

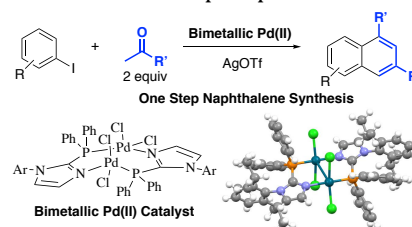
# Bimetallic Cooperativity with a 2-Phosphinoimidazole-Derived Pd(II) Dimer Enables Naphthalene Synthesis via dimeric Pd(III) Catalysis

Chloe C. Ence, S. Hadi Nazari,<sup>†</sup> Mariur Rodriguez Moreno, Manase F. Matu, Samantha G. Kulka, Erin E. Martinez, Kyle J. Gassaway, Gabriel A. Valdivia-Berroeta,<sup>†</sup> Stacey J. Smith, Daniel H. Ess, David J. Michaelis\*

<sup>†</sup>Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602, United States

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**ABSTRACT:** We report the synthesis of bimetallic Pd(I) and Pd(II) complexes scaffolded on bidentate 2-phosphinoimidazole ligands. These complexes display unique catalytic activity and enable the expeditious formation of 1,3-disubstituted naphthalenes via an unprecedented coupling of aryl iodides and methyl ketones in the presence of silver triflate. Excellent substrate scope for naphthalene formation is also demonstrated. Mechanistic studies suggest that the transformation proceeds via Pd-catalyzed arylation of a methyl ketone, followed by cyclization with a second equivalent of ketone. Importantly, this ketone arylation processes occurs under oxidizing conditions, suggesting involvement of higher oxidation state dimeric Pd catalysts. Based on experiments and DFT calculations, we propose a mechanism involving high oxidation state Pd(III) bimetallic catalysis. These new bimetallic complexes possess reactivity that is not seen with monometallic Pd catalysts and we confirm the importance of the palladium catalyst for both arylation and cyclization for naphthalene formation.

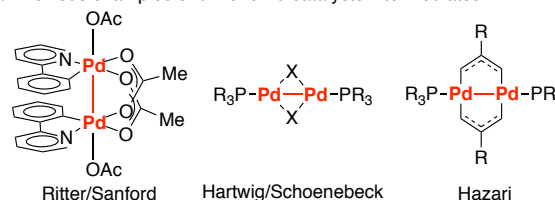


The synthesis of homo- and heterobimetallic transition metal complexes provides an innovative and productive approach to catalyst development because of the unique reactivity that often results from inter-metal cooperativity.<sup>1</sup> The classic example of this type of cooperative benefit is observed in dirhodium tetracarboxylate catalysis, where the presence of a second rhodium center facilitates the formation of higher oxidation state Rh(IV) intermediates in carbene catalysis.<sup>2</sup> More recent examples of synthetically useful bimetallic complexes include work from the Mankad group on Cu–Fe C–H borylations,<sup>3</sup> the Lu group on Ni–M hydrogenations,<sup>4</sup> the Uyeda group on Ni–Ni cycloaddition reactions,<sup>5</sup> and our group on Pd–Ti allylic aminations,<sup>6</sup> among others.<sup>7</sup> Each of these examples of bimetallic catalysis achieve increased efficiency and selectivity or new reaction mechanisms that cannot be accessed in single-metal catalytic systems.

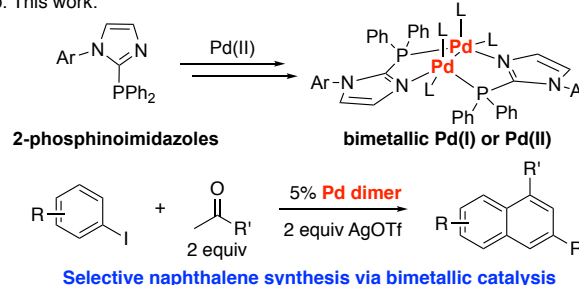
One significant advantage of having two metals participate in a catalytic process is the opportunity to access unique oxidation states and undergo binuclear mechanistic steps that enable new types of reactivity. For example, in the Cu–Fe catalyzed C–H borylations by Mankad,<sup>3</sup> binuclear reductive elimination is proposed to enable catalyst turnover and reformation of the active Cu–Fe species.<sup>8</sup> In addition, palladium(III) dimers have been confirmed as active catalytic species in oxidative transformations under palladium catalysis.<sup>9</sup> Sanford and Ritter have suggested that formation

of palladium (III) dimers helps facilitate binuclear oxidative addition and reductive elimination, which helps eliminate the need to access high energy Pd(IV) intermediates (Figure 1a).<sup>10</sup> Hartwig, Schoenebeck, Hazari, and others have also developed a diverse set of Pd(I) dimer catalysts that

a. Previous examples of dimeric Pd catalysts/intermediates:



b. This work:

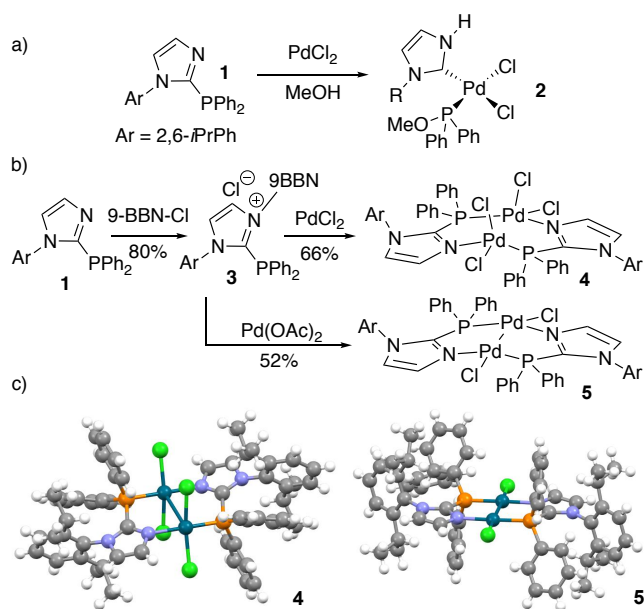


**Figure 1.** Dimeric Pd complexes for catalysis.

efficiently perform a range of cross coupling reactions, including for Suzuki, Negishi, Sonogashira, and Buchwald-Hartwig amination reactions.<sup>11</sup>

Our research efforts are focused on the development of new ligand frameworks capable of assembling catalytically active bimetallic complexes. Previous work from our group, and Nagashima, demonstrated and quantified the exceptional reactivity of datively interacting bimetallic Pd-Ti catalysts for allylic amination reactions, including chiral complexes for enantioselective allylic aminations.<sup>6</sup> Recently, we became interested in 2-phosphinoimidazole ligands because of their unique P-N bidentate structure that we believed could enable formation of homo- and heterobimetallic complexes capable of catalysis. Indeed, several previous reports have demonstrated the formation of palladium(II) dimers when specific palladium precursors were ligated to the 2-phosphinoimidazole ligand framework.<sup>12</sup> In this study, we report the synthesis of both Pd(I) and Pd(II) dimers using 2-phosphinoimidazole ligand scaffolds (Figure 1b). In catalytic studies, we show that these complexes enable a previously unknown tandem reaction process that couples two equivalents of a methyl ketone with an aryl iodide to generate 1,3-disubstituted naphthalene products in high yield. The dinuclear palladium catalysts are proposed to enable formation of a key Pd(III) dimer during catalysis via oxidative addition with an aryl halide. The Pd(III) dimer then facilitates formation of ketone arylation products via bimetallic reductive elimination, followed by cyclization and aromatization to form a new naphthalene product. DFT calculations support our hypothesis that the bimetallic complex remains intact during this transformation.

Our studies began with the attempt to isolate new dimeric palladium complexes from 2-diphenylphosphino-1-arylimidazole ligands. We found that the identity of both the ligand and the palladium precursor had a significant impact on the final structure of the complex obtained. For example, when ligand **1** was mixed with PdCl<sub>2</sub> in methanol, a new monomeric Pd complex (**2**) was obtained where the palladium had inserted between the P-C bond of the ligand (Figure

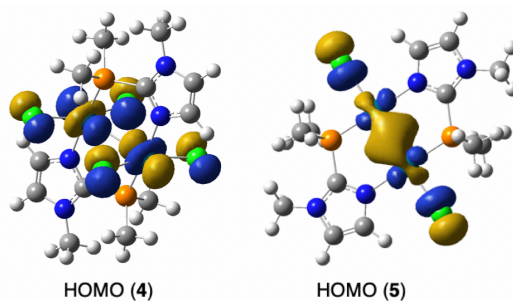


**Figure 2.** Synthesis and structure of bimetallic Pd complexes.

2a). We recently demonstrated that this N-H NHC palladium complex is highly active in palladium-catalyzed Suzuki-Miyaura reactions.<sup>13</sup> In contrast, we found that if ligand **1** was first coordinated with a boron Lewis acid to form **3**, formation of a dimeric Pd(II) complex (**4**) was observed selectively upon addition of PdCl<sub>2</sub> (Figure 2b).

Dimeric Pd(II) complexes similar to complex **4** have been previously reported by Diez et. al, but required the use of PdMeCl as precursor in order to obtain the bimetallic structure.<sup>12a</sup> Alternatively, if Pd(OAc)<sub>2</sub> was employed instead of PdCl<sub>2</sub>, a Pd(I) dimer (**5**) was selectively obtained. We believe that the presence of the boron ligand may help facilitate faster ligand coordination via a transmetalation-like mechanism. For example, when ligand **3** is added to PdCl<sub>2</sub>, complex **4** is generated in 66% yield after 18 h. However, when ligand **1** is employed that does not contain the boron Lewis acid, complex **4** is isolated in 43% yield after 3 days.

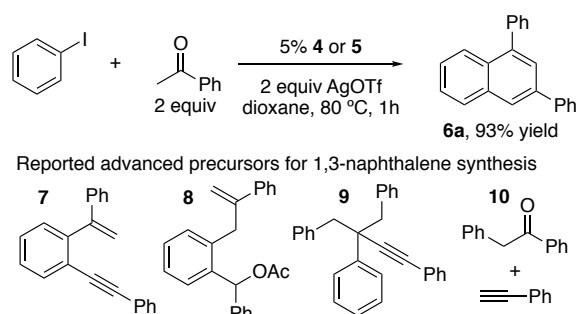
The crystal structures of these bimetallic palladium complexes provide additional insights into their structure and reactivity (Figure 2c). In Pd(II) dimer **4**, the two palladium centers are held within the Van der Waals contact distance for a Pd-Pd bond, but the absence of unpaired electrons prevents Pd-Pd bond formation (Pd-Pd distance = 2.966 Å). Thus, the two palladium centers are distorted out of a true square planar geometry likely to try to avoid interactions between the two filled dz<sup>2</sup> orbitals on each palladium. This distorted geometry in complex **4**, we believe, may lead to unique reactivity such as rapid oxidation to a Pd(III) dimer in order to relieve this repulsion between the two palladium centers (*vide infra*). For Pd(I) dimer **5**, the presence of unpaired electrons on each palladium center serves as a driving force for Pd-Pd bond formation (Pd-Pd distance = 2.591 Å). The square planar geometry of the two palladium centers and their oxidation states are also consistent with metal-metal bond formation. Indeed, the DFT computed orbitals for **4** and **5** confirmed our description. As shown in Figure 3, **4** lacks direct Pd-Pd covalent bonding and the HOMO consists mainly of the two dz<sup>2</sup> orbitals interacting in an antibonding fashion. The HOMO of Pd(I) dimer **5**, in contrast, shows a direct Pd-Pd covalent interaction.



**Figure 3.** M06/6-31G\*\*[LANL2DZ]-calculated HOMOs for complexes **4** and **5**.<sup>14, 15</sup>

Our next goal was to determine the catalytic potential of these new dimeric palladium complexes. While exploring their activity under various conditions, we discovered a multistep reaction process that has not previously been reported. This unique transformation employs an aryl iodide and 2 equivalents of a methyl ketone to generate 1,3-disubstituted naphthalene products (**6**) under oxidative condi-

tions with 2 equiv AgOTf (Figure 4). While synthetic approaches to 1,3-disubstituted naphthalenes have been demonstrated previously, they generally require multistep syntheses to access cyclization precursors such as intermediates **7**, **8**, **9**, or **10**,<sup>16</sup> our newly discovered transformation enables direct access to 1,3-disubstituted naphthalenes in a single step from commercially available aryl iodides and methyl ketones. This expeditious approach to naphthalene core structures is significant because naphthalenes have a variety of technological and pharmacological uses,<sup>17</sup> including as templates to construct carbon nanotubes<sup>18</sup> and as proton conducting solid electrolytes.<sup>19</sup> In addition to the synthetic value of this new transformation, it also provides an opportunity to investigate bimetallic cooperativity and its impact on catalysis, as monometallic palladium catalysts do not achieve the same levels of reactivity as complexes **4** and **5**.



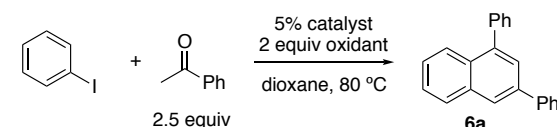
**Figure 4.** Approaches to 1,3-disubstituted naphthalenes.

Our catalyst optimization studies probed the impact of different Lewis acids, temperatures, ligands, and solvents on the reaction efficiency (Table 1). Under our optimized conditions with 2.5 equivalents ketone, 2 equivalents of AgOTf, in dioxane at 80 °C, the reaction proceeded to 100% conversion with bimetallic complexes **4** and **5** and provided 89% and 84% yield of the naphthalene product, respectively (entries 1 and 2). In addition, we found that simply pre-stirring ligand **3** with PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> in dioxane for 15 minutes led to the formation of bimetallic complexes **4** and **5**, as observed by <sup>31</sup>P NMR. This *in situ*-formed catalysts had the same catalytic activity as preformed complexes **4** and **5** (entries 3–4). Varying the Lewis acid in the reaction demonstrated that while Cu(OTf) provided the desired product in good yield, the reaction time was greatly extended (entry 5). Other iron- or copper-based Lewis acids failed to enable product formation (entries 6–8). We next explored the impact of other ligands on the reaction and found that ligand **1**, which lacks the boron Lewis acid, gives much lower yield (entry 9), presumably due to formation of lower concentrations of the active catalyst species. In addition, N-arylimidazole ligands that lack both the boron and 2-diphenylphosphino groups provide no product in the reaction (entry 10). We also screened other mono- and bidentate ligands and found that while PPh<sub>3</sub> as a ligand provided a small amount of product, bisphosphines and diamine ligands did not provide any product formation (entries 11–15). In additional optimization studies, we found that dioxane was the optimal solvent for the reaction and that dropping the reaction temperature below 80 °C lead to a de-

crease in the yield (see supporting information for full optimization details). The reaction also shuts down completely with added TfOH (2 equiv), suggesting that TfOH is not participating in the cyclization mechanism (entry 16). When the palladium is left out of the reaction (entry 17), no product is observed.

Having established optimal reaction conditions for naphthalene formation, we next explored the substrate scope of the reaction with respect to the aryl iodide coupling partner (Figure 5). For 4-substituted iodoarenes, we only ever observed a single isomer for addition of the two acetophenone molecules. Thus, the 1,3-disubstituted naphthalene product contains a phenyl group beta to the carbon that originally contained the iodide (**6b–6g**). Aryl iodides containing substituents at either the meta- (**6i–6l**) or ortho-positions (**6m–6o**) also react to give the naphthalene products in high yield. Aryl iodides with meta Substituents also provided only a single observed regioisomer, where cyclization oc-

**Table 1.** Optimization of reaction conditions.

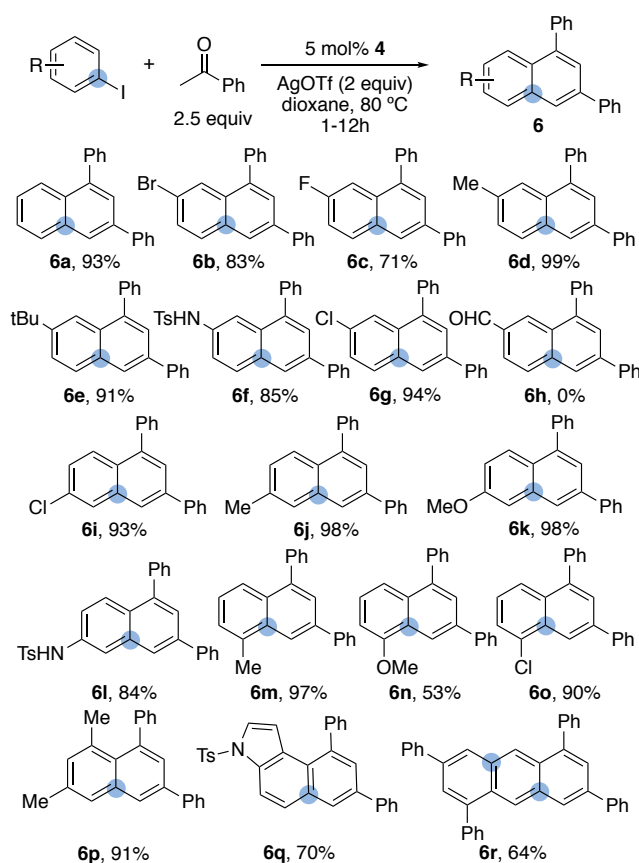


entry <sup>a</sup>	Lewis acid	Cat.	time	% conv. <sup>b</sup>
1	AgOTf	Complex <b>4</b>	1 h	100 (89)
2	AgOTf	Complex <b>5</b>	1 h	100(84)
3	AgOTf	Pd(OAc) <sub>2</sub> + <b>3</b>	1 h	100 (90)
4	AgOTf	PdCl <sub>2</sub> + <b>3</b>	1 h	100 (93)
5	CuOTf	PdCl <sub>2</sub> + <b>3</b>	16 h	85
6	FeOTf	PdCl <sub>2</sub> + <b>3</b>	16 h	NR
7	AgTFA	PdCl <sub>2</sub> + <b>3</b>	16 h	NR
8	AgOAc	PdCl <sub>2</sub> + <b>3</b>	16 h	NR
9	AgOTf	PdCl <sub>2</sub> + <b>1</b>	1 h	45
10	AgOTf	PdCl <sub>2</sub> + DIP-Im <sup>c</sup>	1 h	NR
11	AgOTf	PdCl <sub>2</sub> + PPh <sub>3</sub>	1 h	28
12	AgOTf	PdCl <sub>2</sub> + dppe	1 h	NR
13	AgOTf	PdCl <sub>2</sub> + BINAP	18 h	NR
14	AgOTf	PdCl <sub>2</sub> + DTBM-SEGPBOS	18 h	NR
15	AgOTf	PdCl <sub>2</sub> + <i>c</i> -hex-diamine	18 h	NR
16 <sup>d</sup>	AgOTf	PdCl <sub>2</sub> + <b>3</b>	18 h	NR
17	AgOTf	<b>3</b>	1h	NR

<sup>a</sup> reactions run with 0.5 mmol iodobenzene, 1.25 mmol acetophenone, and 0.025 mmol **4** or **5**, or 10% ligand and 10% PdCl<sub>2</sub> for *in situ* reaction at 0.5 M in dioxane. <sup>b</sup> Conversions determined by <sup>1</sup>H NMR of the crude reaction mixture by comparison to an internal standard (isolated yield in parentheses). <sup>c</sup> DIP-Im = *N*-(2,6-diisopropylphenyl)imidazole. <sup>d</sup> With 2 equiv TfOH.

curred at the less hindered position para to the substituent (**6i–6l**). Only aldehyde functional groups were not tolerated in the reaction (**6h**). We were excited to see that an iodoindole gave the corresponding homologated product (**6q**) in high yield and that 1,4-diiodobenzene gave the anthracene product in good yield via double cyclization (**6r**). With all aryl iodide substrates tested, only a single regioisomeric product was observed, which we believe derives from the mechanism of the reaction.

We next investigated the substrate scope of the reaction with respect to the methyl ketone coupling partner (Figure 6). Acetophenone derivatives containing both electron rich and electron poor aromatic rings perform well in the reaction. Substitution at the meta position is well tolerated (**11h**), but ortho substituents lead to lower isolated yields (**11i**, **11j**). We also investigated the use of dialkyl ketones and found that acetone reacted to give the dimethylnaphthalene derivatives **11k** and **11l** in modest yield. More hindered ketones such as methyl isobutylketone gave higher yield of the product (**11m**, **11n**). We also

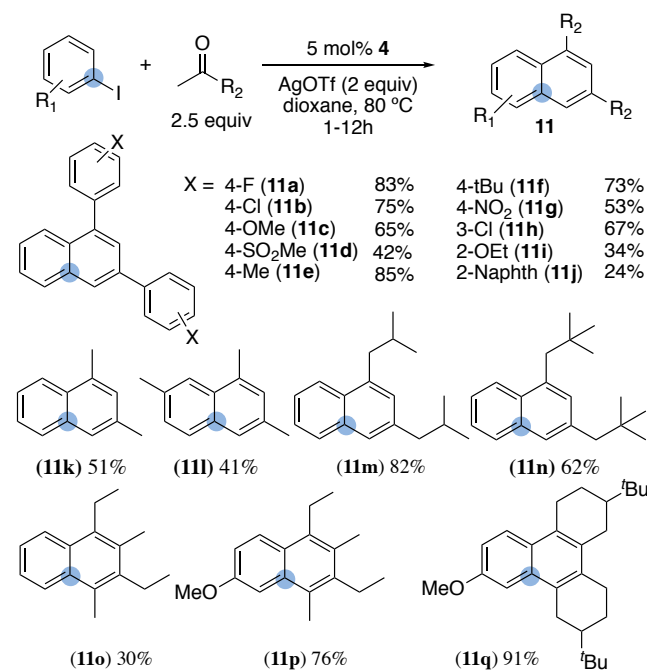


**Figure 5.** Aryl iodide substrate scope.

tried 3-pentanone and found that the corresponding tetrasubstituted naphthalene could be isolated in modest yield with phenyl iodide (**11o**), but with much higher yield with 4-iodoaniline (**11p**). 4-Tert-butylcyclohexanone also reacted to give the tetrasubstituted naphthalene in excellent yield (91%, **11q**). Unfortunately, less hindered alkyl ketones such as 2-butanone gave complex mixtures of regioisomeric products.

In order to obtain a better understanding of the mechanism of this reaction and to shed light on the importance of

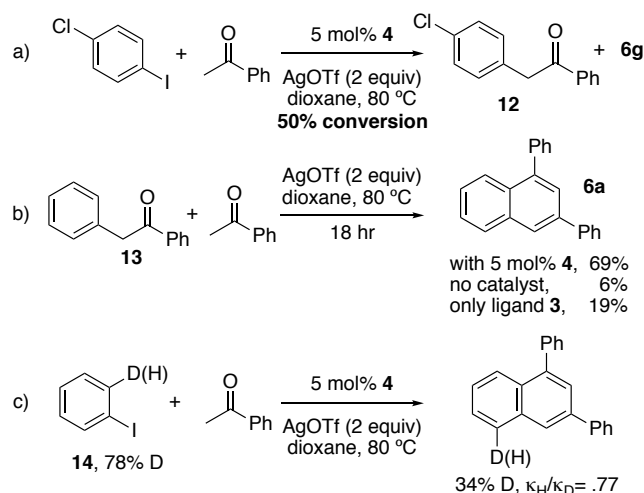
the bimetallic catalyst's structure, we performed a series of mechanistic experiments (Figure 7). First, we ran the reaction to 50% conversion and isolated arylated ketone **12** as a major product present in the reaction (Figure 7a). This intermediate suggests that the reaction proceeds via an initial Pd-catalyzed ketone arylation, followed by addition of a second equivalent of ketone and then cyclization and aromatization. Indeed, we found that when 2-phenylacetophenone (**13**) was subjected to the standard reaction conditions, product **2a** was isolated in 69% yield (Figure 7b). Interestingly, we also found that palladium catalyst **4** was necessary for the cyclization reaction to proceed efficiently, as the reaction with substrate **13** conducted without the Pd catalyst or with just ligand **3** gave only small amounts of product (6% and 19% yield, respectively). We also conducted a kinetic isotope experiment to better understand the cyclization portion of the mechanism (Figure 7c). When mono-deuterioiodobenzene (**14**) was employed in the reaction, a  $k_H/k_D$  of 0.77 was obtained. This inverse secondary kinetic isotope effect suggests that the cyclization step involves re-hybridization of an  $sp^2$  carbon to an  $sp^3$  carbon via a Friedel-Crafts-type mechanism, and does not involve a Pd-mediated C–H activation event.<sup>20</sup>



**Figure 6.** Methyl and dialkyl ketone substrate scope.

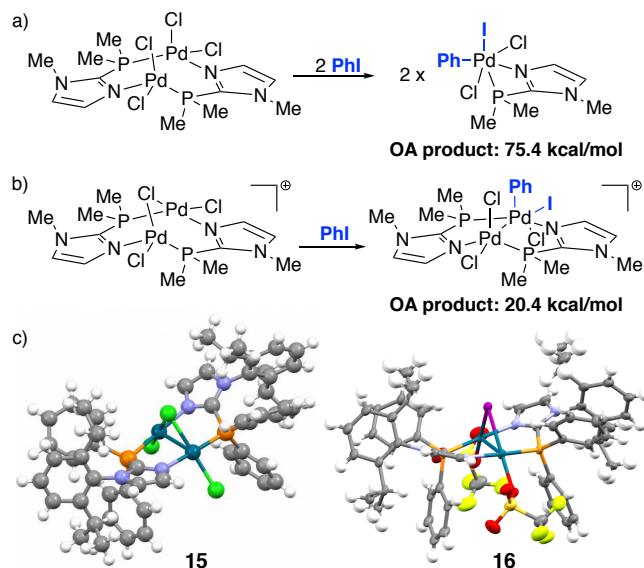
One unusual aspect of this new transformation is that the Pd-catalyzed arylation of the ketone to generate intermediate **12** occurs under oxidizing conditions. Typical Pd-catalyzed  $\alpha$ -arylations of ketones proceed under Pd(0)/Pd(II) catalysis in the presence of base via oxidative addition into the aryl iodide.<sup>21</sup> With bimetallic catalyst **4**, however, the reaction proceeds under oxidizing conditions (2 equiv Ag(OTf)) and the addition of organic or inorganic bases (Et<sub>3</sub>N, NaOtBu, Cs<sub>2</sub>CO<sub>3</sub>) leads to complete loss of reactivity and no product or ketone arylation are observed (see supporting information for details). In addition, no decrease in the rate or yield is observed when the reaction is run under a balloon of oxygen at 80 °C, which also suggests that the reaction does not proceed via Pd(0)/Pd(II) catalysis.





**Figure 7.** Mechanistic experiments.

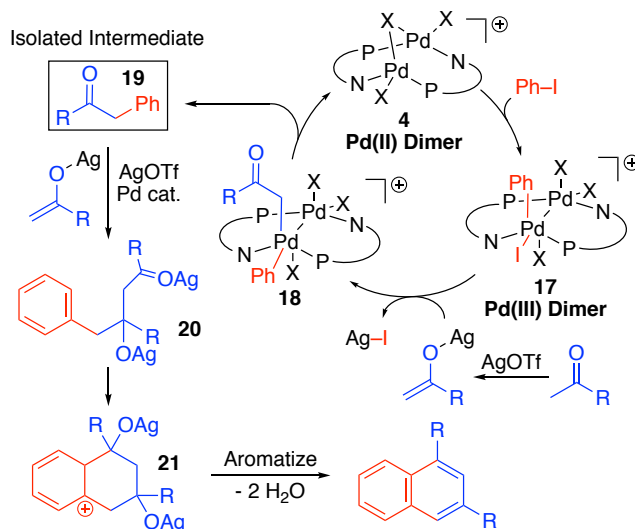
We hypothesize that the Pd(II) dimer likely undergoes oxidative addition to the aryl iodide to generate a key palladium(III) dimer intermediate. This pathway would avoid formation of a high energy Pd(IV) intermediate that results from oxidative addition to a monometallic Pd(II) complex.<sup>10</sup> To probe this hypothesis, we performed DFT calculations and found that breaking apart the Pd(II) dimer into two monometallic palladium phosphinoimidazole complexes (NPPdCl<sub>2</sub>), followed by oxidative addition to a Pd(IV) intermediate was highly endothermic by 75 kcal/mol, which suggests this type of dissociation and addition pathway is unlikely to occur (Figure 8a). In contrast, the enthalpy required for oxidative addition to the cationic chloride-bridged bimetallic complex **15** shown in Figure 8b (to access a Pd(III) dinuclear intermediate) was calculated to be endothermic by only 20.4 kcal/mol. The presence of this



**Figure 8.** M06/6-31G\*\*[LANL2DZ] DFT-calculated thermodynamic values (enthalpies) for oxidative addition forming a) monometallic Pd(IV) intermediates and b) a bimetallic Pd(III) intermediate. c) X-ray crystal structures of cationic bimetallic complexes containing bridging halides. Anions were omitted for clarity.

type of cationic bridging species is likely in the reaction because we isolated and obtained a crystal structure for this cationic complex, as seen in Figure 8c. The crystal of this bridged halide species was grown under the same conditions as those used to produce complex **4**, which suggests that **15** may be in equilibrium with **4** in solution. In addition, we subjected our Pd(II) dimer catalyst **4** to phenyl iodide under our reaction conditions and re-isolated and obtained a crystal structure of a bridging iodide species (**16**) containing two triflate counterions (Figure 8c). The re-isolation of this species suggests that the bimetallic complex remains intact under the reaction conditions, and that oxidative addition and reductive elimination are possible from a bridging halide complex. These studies provide supporting evidence for formation of a Pd(III) dimer intermediate and confirm the importance of the bimetallic catalyst structure in achieving the unique catalysis observed in this study.

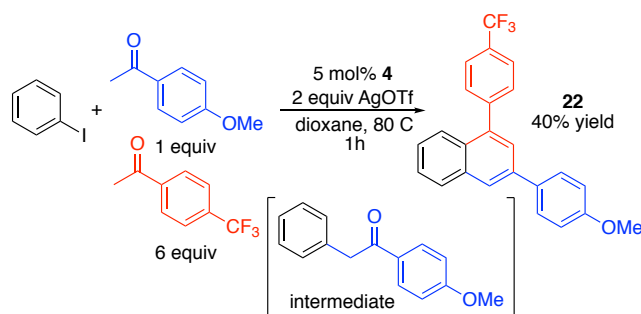
Based on our experimental and computational evidence, we propose the following potential mechanism, as shown in Figure 9. The cycle begins with the bimetallic oxidative addition to the cationic Pd<sup>III</sup> dimer **15** to generate Pd(III) dimer **17**. Enolization of the methyl ketone aided by silver triflate enables transmetalation to install the enolate and aryl group onto the complex (**18**). At this stage, we are unsure if reductive elimination occurs via a binuclear process where both the enolate and the aryl group are on adjacent metals, or if they occur from an intermediate with both groups on the same metal. Regardless, formation of the arylated ketone intermediate (**19**) is confirmed by our isolation studies described above. Previously reported work by Ritter and Sanford also confirms that this type of Pd(III) dimer is active in cross coupling reactions under oxidative conditions.<sup>10</sup> Addition of a second equivalent of the enolate to intermediate **19** would then provide **20**, which then cyclizes via a Friedel-Crafts-type mechanism to give intermediate **21**. Aromatization then occurs via loss of both oxygen functional groups to give the naphthalene product.



**Figure 9.** Mechanism of 1,3-naphthalene formation.

Finally, we attempted to couple two different ketone starting materials to generate non-equivalent aryl naphthalenes (Figure 10). Addition of 4-methoxy acetophenone (1

equiv) and 4-trifluoromethyl acetophenone (6 equiv) to iodobenzene provided product **22** in 40% yield. The minor heterocoupled isomer (where the trifluoromethylacetophenone added first) was formed in 6%, giving a 6.5:1 ratio of isomers. We hypothesized that the electron-deficient ketone would add more rapidly because the lower  $pK_a$  would increase the rate of enolization. However, even when an excess of the trifluoromethylacetophenone was employed (6 equiv), the methoxyacetophenone still underwent arylation faster. We believe that under these reaction conditions, three scenarios are possible: 1) the more electron rich ketone could form a stronger interaction with the silver Lewis acid and thus enolize faster; 2) the more electron-rich enolate binds better to the metal and undergoes faster transmetalation; or 3) the more electron rich enolate helps facilitate faster oxidative addition via precoordination to the Pd(II) dimer.



**Figure 10.** Heterocoupling selectivity in naphthalene synthesis.

In conclusion, we have demonstrated that bimetallic 2-phosphinoimidazole-derived Pd(I) and Pd(II) complexes enable the formation of 1,3-disubstituted naphthalene derivatives via a ketone arylation/cyclization mechanism. This new transformation provides easy and efficient access to substituted naphthalenes from simple aryl iodides and methyl ketones, and tolerates a range of functional groups at the aryl iodide and methyl ketone partners. The bimetallic structure of the catalyst was also shown to be essential to the observed reactivity, and mechanistic studies confirm the role of the catalyst and the observed selectivity. These results represent a new example of bimetallic catalysis and demonstrate the potential of bimetallic complexes to enable new and more efficient transformations for organic synthesis. Our continuing studies are aimed at investigating the different reactivity profiles for Pd(I) dimer **4** and Pd(II) dimer **5**, and in further investigating the cooperative bimetallic mechanism of this reaction.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge from the corresponding author.

Experimental procedures, characterization data, spectral images (PDF).

X-ray crystallographic data (CIF)

## AUTHOR INFORMATION

### Corresponding Author

\* [dmichaelis@chem.byu.edu](mailto:dmichaelis@chem.byu.edu)

<sup>†</sup>Current Locations: S.H.N – Acme Bioscience Inc. 3941 East Bayshore Rd, Palo Alto, California 94303. G.A.V.-B. – Material and Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877.

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