our laboratory has developed diverse metal-catalyzed C-C bond formations that occur through the addition or redistribution of hydrogen.[11] In connection with this work, rhodium-catalyzed formate-mediated aryl iodide-aldehyde and vinyl halide-aldehyde reductive couplings[12b,c] were recently reported, as were palladium-catalyzed formate-mediated deoxygenative Heck-type reactions of vinyl triflates.[13] The ability to promote formate-mediated reductive couplings of aryl halides impelled efforts to develop formate-mediated biaryl cross-couplings;[9,10] however, using homogenous rhodium or heterogenous palladium catalysts, low yields and narrow scope were observed.[9] High-throughput experimentation (HTE) in collaboration with Genentech was applied to the optimization of this process, which has culminated in the first efficient conditions for formate-mediated aryl halide reductive cross-coupling, including challenging 2-pyridyl systems.[14] Additionally, experimental and computational studies corroborate a catalytic cycle wherein the neutral dimeric Pd(I) precatalyst, $[Pd(I)(P^tBu_3)]_2$, is converted to the active dianionic dimeric phosphine-free catalyst, $[Pd_2I_4][NBu_4]_2$, which more readily participates in aryl halide oxidative addition. These studies also illuminate the origins of cross-selectivity. Specifically, facile Pd-to-Pd transmetalation[15] results in a preequilibrium of homo- and hetero-diarylpalladium dimers. The hetero-diarylpalladium dimers are both more stable and engage in more rapid reductive elimination thus promoting cross-selectivity. Notably, formate-mediated aryl halide transfer hydrogenolysis is not a significant competing pathway.[16]

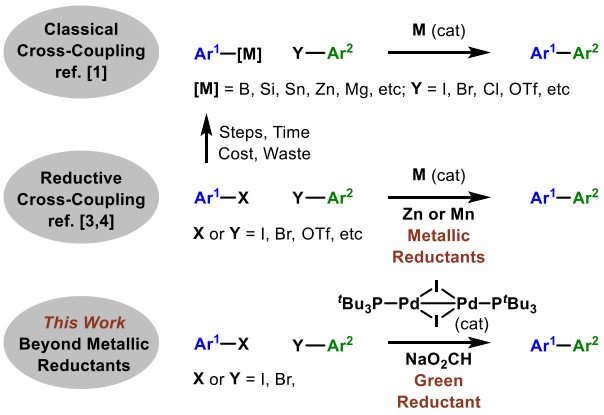
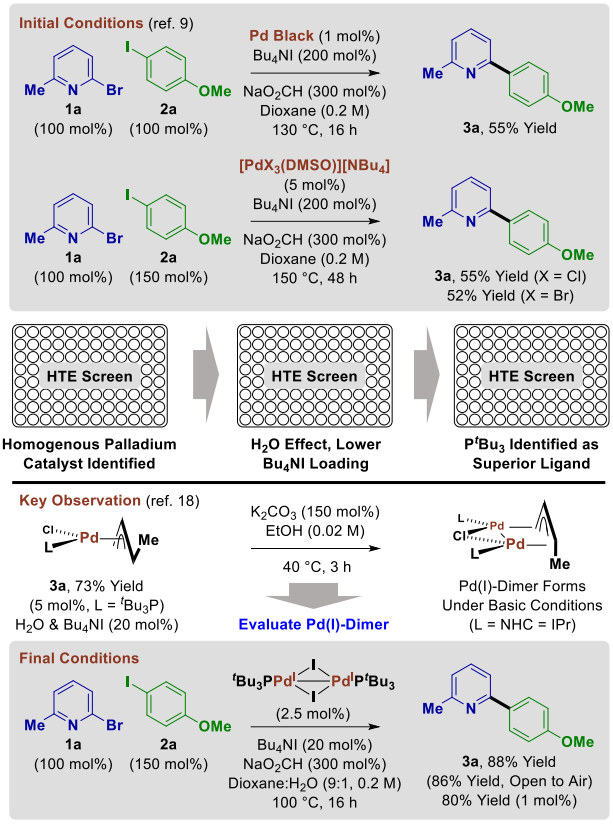


Figure 1. Metal-catalyzed cross-coupling and related reductive cross-couplings of aryl halides.

Figure 2. Optimization of formate-mediated reductive cross-coupling of aryl halides to form biaryl compounds: identification of a Pd(I) catalyst.[a]



[a]See Supporting Information for further details.

Results and Discussion

A concise overview of our optimization is summarized in Figure 2. Initial conditions for palladium-catalyzed aryl halide reductive cross-coupling employed a heterogenous catalyst, palladium black. In the best-case scenario, the coupling of 2-bromo-6-methylpyridine **1a** with 4-iodoanisole **2a**, the product of reductive cross-coupling **3a** was formed in 55% yield.[9] Reproducibility was an issue with this heterogenous catalyst. The requirement of Bu_4NI led us to evaluate the anionic palladium complexes $[PdX_3(DMSO)][NBu_4]$ (X = Cl, Br);[17] however, rather high temperatures were required and the yield of **3a** did not improve. We sought to address key limitations of the initially developed catalyst systems via exploration of experimental parameters using HTE. Specifically, a "tunable" homogenous palladium catalyst that operates with greater efficiency at lower temperature and lower loadings of Bu_4NI was sought. In short, after three rounds of HTE in 96-well plates (See Supporting Information), it was found that $[Pd(\pi\text{-}C_4H_7)(P^tBu_3)Cl]$ (5 mol%), Bu_4NI (20 mol%) in dioxane:H_2O (9:1, 0.2 M) enabled formation of **3a** in 73% yield; however, high temperature (130 ºC) was still required. Application of these conditions at a lower temperature (100 ºC) led to formation of **3a** in 44% yield.

At this point, the alignment of several observations culminated in a significant advance. The Pd(II) complex $[Pd(\pi\text{-}C_4H_7)(IPr)Cl]$ is known to form the Pd(I) dimer $Pd_2(\mu\text{-allyl})(\mu\text{-}Cl)(IPr)_2$ in the presence of base and ethanol, which are reducing conditions.[18] Iodide is known to stabilize Pd(I) dimers of the type $[Pd(X)(P^tBu_3)]_2$ (X = Br *vs* I, 12 kcal/mol),[19,20] and exogenous iodide is required in the present reductive cross-couplings.[21] Finally, as tri-*tert*-butylphosphine was identified by HTE as a superior ligand for the coupling of **1a** with **2a**, the commercially available Pd(I) complex $[Pd(I)(P^tBu_3)]_2$ (2.5 mol%) was evaluated as catalyst at 100 ºC. To our delight, the product of reductive cross-coupling **3a** was formed in 88% yield. When the reaction was run in an open atmosphere, **3a** was formed in a nearly identical 86% yield, and at lower loadings of $[Pd(I)(P^tBu_3)]_2$ (1 mol%) **3a** was isolated in 80% yield.

As $Pd(OAc)_2$ is converted to the Pd(I) dimer $[Pd(I)(P^tBu_3)]_2$ upon exposure to formate, Bu_4NI and $P^tBu_3{\bullet}HBF_4$ (eq. 1),[13] use of $Pd(OAc)_2$ as a precatalyst in the coupling of **1a** with **2a** was explored in the presence and absence of P^tBu_3 (eq. 2). Although somewhat lower yields of **3a** were obtained, substantial quantities of **3a** were formed in the absence of P^tBu_3, demonstrating P^tBu_3 is not required for catalysis and may simply enhance efficiency by stabilizing off-cycle species. Similarly, the coupling of **1a** with **2a** was conducted using the Pd(II) dimer $[Pd_2I_6][NBu_4]_2$ in the presence and absence of P^tBu_3 (eq. 3).[22] Here, conversion to **3a** corroborates the catalytic competence of iodide-bridged Pd(II) dimers and again shows that phosphine-ligated palladium catalysts are not required. Upon exposure of $[Pd(I)(P^tBu_3)]_2$ (100 mol%) to Bu_4NI (400 mol%), free P^tBu_3 was detected by ^{31}P NMR and the dianionic Pd(I) dimer $[Pd_2I_4][NBu_4]_2$ was detected by ESI-HRMS (eq. 4). While the collective data implicate $[Pd_2I_4][NBu_4]_2$ as the active catalyst (eq. 1-4), superior efficiencies were observed using $[Pd(I)(P^tBu_3)]_2$, which was selected to survey reaction scope.

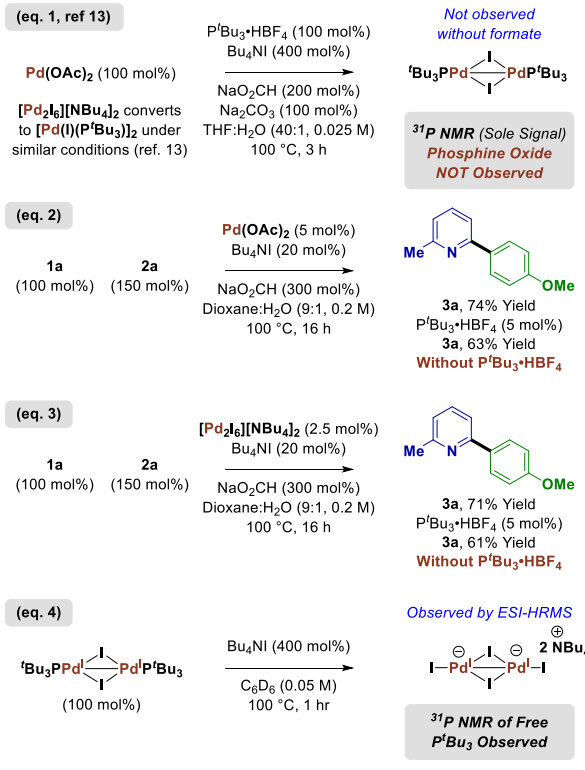
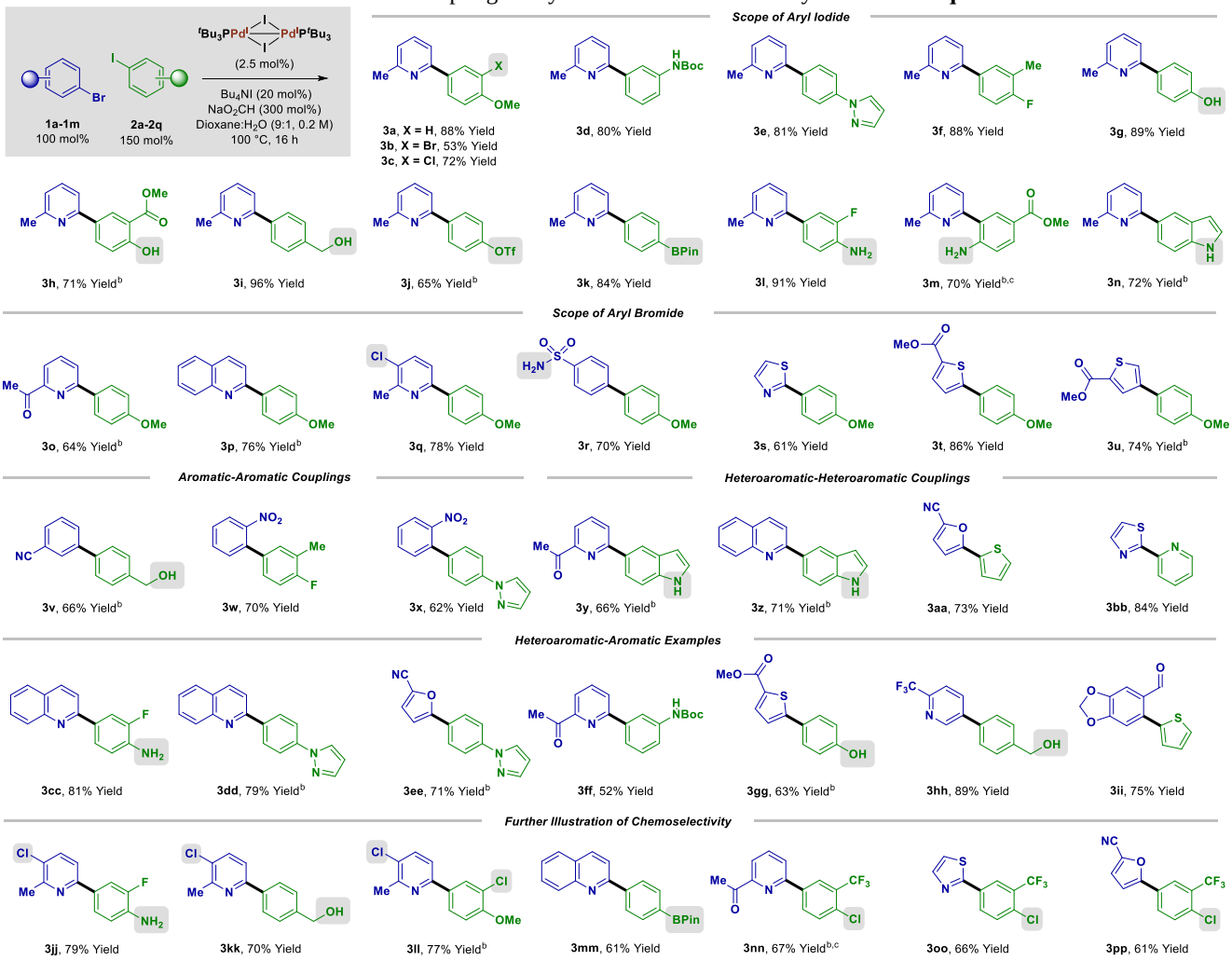


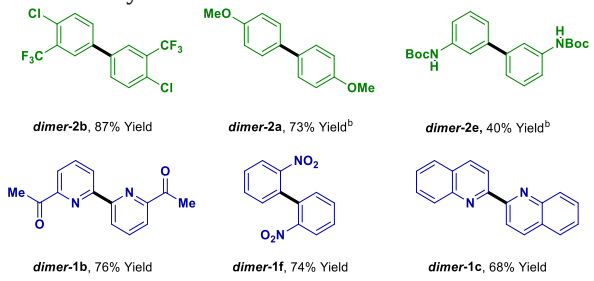
Table 1. Formate-mediated reductive cross-coupling of aryl bromides **1a-1m** with aryl iodides **2a-2q**.[a]



[a]Yields of material isolated by silica gel chromatography. [b]110 ºC. [c]ArI (200 mol%).

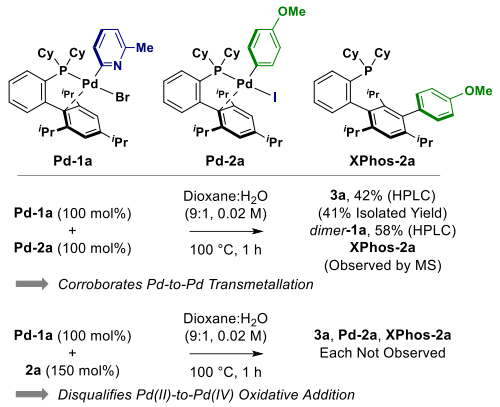
Optimal conditions developed for formation of **3a** were applied to the coupling of aryl bromides **1a-1m** with aryl iodides **2a-2q** (Table 1). An initial set of experiments, the structure of aryl bromide **1a** was held constant and different aryl iodides **2a-2n** were explored. It was found that coupling can occur in the presence of electron rich bromides (**3b**), and the reaction is tolerant of Lewis basic nitrogen heterocycles (**3e**), phenols (**3g**, **3h**) and primary alcohols (**3i**), as well as triflates (**3j**), pinacol boronates (**3k**), anilines (**3l**, **3m**) and unprotected indoles (**3n**). In a similar set of experiments, the structure of iodide **2a** was held constant and different aryl bromides **1b-1h** were explored. Beyond adducts derived from 2-substituted pyridines (**3o**, **3q**) and quinolines (**3p**), it was found that other electron-deficient aryl bromides are tolerated, including 4-bromobenzenesulfonamide (**3r**), 2-bromothiazole (**3s**), as well as methyl 5-bromo- and 4-bromothiophene-2-carboxylate methyl esters (**3t**, **3u**). At this stage, more diverse couplings of activated bromides and electron rich iodides were surveyed, and similarly high levels of functional group compatibility were observed. Notably, pinacol boronates (**3k**, **3mm**) and anilines (**3l**, **3m**, **3cc**, **3jj**) are tolerated, demonstrating orthogonality with respect to Suzuki and Buchwald-Hartwig coupling processes. It also bears mentioning that 2-bromopyridines and related 2-bromoheterocycles are especially effective participants, as corresponding 2-heteroaryl boronates are problematic coupling partners due to facile protodeboronation.[14] In cases where lower yields are obtained, for example, **3ff**, homo-coupling of the bromide or iodide accounted for the majority of the mass balance, likely due to disparate rates of oxidative addition (*vide infra*). Indeed, under standard conditions, homo-coupling of bromides or iodides is an efficient process (Figure 3). Notably, aryl halide transfer hydrogenolysis was seldom observed, although palladium-catalyzed processes of this type are well-established.[16]

Figure 3. Formate-mediated reductive homo-coupling of aryl bromides or aryl iodides.[a]



[a]See Supporting Information for experimental details. [b]110 ºC.

Scheme 1. Stoichiometric reactions of preformed arylpalladium complexes Pd-**1a** and Pd-**2a** corroborate facile palladium-to-palladium transmetalation.[a]



[a]See Supporting Information for experimental details.

Although the present processes appear to involve dimeric palladium species (*vide supra*), we were keen to assess the feasibility of generating diaryl Pd(II) species from monometallic aryl palladium complexes via palladium-to-palladium transmetalation.[15] Hence, the synthesis and stoichiometric reaction of the arylpalladium oxidative addition complexes derived from 2-bromo-6-methylpyridine **1a** and 4-iodoanisole **2a** were explored (Scheme 1). As the P^{t}Bu$_3$-modified complexes Pd(X)(P^{t}Bu$_3$)(Ar) (X = Br, I) could not be isolated in pure form, the more tractable XPhos-modified complexes **Pd-1a** and **Pd-2a** were prepared.[23] Heating equimolar quantities of **Pd-1a** and **Pd-2a** in dioxane:H$_2$O (9:1, 0.02 M) at 100 ºC for 1 hour resulted in formation of the cross-coupled product **3a** in 42% yield. The formation of *dimer*-**1a** accounted for the remaining mass balance of **Pd-1a**. Mass spectrometric analysis of the reaction mixture also revealed the presence of the indicated arylated XPhos derivative **XPhos-2a**, which arises from a known Heck-type side reaction.[24] Although intramolecular transfer of the 4-methoxyphenyl moiety of **Pd-2a** to XPhos limits the yield of **3a**, the conversion of **Pd-1a** and **Pd-2a** to **3a** and *dimer*-**1a** corroborates palladium-to-palladium transmetalation, albeit in a monometallic system.[15] Notably, Pd-**1a** and 4-iodoanisole **2a** do not react under these conditions to form **3a**, suggesting aryl halide oxidative addition to form diaryl Pd(IV) intermediates[25] or mechanisms involving C-X reductive elimination[26] are not operative.

At this stage, density functional theory (DFT) calculations were used to discriminate between the possible reaction mechanisms.[27] An initial question relates to whether oxidative addition occurs by way of the neutral phosphine-modified iodide-bridged Pd(I) dimer [Pd(I)(P^{t}Bu$_3$)]$_2$ (**Pd-A**) or the dianionic Pd(I) dimer [Pd$_2$I$_4$][NBu$_4$]$_2$ (**Pd-B**). The oxidative addition of 2-bromo-6-methylpyridine **1a** and 2-fluoro-5-iodotoluene **2c** to **Pd-A** were determined to be endergonic with activation barriers of 28.3 and 20.2 kcal/mol (**TS1a** and **TS1b**, respectively, Figure 4a). This result is consistent with previous DFT calculations by Schoenebeck on the reverse process (the C–Br reductive elimination of a Br/I-bridged Pd(II) dimer to form PhBr and **Pd-A**), which is exergonic by 11.9 kcal/mol.[20] In contrast, oxidative addition of aryl halides **1a** and **2c** to **Pd-B** were found to be exergonic and require lower kinetic barriers (21.2 and 15.7 kcal/mol, respectively) (Figure 4b). These results indicate that the electron-rich dianionic complex **Pd-B** is more reactive in oxidative addition than the phosphine-modified complex **Pd-A**. It should be noted that the equilibrium between **Pd-A** and **Pd-B** may affect the concentrations of these dimeric Pd(I) species, and thus the relative rates of the two oxidative addition pathways. Although the conversion of **Pd-A** to **Pd-B** is computed to be endergonic (ΔG = +16.0 kcal/mol) (Figure S1), the concentration of exogenous iodide is high compared to free P^{t}Bu$_3$ and increases over the course of the reaction. Hence, we posit that oxidative addition occurs from the phosphine-free dianionic complex **Pd-B** to form the dimeric aryl Pd(II) complexes **5a** and **5b**. Ligand exchange to replace iodide with P^{t}Bu$_3$ in **5a** and **5b** was found to be highly disfavored (Figure S2). The stronger binding of iodide to the oxidative addition complexes **5a** and **5b** compared to that of phosphine is an important factor that promotes the oxidative addition with the phosphine-free dianionic Pd(I) dimer **Pd-B**.

Our DFT calculations indicate dissociation of the dimeric oxidative addition complexes **5a** and **5b** to form monomeric anionic T-shaped Pd(II) complexes is highly endergonic (Figure S3), although such species could be present in small concentrations.[13,28] An equilibrium between **5a** and **5b** with several aryl Pd(II) iodide dimers (**6a-1**, **6a-2**, **6a-3**) via exchange and isomerization is more facile (Figure 5). The most stable isomer **6a-1** involves chelation of the pyridine nitrogen to the adjacent Pd center (2.10 Å) (Figure S7), accounting for the unusual facility of couplings adjacent to heteroaromatic ring nitrogen atoms.[14] The transmetalation process is thermodynamically driven by the exergonicity of reduction of [Pd$_2$I$_6$]$^{2-}$ (**Pd-C**) by formate to regenerate Pd(I) dimer [Pd$_2$I$_4$]$^{2-}$ (**Pd-B**).

Figure 4. Computed energy profiles indicate that the [Pd$_2$I$_4$]$^{2-}$ dimer **Pd-B** is more reactive in aryl halide oxidative addition than the P^{t}Bu$_3$-modified dimer **Pd-A**.

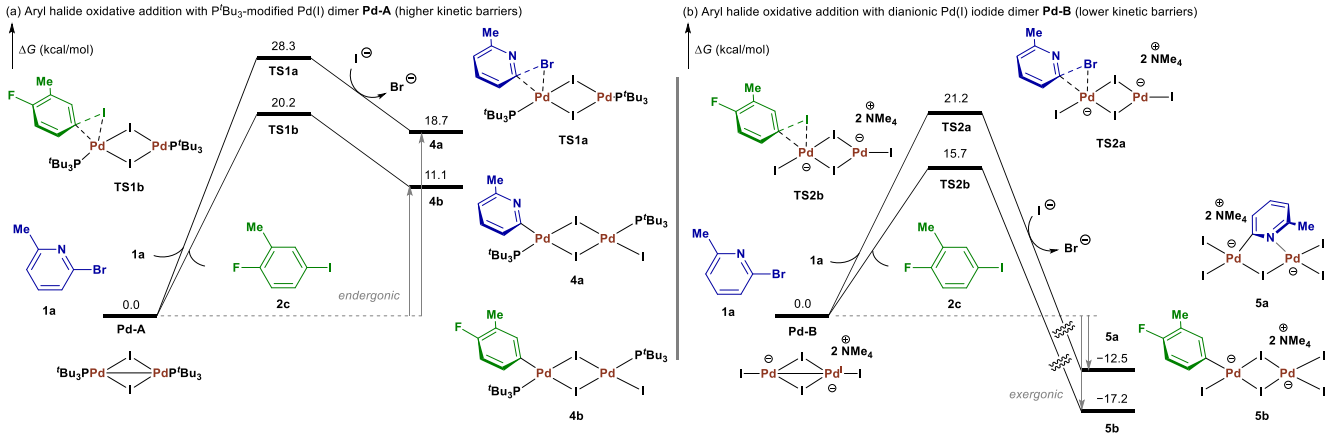
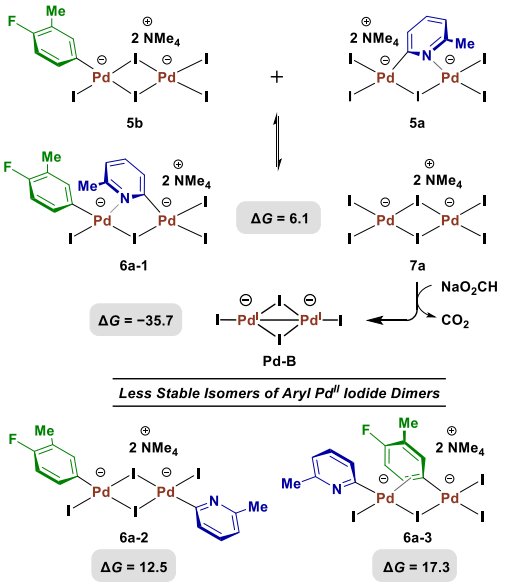


Figure 5. Formation of aryl Pd(II) iodide dimers **6a-1**, **6a-2**, and **6a-3**.[a]



[a]Gibbs free energies are in kcal/mol with respect to **5a** and **5b**.

As for **5a** and **5b**, dissociation of **6a-1** to monomeric Pd(II) complexes is highly endergonic (Figure S3). Therefore, Pd-to-Pd transmetalation is expected to occur from the dimeric Pd(II) complexes (Figure 6a). From **6a-3**, a higher energy isomer of **6a-1**, the transmetalation of the 4-fluoro-3-methylphenyl group between Pd(II) centers within the dimeric complex was found to be kinetically facile (**TS3a**), with a low barrier of only 2.7 kcal/mol relative to **6a-3** and 13.9 kcal/mol with respect to the more stable isomer of the Pd(II) dimer **6a-1**. The Pd-to-Pd transmetalation transition state **TS3a** features a four-membered cyclic structure involving the migrating *ipso* carbon, the bridged iodide, and the two Pd centers. The low barrier to transmetalation is likely due to π-complexation of the migrating aryl group with the adjacent Pd center (2.43 Å) (Figure S7) and the bridging iodide in **6a-3**, which causes minimal structural distortion in the developing transition state. The alternative transmetalation pathway involving migration of the 6-methyl-2-pyridyl group from **6a-1** was also considered and was found to be less favorable (see Supporting Information). The transmetalation leads to the diaryl Pd(II) complex **7a**, which is 7.2 kcal/mol less stable than **6a-1**. The C(sp^2)–C(sp^2) reductive elimination (**TS4a**) then takes place from the Pd(II) dimer[29] to form the cross-coupling product **3f** and regenerate the Pd(I) dimer **Pd-B**.

Next, we investigated the origin of selectivity for cross-coupling versus homo-coupling (Figure 6b). Based on the computed reaction energy profiles, the Pd-to-Pd transmetalation is reversible, and the C(sp^2)–C(sp^2) reductive elimination is the selectivity-determining step.[29,30] In the competing pathways leading to the homo-coupling products, the aryl Pd(II) iodide dimers **6b** and **6c** were found to be 9.2 and 6.6 kcal/mol less stable than **6a-1**. After the reversible Pd-to-Pd transmetalation (**TS3b** and **TS3c**), the reductive elimination transition states from **7b** and **7c** leading to the two homo-coupling products (**TS4b** and **TS4c**) require 28.0 and 30.6 kcal/mol, respectively, which are both substantially higher than the reductive elimination transition state leading to the cross-coupling product (**TS4a**). Compared to the homo-coupling reductive elimination transition states, **TS4a** is

Figure 6. Computed reaction energy profiles leading to cross- and homo-coupling products.

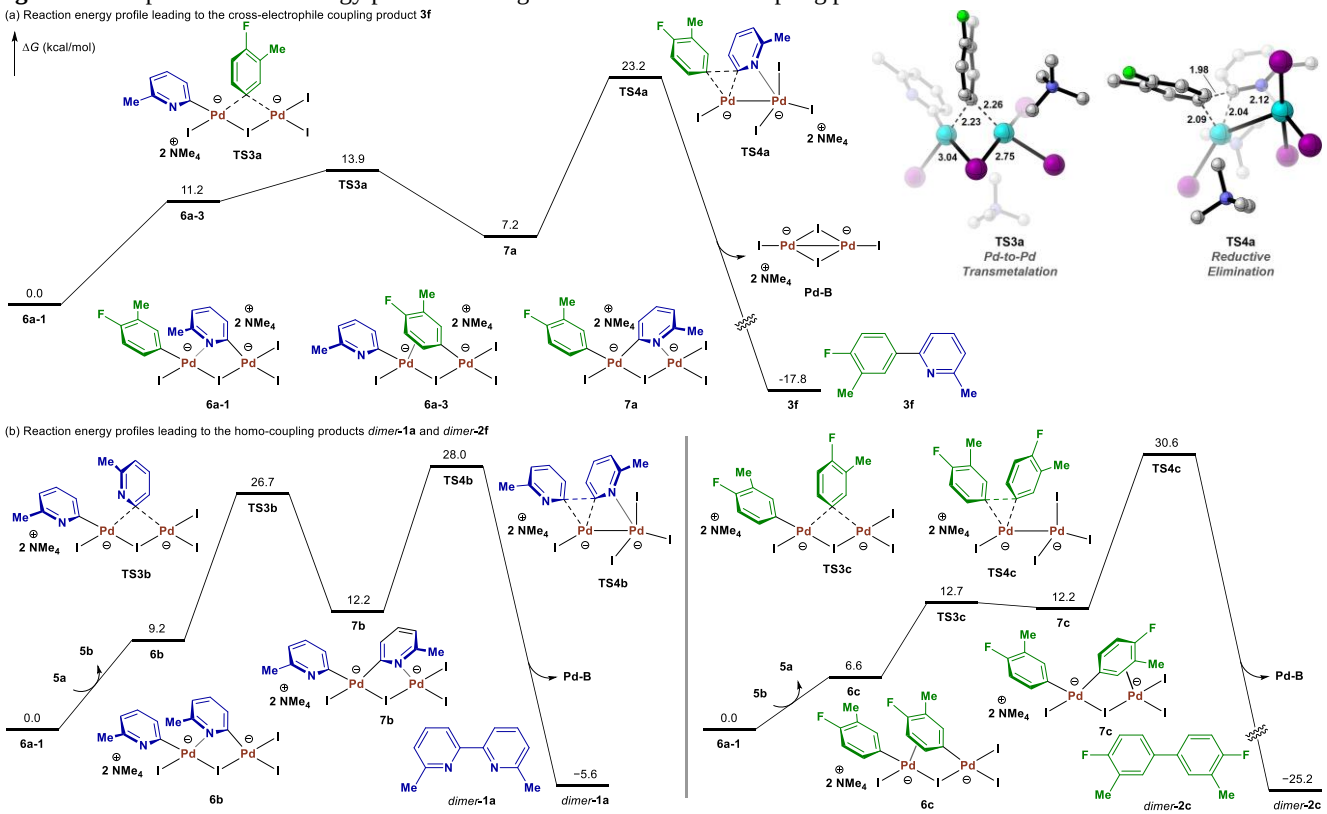
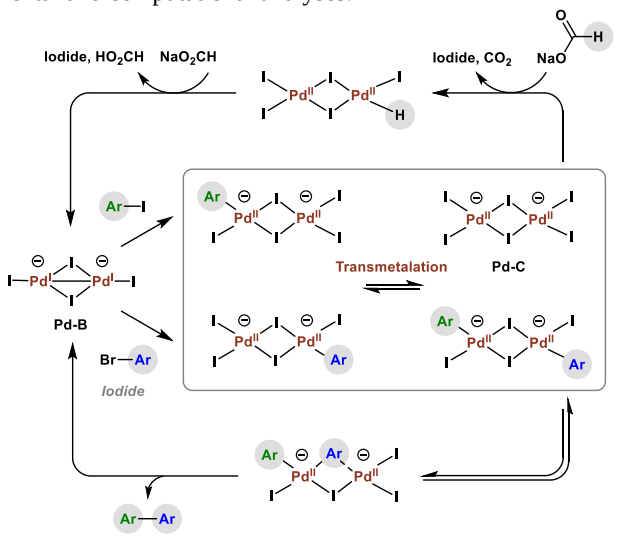


Figure 7. General catalytic cycle as corroborated by experimental and computational analyses.



stabilized by two factors. First, reductive elimination *en route* to hetero-coupled product is faster than reductive elimination *en route* to homo-coupled products.[30] Second, **TS4a** is stabilized by coordination of Pd to the pyridyl nitrogen ($d_{(N\cdots Pd)}$ = 2.12 Å) in the dimeric complex, once again accounting for the unusual facility of couplings adjacent to heteroaromatic ring nitrogens.[14]

Based on the collective experimental and computational data, a simplified catalytic cycle for formate-mediated reductive crossed-coupling is as follows (Figure 7). The Pd(I) precatalyst $[Pd(I)(P^tBu_3)]_2$ (**Pd-A**) is converted to the dianionic Pd(I) dimer $[Pd_2I_4][NBu_4]_2$ (**Pd-B**), which is more reactive toward oxidative addition. Upon oxidative addition, the resulting mono-arylpalladium dimers participate in rapid, reversible Pd-to-Pd transmetalation[15] to form iodide-bridged diarylpalladium dimers in a process driven by the highly exergonic reduction of $[Pd_2I_6][NBu_4]_2$ (**Pd-C**) (a known, catalytically competent dimer)[22] by formate to regenerate the Pd(I) dimer $[Pd_2I_4][NBu_4]_2$ (**Pd-B**). The hetero-diarylpalladium dimers are more stable than the homodimers and have lower barriers to reductive elimination,[29,30] which results in high cross-selectivity. Notably, monometallic reactive intermediates are not believed to intervene due to the highly endergonic dissociation of the iodide bridged dimers.

In summary, we report the first efficient reductive cross-couplings of aryl halides mediated by an abundant feedstock reductant, sodium formate. These processes, which are uniquely enabled by air-stable Pd(I) iodide dimers, occur through a novel mechanism and display selectivities that complement classical cross-coupling protocols. For example, due to chelation of σ-(2-pyridyl)palladium dimers, normally challenging coupling adjacent to heteroaromatic ring nitrogen atoms occur with great facility. Additionally, as pinacol boronates and anilines are tolerated, the present protocol is orthogonal to Suzuki and Buchwald-Hartwig couplings. Finally, unactivated aryl chlorides and bromides do not suffer formate-mediated transfer hydrogenolysis. Our combined experimental and computational studies are consistent with conversion of the neutral Pd(I) precatalyst $[Pd(I)(P^tBu_3)]_2$ (**Pd-A**) to the dianionic Pd(I) dimer $[Pd_2I_4][NBu_4]_2$ (**Pd-B**), which is more reactive toward oxidative addition. Following rapid, reversible Pd-to-Pd transmetalation, iodide-bridged diarylpalladium dimers are formed. The hetero-diarylpalladium dimers are both more stable than the homodimers and have lower barriers to reductive elimination, resulting in high cross-selectivity. These processes and other work from our laboratory demonstrate the broad applicability of hydrogenative protocols as alternatives to reactions that traditionally require premetalated reagents or metallic reductants.

Supporting Information. Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), computational details, additional computational results and Cartesian coordinates of computed structures.

Accession Codes. There is no crystallographic data associated with this manuscript.

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Notes
The authors declare no competing financial interest.

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