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Forum

Reactions of Hypervalent Iodine Reagents with Palladium: Mechanisms and Applications in Organic Synthesis

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The unique reactivity of hypervalent iodine reagents with Pd^0 and Pd^{II} complexes has been exploited for a variety of synthetically useful organic transformations. For example, I^{III} reagents have been used in place of aryl halides for diverse Pd-catalyzed C–C and C–heteroatom bond-forming cross-coupling reactions. In addition, these reagents have found application in Pd-catalyzed oxidation reactions, including the oxidative functionalization of C–H bonds and the 1,2-aminooxygenation of olefinic substrates. This review discusses both the synthetic utility and the interesting mechanistic features of these transformations.

Introduction

Over the past 30 years, I^{III} compounds have been widely used in organic synthesis as selective oxidants and as ligand-transfer reagents.[1] In particular, these compounds have found extensive application in Pd-catalyzed transformations. They possess two key features that make their reactions with Pd synthetically useful and mechanistically intriguing. First, hypervalent I^{III} reagents are both strong electrophiles and powerful oxidants. As a result, they can react with Pd complexes in different oxidation states (Pd^0 and Pd^{II}) and promote transformations that proceed via two distinct redox cycles ($Pd^{0/II}$ and $Pd^{II/IV}$). Second, I^{III} derivatives of the general structure ArI(X)(Y) (Figure 1) are typically stable compounds that are commercially available or easily synthesized. As such, these reagents can be used to transfer a diverse range of groups (X, Y = Ar, vinyl, alkynyl, OAc, Cl, F) to Pd centers in catalytic transformations.

This review aims to highlight both the synthetic utility and the interesting mechanistic features of reactions between hypervalent iodine reagents and Pd. It is divided into three parts based on both the type of reaction (catalytic vs stoichiometric) and the most widely proposed mechanism ($Pd^{0/II}$ vs $Pd^{II/IV}$) of these transformations. However, it is important to note that the mechanisms of these reactions (particularly those that are frequently proposed to proceed via $Pd^{0/II}$ manifolds) have not been firmly established to date. Part 1 summarizes the applications of I^{III} compounds in $Pd^{0/II}$-catalyzed cross-coupling reactions (Scheme 1). Part 2 details the stoichiometric reactions of Pd^{II}−alkyl, −aryl, and −vinyl complexes with hypervalent iodine reagents (Scheme 2). Finally, part 3 discusses the applications of I^{III} reagents in $Pd^{II/IV}$-catalyzed oxidation reactions, including the oxidative functionalization of C−H bonds (Scheme 3) and the 1,2-aminooxygenation of olefinic substrates.

Part 1. Hypervalent Iodine Reagents in Pd-Catalyzed Cross-Coupling

$Pd^{0/II}$-catalyzed cross-coupling reactions are powerful synthetic methods for the construction of C−C and C−heteroatom bonds.[2] Traditionally, these transformations have involved the coupling of a functionalized starting material with an aryl halide or an aryl triflate (ArX). However, in many cases, ArX can be substituted with an I^{III} reagent, and this substitution can offer significant advantages with respect to the rate, time, temperature, yield, and scope of a given transformation.

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(1) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178. (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179−1255. (c) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271−1287. (d) Okuyama, T. *Acc. Chem. Res.* **2002**, *35*, 12−18. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (f) Wirth, T., Ed. Hypervalent Iodine Chemistry, Modern Developments in Organic Synthesis. *Topics in Current Chemistry*; Springer: New York, 2003; Vol. 224.

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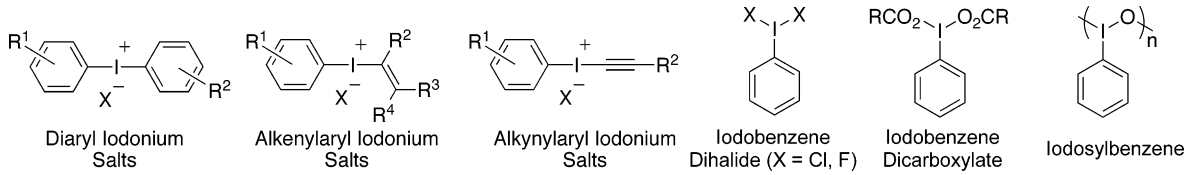
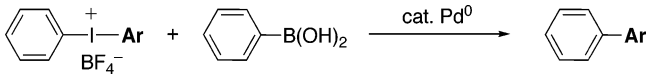
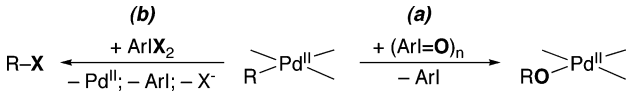


Figure 1. Commonly used iodonium reagents for Pd-catalyzed reactions.

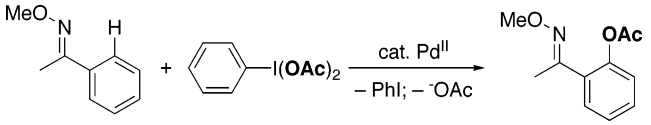
Scheme 1. Example of a Pd-Catalyzed Cross-Coupling Reaction with an I^{III} Reagent



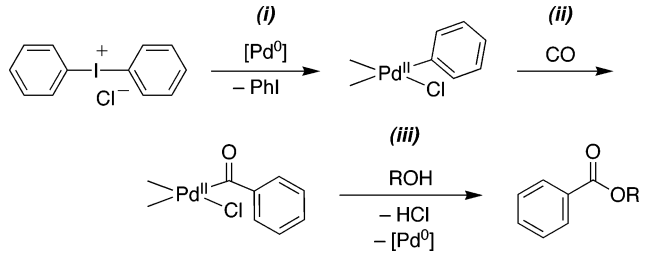
Scheme 2. Examples of Stoichiometric Reactions of Pd^{II} Complexes with I^{III} Reagents



Scheme 3. Example of a $Pd^{II/IV}$-Catalyzed C−H Activation/Functionalization Reaction with an I^{III} Reagent



Scheme 4. First Pd-Catalyzed Reaction with I^{III} Reagents: Alkoxycarbonylation of Diaryliodonium Salts



The first use of I^{III} reagents in Pd-catalyzed cross-coupling reactions was reported in 1982.[3] This paper described the room-temperature reaction of $[Ar_2I]Cl$ with CO in alcohol solvents to form alkoxycarbonylation products. The transformation was proposed to proceed via a traditional $Pd^{0/II}$ mechanism involving (i) oxidative addition of $[Ar_2I]Cl$ to Pd^0, (ii) CO insertion, and (iii) reductive elimination to form the ester C−O bond and regenerate the Pd^0 catalyst (Scheme 4).

This early report illustrates several of the significant advantages of using I^{III} reagents in place of ArX for cross-coupling reactions. First, these alkoxycarbonylations proceeded under mild conditions (just 50 °C for <3.5 h). Such mild conditions are a general and highly attractive feature of most Pd-catalyzed cross-couplings with aryliodonium salts. In addition, ancillary ligands such as phosphines or N-heterocyclic carbenes were not necessary to achieve high yields and fast rates; instead, commercially available Pd^{II} salts [e.g., $Pd(OAc)_2$ and $PdCl_2$] served as efficient catalysts for these reactions. As discussed in detail below, these favorable characteristics are typically attributed to the excellent leaving group ability of ArI, which is believed to accelerate the oxidative addition step of such catalytic cycles. Importantly, these reagents do suffer from the disadvantage (relative to aryl halides) that they generate stoichiometric quantities of ArI as a byproduct with each catalytic turnover. However, the ArI can potentially be recovered and recycled, because it serves as a starting material for the synthesis of the aryliodonium reagents.

Hypervalent iodine reagents have subsequently been used as aryl, alkenyl, and alkynyl sources in nearly all types of Pd-catalyzed C−C and C−heteroatom[3,4] bond-forming reactions, including carbonylations,[3,5] reductive couplings,[5c,6] Stille,[5l−n,7] Suzuki−Miyaura,[5i,m,p,7h,8] Heck,[5u,7j,8d,9] and Sono-

(2) Suzuki−Miyaura reactions: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. Stille reactions: (d) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−523. (e) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. Sonogashira reactions: (f) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017. Heck reactions: (g) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. C−O and C−N reactions: (h) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (i) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (j) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (k) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

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(4) C−heteroatom bond formation: (a) Stang, J. P.; Surber, B. W.; Chen, Z.-C.; Roberts, K. A.; Anderson, A. G. *J. Am. Chem. Soc.* **1987**, *109*, 228−235. (b) Kang, S.-K.; Lee, H.-W.; Choi, W.-K.; Hong, R.-K.; Kim, J.-S. *Synth. Commun.* **1996**, *26*, 4219−4224. (c) Beletskaya, I. P.; Davydov, D. V.; Moreno-Manas, M. *Tetrahedron Lett.* **1998**, *39*, 5621−5622. (d) Zhou, T.; Chen, Z.-C. *J. Chem. Res.* **2000**, 474−475. (e) Wang, L.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 1227−1232. (f) Zhou, T.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 3289−3294. (g) Thielges, S.; Bisseret, P.; Eustache, J. *Org. Lett.* **2005**, *7*, 681−684.

(5) Carbonylation: (a) Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Chem. Lett.* **1983**, 1201−1202. (b) Uchiyama, M.; Suzuki, Yamazaki, Y. *Nippon Kagaku Kaishi* **1984**, 580−584. (c) Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Nippon Kagaku Kaishi* **1984**, 585−591. (d) Ochiai, M.; Sumi, K.; Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1985**, *26*, 2351−2354. (e) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095−4112. (f) Grushin, V. V.; Alper, H. *J. Org. Chem.* **1993**, *58*, 4794−4795. (g) Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* **1997**, 874−876. (h) Kang, S.-K.; Yamaguchi, T.; Hong, R.-K.; Kim, T.-H.; Pyun, S.-J. *Tetrahedron* **1997**, *53*, 3027−3034. (i) Kang, S.-K.; Yamaguchi, T.; Ho, P.-S.; Kim, W.-Y.; Yoon, S.-K. *Tetrahedron Lett.* **1997**, *38*, 1947−1950. (j) Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Yoon, S.-K.; Son, H.-J. *Synth. Commun.* **1998**, *28*, 1481−1489. (k) Kang, S.-K.; Yamaguchi, T.; Ho, P.-S.; Kim, W.-Y.; Ryu, H.-C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 841−842. (l) Kang, S.-K.; Ho, P.-S.; Yoon, S.-K.; Lee, J.-C.; Lee, K.-J. *Synthesis* **1998**, 823−825. (m) Kang, S.-K.; Kim, J.-S.; Choi, S.-C.; Lim, K.-H. *Synthesis* **1998**, 1249−1251. (n) Kang, S.-K.; Lee, Y.-T.; Lee, S.-H. *Tetrahedron Lett.* **1999**, *40*, 3573−3576. (o) Hara, S.; Yamamoto, K.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1999**, *40*, 7815−7818. (p) Xia, M.; Chen, Z.-C. *J. Chem. Res.* **1999**, 400−401. (q) Xia, M.; Chen, Z.-C. *J. Chem. Res.* **1999**, 328−329. (r) Al-Qahtani, M. H.; Pike, V. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1033−1036. (s) Zhou, T.; Chen, Z.-C. *J. Chem. Res.* **2001**, 116−117. (t) Ryu, H.-C.; Hong, Y.-T.; Kang, S.-K. *Heterocycles* **2001**, *54*, 985−988. (u) Kina, A.; Miki, H.; Cho, Y.-H.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1728−1732.

(6) Reductive coupling: (a) Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Chem. Lett.* **1983**, 1165−1166. (b) Kang, S.-K.; Hong, R.-K.; Kim, T.-H.; Pyun, S.-J. *Synth. Commun.* **1997**, *27*, 2351−2356. (c) Zhou, T.; Chen, Z.-C. *J. Chem. Res.* **2001**, 153−155.

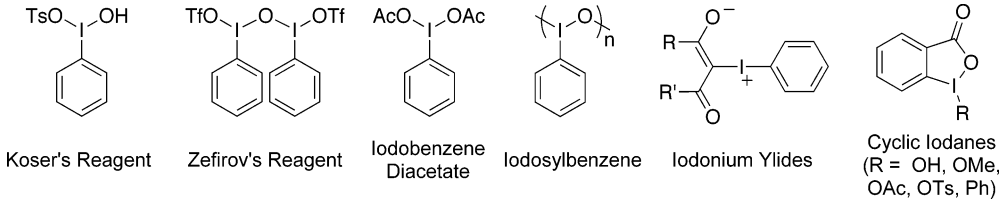
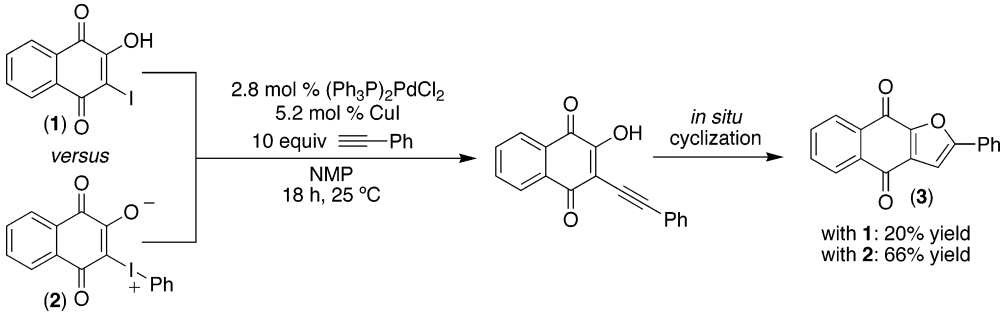


Figure 2. Alternative hypervalent iodine reagents used in cross-coupling reactions.

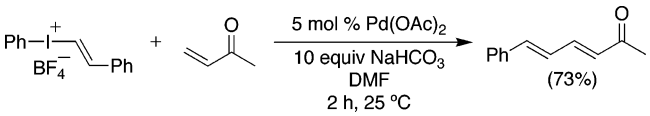
Scheme 5. Direct Comparison of the Reactivity of I^{III} Reagents Relative to Aryl Iodides



gashira reactions,[5g,m,8d,10] cross-coupling with other transmetalating reagents,[5h,7g,11] and several related transformations.[12] While these reactions most commonly involve I^{III} salts of the general structure $[R-I^{III}-R^1]X$ (R = aryl, R^1 = aryl, vinyl, or alkynyl, and X = various counterions), other I^{III} and I^{V} compounds, such as Koser's reagent [PhI(OH)OTs], Zefirov's reagent (μ-oxobis[(OTf)(phenyl)iodine]), cyclic iodanes, $PhI(OAc)_2$, $PhI(OTFA)_2$, $[PhI{=}O]_n$, iodonium ylides (Figure 2), and iodylbenzene $[(PhIO_2)_n]$, have also been used sporadically as sources of "Ph^+". This area has been reviewed extensively;[1] therefore, this account does not aim to comprehensively survey the applications of I^{III} reagents in cross-coupling reactions. Instead, we focus on (i) the synthetic utility and challenges associated with these transformations and (ii) the key mechanistic questions that remain in this area.

Synthetic Utility. In general, cross-coupling reactions with I^{III} compounds proceed with improved yields relative to those with ArI. For example, the Sonogashira coupling/cyclization of iodonium ylide **2** provided **3** in 66% yield, while the corresponding aryl iodide (**1**) afforded only 20% yield of the desired product (Scheme 5).[10d] Similarly, Stille couplings of aryl- and vinyliodonium salts with 1,2-bis(trimethylstannyl)ethenes proceeded in high (>67%) yields, while the analogous reactions with ArI generated only traces of coupled products.[5n]

Scheme 6. Heck Coupling of Alkenyliodonium Salts with Methyl Vinyl Ketone



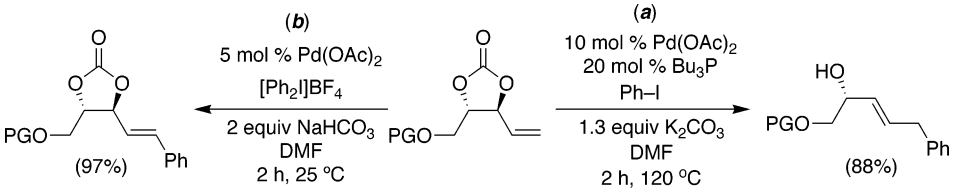
Hypervalent iodine reagents are also useful in cross-coupling reactions where one of the substrates is prone to decomposition or other side reactions. For example, Heck reactions between methyl vinyl ketone and aryl or vinyl halides generally proceed in low yields because significant competing polymerization of the olefin takes place at the elevated temperatures required for these transformations. In contrast, Heck couplings of methyl vinyl ketone with alkenylphenyliodonium salts were shown to proceed in high (>60%) yield at room temperature (Scheme 6).[9c] In a related example, Heck reactions between cyclic allylic carbonates and PhI[9f] required high temperatures and long times (>85 °C for 1−10 h) and led to carbonate ring opening to afford allylic alcohol products (Scheme 7a). In contrast, $[Ph_2I]BF_4$ reacted at room temperature (>85% yield within 1.5−2 h), and the carbonate core structure remained unperturbed (Scheme 7b).

The higher yields, accelerated reaction rates, and milder conditions observed in cross-coupling reactions with [Ar−I−R]X salts are typically attributed to the excellent leaving group ability of ArI, which results in dramatically increased rates of oxidative addition to Pd^0. However, another potentially important factor is that I^{III} reagents containing noncoordinating counterions (X) react to form cationic Pd^{II} intermediates, which are likely to be more reactive in

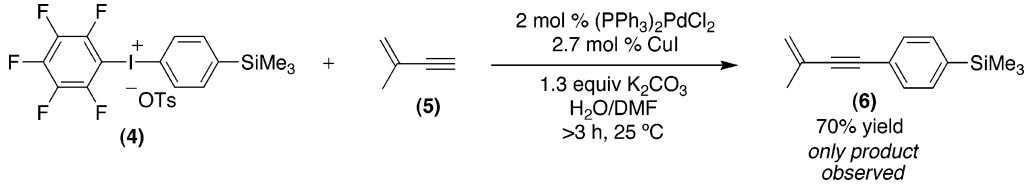
(7) Stille coupling: (a) Moriarty, R. M.; Epa, W. R. *Tetrahedron Lett.* **1992**, *33*, 4095−4098. (b) Bumagin, N. A.; Sukhomlinova, L. I.; Igushkina, S. O.; Banchikov, A. N.; Tolstaya, T. P.; Beletskaya, I. P. *Russ. Chem. Bull.* **1992**, 2128−2129. (c) Hinkle, R. J.; Poulter, G. T.; Stang, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 11626−11627. (d) Kang, S.-K.; Lee, H.-W.; Kim, J.-S.; Choi, S.-C. *Tetrahedron Lett.* **1996**, *37*, 3723−3726. (e) Ryan, J. H.; Stang, P. J. *J. Org. Chem.* **1996**, *61*, 6162−6165. (f) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Kim, J.-S. *Synth. Commun.* **1996**, *26*, 4311−4318. (g) Huang, X. A.; Zhong, P. *J. Chem. Soc., Perkin Trans.* **1999**, 1543−1545. (h) Roh, K. R.; Kim, J. Y.; Kim, Y. H. *Tetrahedron Lett.* **1999**, *40*, 1903−1906. (i) Frayssse, S.; Coudret, C.; Launay, J.-P. *Eur. J. Inorg. Chem.* **2000**, 1581−1590. (j) Yoshida, M.; Nagahara, D.; Fukuhara, T.; Yoneda, N.; Hara, S. *J. Chem. Soc., Perkin Trans.* **2001**, 2283−2288.

(8) Suzuki−Miyaura coupling: (a) Bumagin, N. A.; Luzikova, E. V.; Sukhomlinova, L. I.; Tolstaya, T. P.; Beletskaya, I. P. *Russ. Chem. Bull.* **1995**, *44*, 385−386. (b) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S. *J. Org. Chem.* **1996**, *61*, 4720−4724. (c) Bumagin, N. A.; Tsarev, D. A. *Tetrahedron Lett.* **1998**, *39*, 8155−8158. (d) Kang, S.-K.; Yoon, S.-K.; Lim, K.-H.; Son, H.-J.; Baik, T.-G. *Synth. Commun.* **1998**, *28*, 3645−3655. (e) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457−2465. (f) Xia, M.; Chen, Z.-C. *Synth. Commun.* **2000**, *30*, 63−68. (g) Yoshida, M.; Ota, D.; Fukuhara, T.; Yoneda, N.; Hara, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 384−389. (h) Zhu, Q.; Wu, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 3333−3336. (i) Yang, D.-Y.; Wang, Y.-D.; Yan, J.-B.; Huang, X. *J. Chem. Res.* **2002**, 192−193. (j) Yan, J.; Zhongshi, Z.; Zhu, M. *Synth. Commun.* **2006**, *36*, 1495−1502.

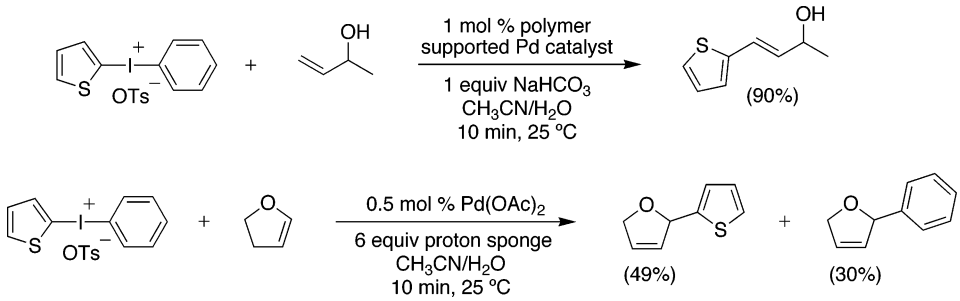
Scheme 7. Dramatic Changes in Product Distribution Based on Coupling Partner: $[Ph_2I]BF_4$ versus PhI



Scheme 8. Selectivity for Transfer of Electron-Rich over Electron-Deficient Ar Substituents



Scheme 9. Selective and Unselective Heck Couplings of Unsymmetrical Aryliodonium Salts under Similar Conditions



subsequent steps of the catalytic cycle (e.g., olefin or CO insertion[5j,p,13] or transmetalation[8b]) relative to their neutral analogues. While little work has systematically explored the role of counterions in these transformations, sporadic reports have shown that the choice of counterion can affect both reaction times and yields. For example, the carbonylative coupling of $[Ph_2I]BF_4$ with $PhBF_3K$ afforded benzophenone in 92% yield within 2 h, while the corresponding reactions with $[Ph_2I]OTf$ or $[Ph_2I]Cl$ proceeded in significantly lower (57%) yields over longer reaction times.[5p]

Another important consideration for these cross-coupling reactions is the selectivity of transfer from unsymmetrical iodonium reagents such as [Ph−I−Ar]X, [Ph−I−alkynyl]X, or [Ph−I−alkenyl]X. In general, these unsymmetrical reagents are easier to synthesize than the analogous symmetrical compounds. As a result, high selectivity for the transfer of aryl, alkynyl, or alkenyl (relative to Ph) is critical to the utility of these transformations.

In reagents containing two different Ar groups [Ar−I−Ar[1]]X, the more electron-rich Ar is generally transferred selectively. For example, Stang has demonstrated that Sonogashira coupling of enyne **5** with $[C_6F_5-I-(p\text{-}Si(Me)_3C_6H_4)]X$ (**4**) produces the *p*-$SiMe_3$ product **6** exclusively (Scheme 8).[10f] Similarly, *p*-methoxyphenyl, 2-thienyl, and 2-furyl have been shown to transfer selectively over Ph in a variety of carbonylation,[5o] Stille,[5l,7f] Suzuki−Miyaura,[5p,8b,e,j] Sonogashira,[5g,10c,f] and Heck[9i] reactions with [Ph−I−Ar]X.

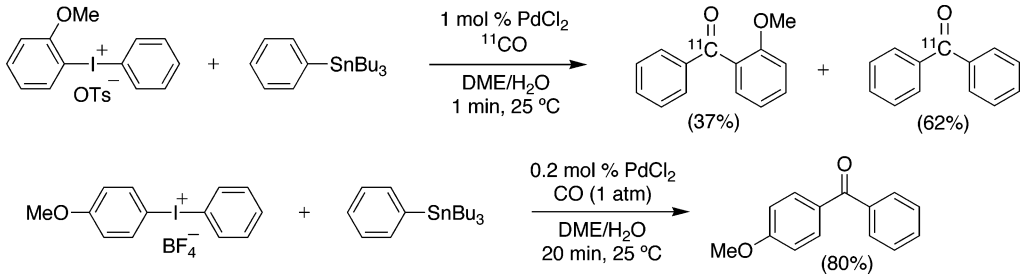
However, a number of exceptions to this trend have been reported.[5r,8d,9h] For example, Heck reactions with [2-thienyl−I−Ph]BF_4 have been shown to afford dramatically different ratios of thiophene versus Ph transfer under very similar conditions (Scheme 9).[9h,i] While there are clearly some differences between these reactions (e.g., the catalyst, base, and substrate), the lack of a convincing explanation for these[9h] (and related)[5r,8d] discrepancies highlights the need for

(9) Heck reactions: (a) Sugioka, K.; Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Nippon Kagaku Kaishi* **1985**, 527−532. (b) Nishimura, A.; Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Nippon Kagaku Kaishi* **1985**, 558−560. (c) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *J. Am. Chem. Soc.* **1991**, *113*, 6315−6317. (d) Bumagin, N. A.; Sukhomlinova, L. I.; Banchikov, A. N.; Tolstaya, T. P.; Beletskaya, I. P. *Russ. Chem. Bull.* **1993**, 2130. (e) Kurihara, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Pharm. Bull.* **1994**, *42*, 2357−2359. (f) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Jang, S.-B. *Tetrahedron Lett.* **1995**, *36*, 8047−8050. (g) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604−2605. (h) Kang, S.-K., Yamaguchi, T.; Kim, J.-S.; Choi, S.-C.; Ahn, C. *Synth. Commun.* **1997**, *27*, 1105−1110. (i) Jang, S.-B. *Tetrahedron Lett.* **1997**, *38*, 4421−4424. (j) Liang, Y. M.; Jing, H. W.; Liu, C. M.; Wu, X. L.; Ma, Y. X. *Tetrahedron Lett.* **1998**, *39*, 7143−7146. (k) Liang, Y. M.; Luo, S. J.; Liu, C. M.; Wu, X. L.; Ma, Y. X. *Tetrahedron* **2000**, *56*, 2961−2965. (l) Yoshida, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **2000**, *41*, 3887−3890. (m) Xia, M.; Chen, Z.-C. *Synth. Commun.* **2000**, *30*, 1281−1285.

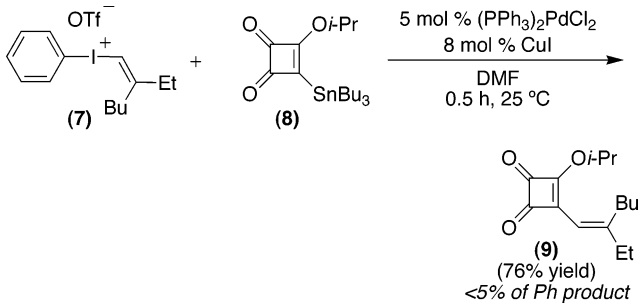
(10) Sonogashira coupling: (a) Luzikova, E. V.; Sukhomlinova, L. I.; Tolstaya, T. P.; Bumagin, N. A.; Beletskaya, I. P. *Russ. Chem. Bull.* **1995**, *44*, 556−557. (b) Bumagin, N. A.; Sukhomlinova, L. I.; Luzikova, E. V.; Tolstaya, T. P.; Beletskaya, I. P. *Tetrahedron Lett.* **1996**, *37*, 897−900. (c) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S. *Chem. Commun.* **1996**, 835−836. (d) Kobayashi, K.; Uneda, T.; Kawakita, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **1997**, *38*, 837−840. (e) Pirguliyev, N. Sh.; Brel, V. K.; Zefirov, N. S.; Stang, P. J. *Tetrahedron* **1999**, *55*, 12377−12386. (f) Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859−860. (g) Yoshida, M.; Yoshikawa, S.; Fukuhara, T.; Yoneda, N.; Hara, S. *Tetrahedron* **2001**, *57*, 7143−7148.

(11) Transmetalation from other metals: (a) Huang, X.; Sun, A.-M. *Synth. Commun.* **1998**, *28*, 773−778. (b) Kang, S.-K.; Choi, S.-C.; Baik, T.-G. *Synth. Commun.* **1999**, *29*, 2493−2499. (c) Wang, L.; Chen, Z.-C. *Synth. Commun.* **2000**, *30*, 3607−3612. (d) Hinkle, R. J.; Leri, A. C.; David, G. A.; Erwin, W. M. *Org. Lett.* **2000**, *2*, 1521−1523. (e) Kang, S.-K.; Lee, S.-W.; Kim, M.-S.; Kwon, H.-S. *Synth. Commun.* **2001**, *31*, 1721−1725. (f) Kang, S.-K.; Ryu, H.-C.; Kim, J.-W. *Synth. Commun.* **2001**, *31*, 1021−1026. (g) Kang, S.-K.; Yoon, S.-K. *J. Chem. Soc., Perkin Trans.* **2002**, 459−461.

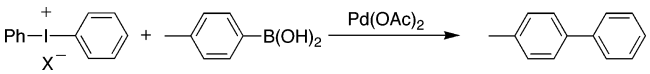
Scheme 10. Selectivity in Cross-Coupling Reactions of Sterically Differentiated Aryliodonium Reagents



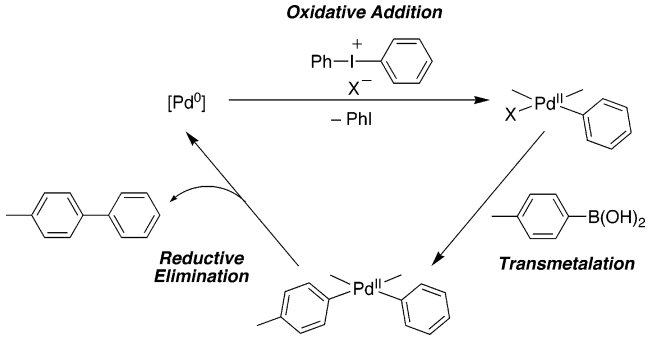
Scheme 11. Generally Observed High Selectivity for Alkenyl versus Ph Transfer



Scheme 12. Representative Suzuki Coupling Reaction with $[Ph_2I]X$



Scheme 13. Mechanistic Possibility A: $Pd^{0/II}$ Catalytic Cycle



more systematic studies to explore the selectivity of group transfer from electronically differentiated iodonium salts. Such experiments are particularly critical because the inability to predictably transfer electronically diverse arenes and heteroarenes remains the major synthetic limitation of cross-coupling reactions with iodonium salts. In addition, studies of these electronic effects will provide more definitive evidence about the mechanisms of these transformations (vide infra).

Steric differentiation of the Ar substituents can also play a role in the selectivity of Ar transfer, with smaller substituents generally being transferred in preference to larger groups. This is exemplified by the carbonylative Stille reaction of [*o*-$MeOC_6H_4$−I−Ph]OTs with $PhSnBu_3$, which afforded a 3:2 mixture of benzophenone to *o*-MeO-substituted benzophenone (Scheme 10).[5r] In comparison, the electron-rich *p*-MeO−C_6H_4 group was transferred exclusively in the analogous reaction of [*p*-$MeOC_6H_4$−I−Ph]BF_4 (Scheme 10).[5l]

In cross-coupling reactions of [Ph−I−alkynyl]X or [Ph−I−alkenyl]X, the alkenyl or alkynyl substitutents are typically transferred with good to excellent selectivity over the Ph group. For example, Stang has shown that Stille cross-coupling of **7** with **8** provides **9** in high yield, along with only traces (0−4%) of the corresponding Ph product (Scheme 11).[7c] Similarly high selectivity for alkenyl or alkynyl transfer has been observed in other Stille,[5l,n,7a,c,e,f,h,i] Suzuki−Miyaura,[5i,p,7h,8b,h,j] Sonogashira,[5g,10c−e] and Heck[9c,e−i,l] reactions. There are only a few cases in which alkenyl and Ph transfer products are obtained as mixtures, and these generally appear to be due to other steric and/or electronic factors.[5t,7j,8g,10g]

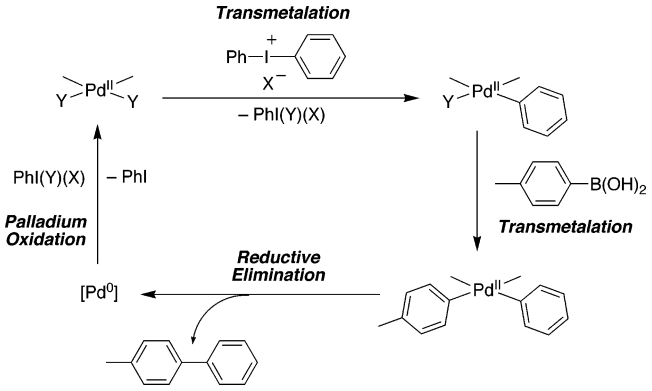
Key Mechanistic Considerations. While the scope and synthetic applications of aryliodonium salts in cross-coupling reactions have been extensively explored, detailed mechanistic insights into these transformations remain limited. Three distinct mechanistic possibilities (**A**−**C**) are presented below in the context of the $Pd(OAc)_2$-catalyzed Suzuki−Miyaura reaction between $[Ph_2I]X$ and *p*-tolylboronic acid (Scheme 12). Analogous mechanistic considerations should be relevant to other Pd-catalyzed cross-coupling reactions with I^{III} reagents.

The most commonly proposed mechanism for these transformations (mechanism A, Scheme 13) involves a classic $Pd^{0/II}$ catalytic cycle that requires in situ reduction of $Pd^{II}(OAc)_2$ to Pd^0. Oxidative addition of $[Ph_2I]X$ to the Pd^0 center would then release PhI and afford a Pd^{II}−phenyl complex. From there, transmetalation between boron and Pd^{II} followed by C−C bond-forming reductive elimination would liberate the biaryl product and regenerate the Pd^0 catalyst. As alluded to above, mechanism A has been proposed (although not confirmed) for the vast majority of Pd-catalyzed cross-coupling reactions with I^{III} reagents. However, interestingly, this mechanism appears to be inconsistent with the electronic effects reported for many of these systems. In general, oxidative addition reactions to low-valent Pd complexes are accelerated with more electron-withdrawing

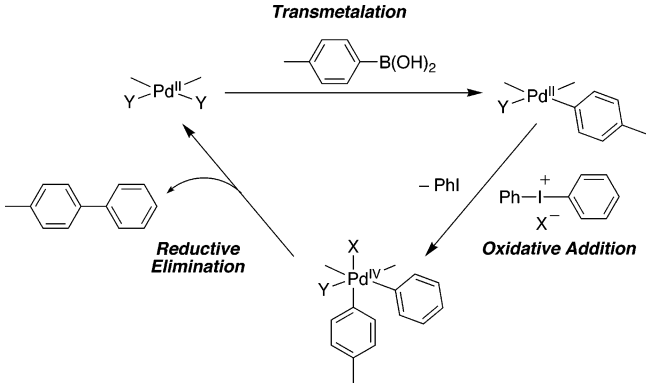
(12) Cyclization reactions: (a) Kang, S.-K.; Yamaguchi, T.; Pyun, S.-J.; Lee, Y.-T.; Baik, T.-G. *Tetrahedron Lett.* **1998**, *39*, 2127−2130. (b) Kang, S.-K.; Baik, T.-G.; Hur, Y. *Tetrahedron* **1999**, *55*, 6863−6870. (c) Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324−326. *o*-Hydroxyaldehyde arylation: (d) Xia, M.; Chen, Z.-C. *Synth. Commun.* **2000**, *30*, 531−536. (e) Chen, D.-J.; Chen, Z.-C *Synlett* **2000**, 1175−1177. Malonate arylation: (f) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338−1340.

(13) Kitamura, T.; Mihara, I.; Taniguchi, H.; Stang, P. J. *J. Chem. Soc., Chem. Commun.* **1990**, 614−615.

Scheme 14. Mechanistic Possibility B: Transmetalation from I^{III} to Pd^{II}



Scheme 15. Mechanistic Possibility C: $Pd^{II/IV}$ Catalytic Cycle



Ar donors;[14] *in contrast, cross-coupling reactions with [Ar−I−Ar¹]X tend to show high selectivity for the transfer of electron-rich Ar substituents.*[5g,l,o,p,7f,8b,e,j,9i,10c,f] To our knowledge, this discrepancy has not been addressed or reconciled in any prior mechanistic discussions of these transformations.

A second possible mechanism (B, Scheme 14) involves initial transmetalation between I^{III} and $Pd(OAc)_2$ to generate a Pd^{II}−phenyl complex and ArI(X)(OAc).[15] Subsequent boron/Pd transmetalation and C−C bond-forming reductive elimination would release the biaryl product along with Pd^0. Pd^0 would then undergo oxidation by PhI(X)(OAc) to regenerate the Pd^{II} catalyst and complete the cycle. [The order of the transmetalation steps could also be reversed (with boron/Pd exchange preceding iodine/Pd exchange) without changing the overall outcome of the reaction.] Mechanism B was originally proposed by Moriarty et al. in 1991; however, this intriguing possibility does not appear to have been investigated further.[9c] Importantly, the electronic effects observed in Ar transfer from [Ar−I−Ar¹]X (with electron-rich Ar substituents transferring in preference to electron-deficient groups)[5g,l,o,p,7f,8b,e,j,9i,10c,f] are consistent with the electronic requirements of transmetalation reactions.[16]

The final mechanistic possibility (C, Scheme 15) begins with transmetalation between boron and Pd^{II} to afford a Pd^{II}−tolyl intermediate. From there, oxidation of the electron-rich Pd^{II} species by the aryliodonium salt would afford a Pd^{IV} complex, which would undergo C−C bond-forming reductive elimination to afford the biaryl product and regenerate the Pd^{II} catalyst. While this mechanism has not, to our knowledge, been proposed in the literature, several recent reports by Canty[17−19] as well as from our group[20] indicate that such a $Pd^{II/IV}$ mechanism should be both kinetically and thermodynamically accessible (vide infra). However, it is important to note that, as with mechanism A, the observed preference for transfer of electron-rich over electron-deficient Ar groups in some transformations appears to be inconsistent with this pathway (vide infra).[14]

In conclusion, while 15 years of conventional wisdom have implicated a $Pd^{0/II}$ mechanism for these cross-coupling reactions, we believe that significant mechanistic ambiguities remain. Very little systematic data are currently available, which precludes a thorough evaluation of mechanisms A−C at this time. Nonetheless, in the reactions where electronically diverse aryliodonium salts have been explored, the observed product distributions appear most consistent with mechanism B. Clearly, further investigations will be required to distinguish between mechanisms A−C, and it seems plausible (even likely) that each of these mechanisms is accessible, depending on the catalyst, reagent, and reaction conditions.

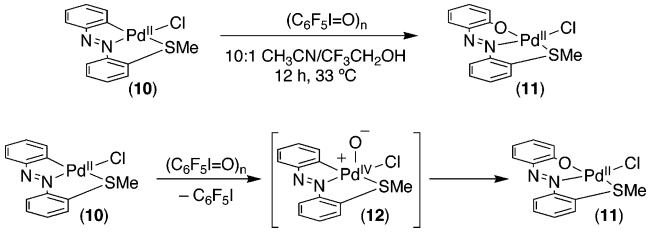
Part 2. I^{III} Reagents in the Stoichiometric Functionalization of Pd^{II}−C Bonds

Over the same time period that the organic community has explored Pd-catalyzed cross-coupling reactions with hypervalent iodine reagents, inorganic chemists have focused on stoichiometric reactions between I^{III} compounds [e.g., $[PhI{=}O]_n$, $[PhI{=}NTs]_n$, $PhICl_2$, $[Ph_2I]OTf$, and $PhI(OAc)_2$] and Pd−alkyl, −aryl, and −vinyl complexes. These stoichiometric reactions generally result in clean and high-yielding functionalization/cleavage of the Pd−C bond. In many cases, the mechanisms of these transformations have been investigated in detail, and most are believed to proceed via Pd^{IV} intermediates.

Early work focused on the reactions of cyclometalated Pd^{II} complexes with $(ArI{=}O)_n$ (Ar = Ph or C_6F_5).[21−23] As shown

(14) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434−442.
(15) Analogous transmetalation reactions are well-known to occur in cross-coupling reactions with organomercury and organothallium reagents. (a) Uemura, S.; Zushi, K.; Okano, M.; Ichikawa, K. *J. Chem. Soc., Chem. Commun.* **1972**, 234−235. (b) Larock, R. C. *Angew. Chem., Int. Ed.* **1978**, *17*, 27. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345−390. (d) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer-Verlag: New York, 1985. (e) Kjonaas, R. A. *J. Org. Chem.* **1986**, *51*, 3708−3710.
(16) (a) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598−11599. (b) In *Innovations in Organic Synthesis: Transition Metal Reagents and Catalysts*; Tsuji, J., Ed.; John Wiley and Sons, Ltd.: New York, 2000. (c) In *Fundamentals of Molecular Catalysis*; Kurosawa, H., Yamamoto, A., Eds.; Elsevier: New York, 2003. (d) Espinet, P.; Echavarren *Angew. Chem., Int. Ed.* **2004**, *43*, 4704−4734.
(17) Canty, A. J.; Patel, J.; Rodemann, T.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 3466−3473.
(18) Bayler, A.; Canty, A. J.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Inorg. Chem. Commun.* **2000**, *3*, 575−578.
(19) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Organometallics* **2006**, *25*, 3996−4001.
(20) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791.
(21) Kamaraj, K.; Bandyopadhyay, D. *Organometallics* **1999**, *18*, 438−446.
(22) Kamaraj, K.; Bandyopadhyay, D. *J. Am. Chem. Soc.* **1997**, *119*, 8099−8100.
(23) Bhawmick, R.; Biswas, H.; Bandyopadhyay, P. *J. Organomet. Chem.* **1995**, *498*, 81−83.

Scheme 16. O Insertion into a Pd^{II}−C Bond with $(C_6F_5I{=}O)_n$



in Scheme 16, these transformations generally lead to the insertion of an O atom into the Pd−C bond with concomitant release of PhI. Our group has recently found that $[PhI{=}NTs]_n$ undergoes analogous reactions to effect "NTs" insertion into Pd^{II}−aryl and Pd^{II}−alkyl bonds.[24] No discrete high-oxidation-state Pd intermediates have been observed in any of these transformations; however, Bandyopadhyay has proposed a mechanism that involves (i) coordination of $(ArI{=}O)_n$ to palladacycle **10**, (ii) oxidation to the Pd^{IV}−oxo species **12**, and (iii) intramolecular insertion of the oxo into the Pd^{IV}−C bond to afford **11**. Interestingly, similar Pd^{IV}−oxo intermediates have been proposed by van Koten and Boersma in reactions of peroxide oxidants with palladacycles.[25]

The chlorination of Pd^{II}−C bonds with $PhICl_2$ is another transformation that has been extensively explored. Both Pd^{II}−aryl and −vinyl species have been shown to react stoichiometrically with $PhICl_2$ to afford aryl and vinyl chlorides,[26−30] and these chlorinations are believed to proceed via C−Cl bond-forming reductive elimination from Pd^{IV} intermediates. (Notably, C−Cl bond-forming reductive elimination from Pd^{IV} is highly thermodynamically favorable, while, in contrast, analogous reactions at Pd^{II} centers have K_{eq} of $\sim 10^{-2}$.)[31] For example, van Koten has shown that pincer complex **13** reacts with $PhICl_2$ to afford the Pd^{IV} intermediate **14**, which can be detected and characterized by ^{1}H NMR spectroscopy at room temperature. Complex **14** decomposed over several minutes, and although the organic product was not fully characterized, it was believed to be the free chlorinated ligand **15** (Scheme 17).[32]

Recent work by Canty and co-workers has explored the reactions of Pd^{II} complexes with diaryliodonium salts of the general structures $[Ar_2I]X$[17,18] and [Ar−I−alkynyl]X.[19] Notably, these same I^{III} reagents have been used extensively in "$Pd^{0/II}$" cross-coupling reactions (vide supra). When the electron-rich Pd^{II} complex (bpy)$Pd^{II}(C_4H_8)$ (**16**) was treated with $[Ph_2I]OTf$ at −50 °C, a 1:1 mixture of the cis and trans isomers of (bpy)$Pd^{IV}OTf(C_4H_8)Ph$ (**17** and **18**, respectively) was observed by ^{1}H NMR spectroscopy (Scheme 18). The structures of **17** and **18** were confirmed through the synthesis of stable Pt^{IV} analogues of these transient Pd^{IV} species.

Pd^{IV} complexes **17** and **18** showed moderate stability at −50 °C, but warming to room temperature resulted in rapid decomposition to afford a mixture of C−C bond-forming reductive elimination and β-hydride elimination products, including isomers of phenylbutene (70%), butylbenzene (22%), and 1-phenyl-1-butanone (7%). (The latter product was formed from phenylbutene via a Wacker oxidation process.) These studies clearly demonstrate (i) that the oxidation of Pd^{II} complexes with diaryliodonium salts can be rapid under extremely mild conditions and (ii) that the resulting Pd^{IV} complexes can undergo facile C−C bond-forming reductive elimination. This work further raises the intriguing possibility that a $Pd^{II/IV}$ pathway may be involved in cross-coupling reactions with [Ar−I−R]X reagents.

Finally, our laboratory has studied the reaction of $(phpy)_2Pd^{II}$ [phpy = 2-phenylpyridine] (**19**) with $PhI(O_2CPh)_2$ to form isolable palladium(IV) carboxylate complex $(phpy)_2Pd^{IV}(O_2CPh)_2$ (**20**; Scheme 19).[20] Complex **20** and its derivatives exhibited unusually high stability (they did not decompose over hours in solution at room temperature) and were characterized by both ^{1}H NMR spectroscopy and X-ray crystallography. When heated to 60 °C, **20** underwent clean C−O bond-forming reductive elimination to afford the oxygenated organic product **21**. This reductive elimination reaction was studied extensively, and Eyring analysis, solvent effects, crossover experiments, Hammett plots, and ligand rigidity studies have all implicated a mechanism involving (i) dissociation of one arm of the phenylpyridine ligand followed by (ii) C−O bond-forming reductive elimination from the resulting five-coordinate intermediate **22** (Scheme 20). Importantly, these reactions were significantly less sensitive to electronic perturbation of the O donor or of the Ar group than analogous C−O bond-forming reductive eliminations from Pd^{II} centers.[33] This exemplifies the potential advantage of accessing Pd^{IV} intermediates in catalysis, because they can undergo reductive elimination reactions that are complementary to those currently accessible via $Pd^{0/II}$ pathways.

Part 3. Catalytic $Pd^{II/IV}$ Reactions

The stoichiometric reactions discussed in part 2 suggested that hypervalent iodine reagents could be used to form Pd^{IV} intermediates in catalytic transformations, and over the past several years, a variety of such $Pd^{II/IV}$-catalyzed reactions have been developed. The vast majority of these are C−H activation/functionalization reactions, which are believed to proceed via (i) C−H activation at Pd^{II}, (ii) oxidation of the resulting electron-rich Pd^{II}−aryl or −alkyl complex to Pd^{IV} with an I^{III} reagent, and (iii) reductive elimination to release

(24) Dick, A. R.; Remy, M. R.; Kampf, J. W.; Sanford, M. S. *Organometallics*, in press.
(25) (a) Alsters, P. L.; Teunissen, H. T.; Boersma, J.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 4691−4696. (b) Valk, J.-M.; Boersma, J.; van Koten, G. *Organometallics* **1996**, *15*, 4366−4372.
(26) Vicente, J.; Chicote, M. T.; Martin, J.; Artigao, M.; Solans, X.; Font-Altaba, M.; Aguilo, M. *J. Chem. Soc., Dalton Trans.* **1988**, 141−147.
(27) Canty, A. J.; Fritshe, S. D.; Jin, H.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1995**, *490*, C18−C19.
(28) Canty, A. J.; Jin, H.; Roberts, A. S.; Skelton, B. W.; White, A. H. *Organometallics* **1996**, *15*, 5713−5722.
(29) van Belzen, R.; Elsevier, C. J.; Dedieu, A.; Veldman, N.; Spek, A. L. *Organometallics* **2003**, *22*, 722−736.
(30) van Belzen, R.; Hoffmann, H.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 1743−1745.
(31) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533−1541.
(32) Lagunas, M.-C.; Gossage, R. A.; Spek, A. L.; van Koten, G. *Organometallics* **1998**, *17*, 731−741.
(33) (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13100. (b) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787−6795. (c) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504−6511.

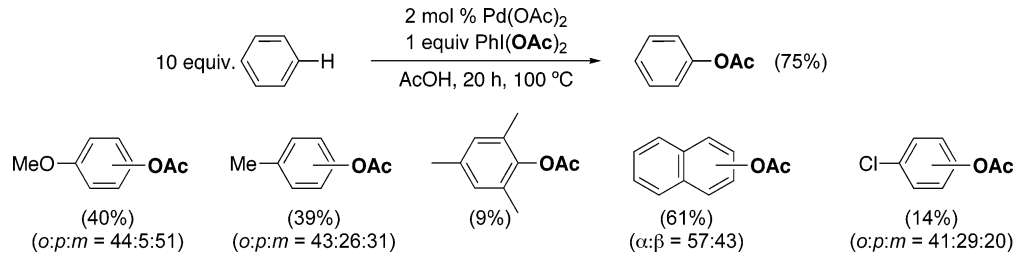
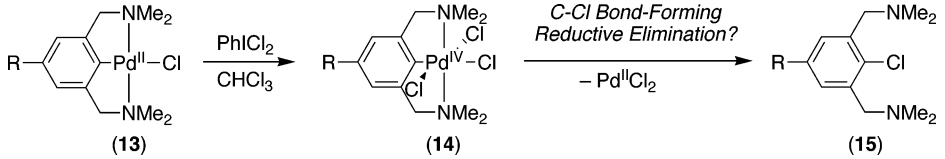
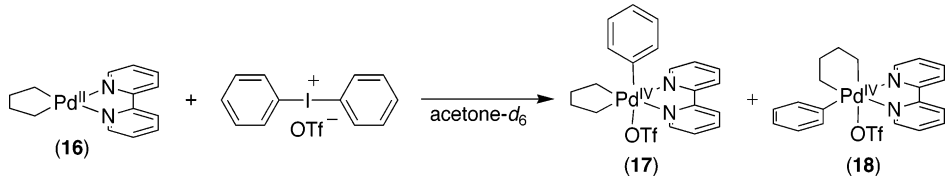


Figure 3. Pd-catalyzed C−H activation/acetoxylation of arenes with $PhI(OAc)_2$.

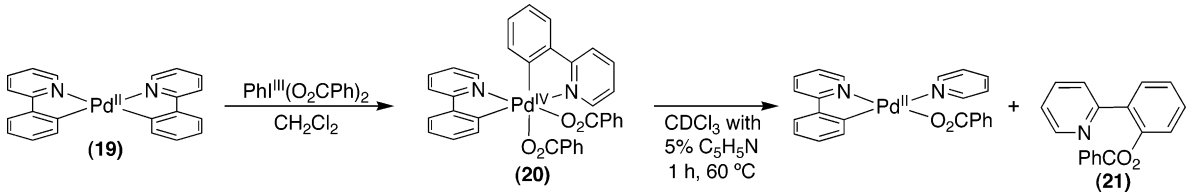
Scheme 17. Oxidation of Pd^{II} to Pd^{IV} with $PhICl_2$



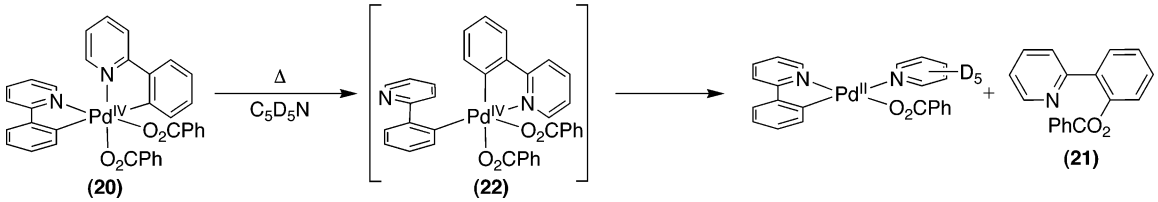
Scheme 18. Oxidation of Pd^{II} to Pd^{IV} with $[Ph_2I]OTf$



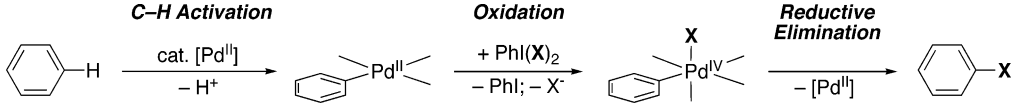
Scheme 19. Oxidation of Pd^{II} to Pd^{IV} with $PhI(OAc)_2$



Scheme 20. Proposed Mechanism of C−O Bond-Forming Reductive Elimination from Pd^{IV}



Scheme 21. Mechanism of C−H Activation/Oxidative Functionalization Reactions



the functionalized product (Scheme 21). $Pd^{II/IV}$ catalysis offers several significant advantages over $Pd^{0/II}$ catalytic cycles. First, the bond constructions available through this mechanism can be highly complementary to those accessed via typical $Pd^{0/II}$ cross-couplings. For example, sp^2 and sp^3 C−OAc, C−OCH_2CF_3, C−I, and C−F bonds are all readily formed via $Pd^{II/IV}$ catalysis (vide infra). In addition, $Pd^{II/IV}$ reactions are typically operationally simple and do not require the use of strong bases and/or the exclusion of ambient air and moisture. Finally, $Pd^{II/IV}$ reactions exhibit complementary functional group tolerance to $Pd^{0/II}$ transformations; for example, aryl bromides and aryl iodides (which would be highly reactive with Pd^0 intermediates) are completely stable under these oxidative catalytic conditions.

An early example of $Pd^{II/IV}$-catalyzed C−H bond functionalization was reported by Yoneyama and Crabtree, who discovered that $Pd(OAc)_2$ catalyzes the conversion of benzene to phenyl acetate with $PhI(OAc)_2$ as a terminal oxidant (Figure 3).[34] While prior reports had described the Pd-catalyzed C−H activation/acetoxylation of benzene with other oxidants (e.g., dioxygen,[35] dichromate,[36] peroxydisulfate[37]), $PhI(OAc)_2$ proved far superior with respect to both

(34) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35−40.
(35) (a) Eberson, L.; Gomez-Gonzales, L. *J. Chem. Soc., Chem. Commun.* **1971**, 263−264. (b) Eberson, L.; Gomez-Gonzalez, L. *Acta. Chem. Scand.* **1973**, *27*, 1249−1254.
(36) (a) Henry, P. M. *J. Org. Chem.* **1971**, *36*, 1886−1890. (b) Stock, L. M.; Tse, K.; Vorvick, L. J.; Walstrum, S. A. *J. Org. Chem.* **1981**, *46*, 1757−1759.

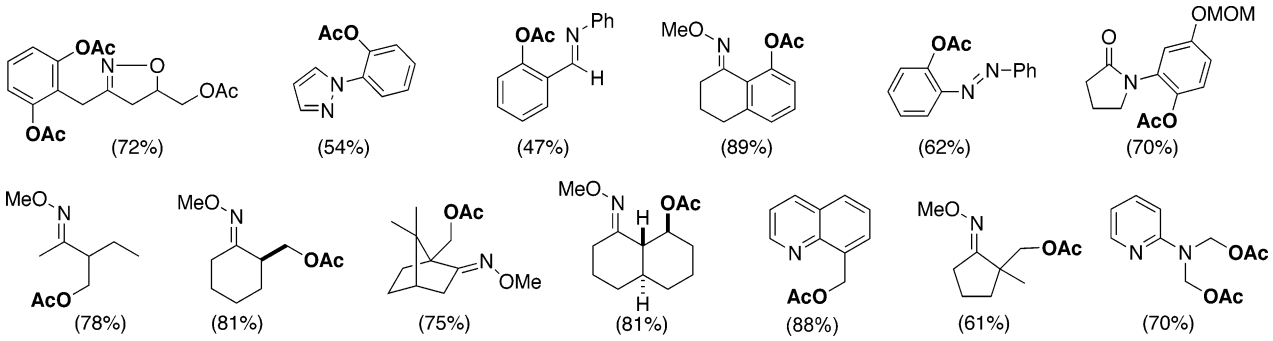
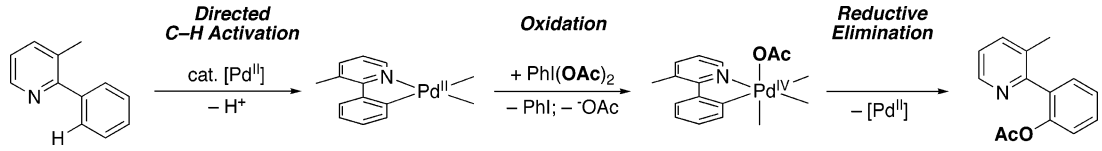
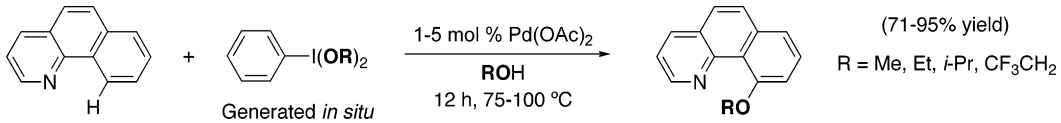


Figure 4. Selected products obtained from ligand-directed C−H bond acetoxylation with $PhI(OAc)_2$.

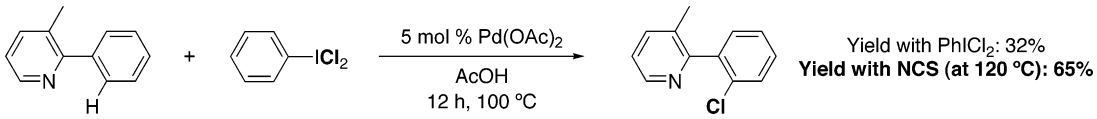
Scheme 22. Highly Regioselective Ligand-Directed C−H Bond Acetoxylation with $PhI(OAc)_2$



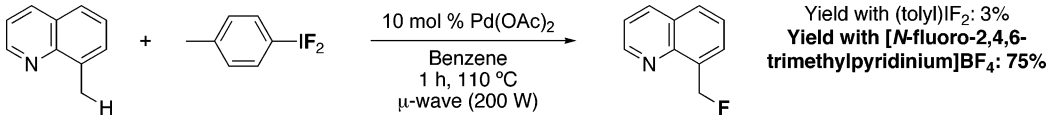
Scheme 23. Pd-Catalyzed C−H Bond Etherification with $PhI(OR)_2$



Scheme 24. Pd-Catalyzed C−H Bond Chlorination with $PhICl_2$



Scheme 25. Pd-Catalyzed C−H Bond Fluorination with (tolyl)$I(F)_2$



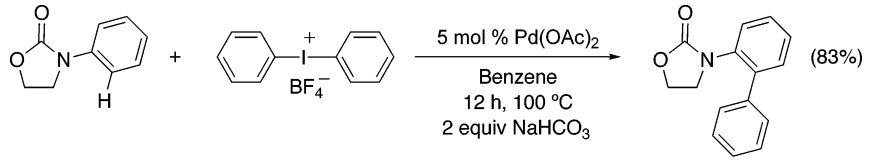
yield (75%) and turnover number (up to 78). This procedure was also applied to the C−H bond acetoxylation of substituted arenes, including anisole, toluene, chlorobenzene, naphthalene, and mesitylene (Figure 3). However, these transformations were limited by modest yields and by the formation of complex mixtures of ortho-, meta-, and para-acetoxylated products.

Our group recognized that these C−H activation/oxidation reactions could be extremely synthetically useful for the functionalization of complex organic substrates if they proceeded with high selectivity for a specific C−H bond. We aimed to achieve this goal by using Pd^{II} catalysts and $PhI(OAc)_2$ for the selective acetoxylation of C−H bonds adjacent to coordinating functional groups (e.g., pyridine in Scheme 22).[38] We have shown that this strategy is highly effective for the acetoxylation of both sp^2 and sp^3 C−H bonds in diverse organic molecules, including pyridine, pyrazole, imine, oxime ether, amide, and azobenzene derivatives (Figure 4).[39−43] These transformations are compatible with a wide variety of functionalities, including benzylic C−H bonds, aldehydes, aryl bromides, and enolizable ketones, highlighting the mild nature of the I^{III}-based oxidant. These reactions proceed with high levels of chemo-, regio-,[41] and diastereoselectivity,[40] and our group is currently working toward developing enantioselective versions of these transformations.

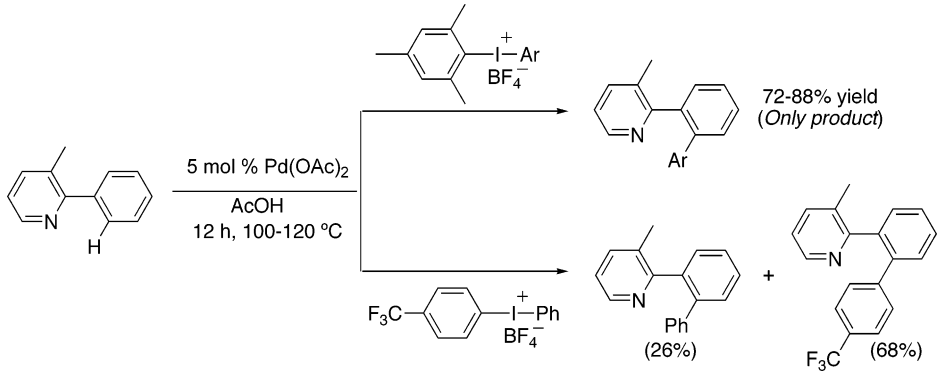
On the basis of the stoichiometric reactions discussed in part 2, we reasoned that substituting $PhI(OAc)_2$ with alternative I^{III} reagents might promote novel C−H bond functionalization reactions. Our first efforts aimed to generate the alkoxide iodine(III) reagents $PhI(OR)_2$ (R = Me, Et, *i*-Pr,

(37) (a) Eberson, L.; Jonsson, L. *J. Chem. Soc., Chem. Commun.* **1974**, 885−886. (b) Eberson, L.; Jonsson, L. *Acta. Chem. Scand. B* **1976**, *30*, 361−365. (c) Eberson, L.; Jonsson, L. *Liebigs Ann. Chem.* **1977**, 233−241.
(38) For reviews that discuss catalytic-directed C−H activation/C−C bond formation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507−514. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101.
(39) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301.
(40) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543.
(41) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149−4152.
(42) Kalberer, E. W.; Whitfield, S. R.; Sanford, M. S. *J. Mol. Catal. A* **2006**, *251*, 108−113.
(43) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141−1144.

Scheme 26. Pd-Catalyzed-Directed C−H Arylation with $[Ph_2I]BF_4$



Scheme 27. Pd-Catalyzed-Directed C−H Arylation with Unsymmetrical Iodonium Salts



CF_3CH_2) in situ by stirring $PhI(OAc)_2$ in the corresponding alcohol solvent.[44] As shown in Scheme 23, this led to the formation of the corresponding ether products in excellent yields.[45]

We have also explored Pd-catalyzed reactions for replacing C−H bonds with halogens using $PhICl_2$ and (p-$CH_3C_6H_4$)-IF_2.[46−48] The desired halogenated products were formed with both reagents (Schemes 24 and 25, respectively); however, the yields were modest because of competing side reactions (with $PhICl_2$) and/or the low reactivity [with (p-$CH_3C_6H_4$)-IF_2] of these oxidants. Nonetheless, the insights gained from these studies led to the identification of alternative reagents for introducing chlorine, bromine, iodine (*N*-halosuccinimides),[46,47] and fluorine (*N*-fluoropyridinium reagents).[48] Yu and co-workers have also reported $Pd^{II/IV}$-catalyzed C−H bond halogenation reactions using a combination of PhI-$(OAc)_2$ and I_2. However, in these systems, the authors have proposed that $PhI(OAc)_2$ promotes iodine/OAc ligand exchange at Pd to generate a more soluble catalyst, while I_2 acts as the ultimate oxidant and halogen source.[49]

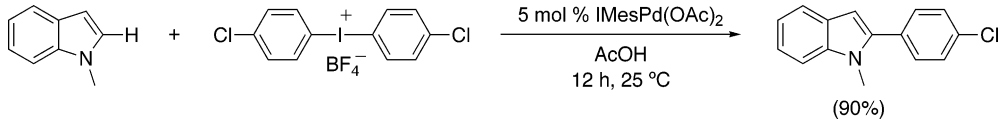
Our group has also demonstrated that $[Ph_2I]BF_4$ can serve as a source of "Ph" for Pd-catalyzed directed C−H activation/phenylation reactions of arylpyridine, quinoline, and amide substrates (Scheme 26).[50] (Notably, Daugulis and Zaitsev simultaneously reported an analogous reaction between $[Ph_2I]$-PF_6 and benzanilides.)[51] Sterically differentiated unsymmetrical iodonium salts [mesityl−I−Ar]BF_4 were used for the installation of diverse Ar groups, with the smaller Ar transferring with excellent selectivity over the larger mesityl (Scheme 27). This steric effect is similar to that observed in the cross-coupling reactions described in part 1; however, interestingly, electronic differentiation of the two Ar substituents led to very different selectivities in these systems. In general, the unsymmetrical I^{III} reagents [Ph−I−Ar]BF_4 yielded mixtures of arylated and phenylated products, with electron-deficient Ar (e.g., p-$CF_3C_6H_4$) transferring with modest (∼3:1) preference over Ph. In contrast, electron-rich Ar groups (e.g., *p*-OMe, thiophene) are typically transferred with high levels of selectivity in cross-coupling reactions (for example, see Schemes 8 and 10).

Preliminary mechanistic studies of these C−H arylation reactions have implicated a mechanism involving (i) directed C−H activation at Pd^{II}, (ii) oxidation of this Pd^{II} intermediate with $[Ar_2I]BF_4$ to afford a transient (and thus far undetectable) Pd^{IV} intermediate, and (iii) C−C bond-forming reductive elimination to afford the biaryl product and regenerate the Pd^{II} catalyst. Ongoing investigations aim to establish the origin of the observed steric and electronic effects and their relationship to analogous cross-coupling reactions. As discussed above, the electronic effects in these C−H arylation reactions (with *electron-deficient* Ar groups transferring in preference to *electron-rich* substituents) are opposite to those observed in Pd-catalyzed cross-coupling, and this data may implicate fundamentally different pathways for these two transformations.

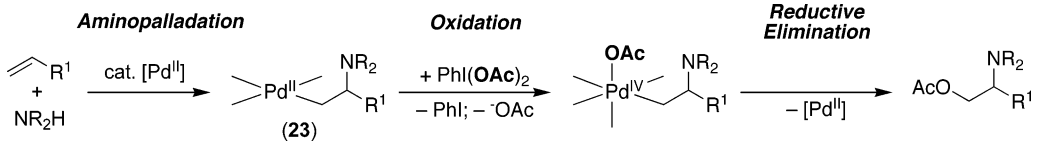
We have also shown that diaryliodonium salts can serve as sources of "Ar" for the Pd^{II}-catalyzed C−H arylation of indole derivatives (Scheme 28).[52] These transformations take place under extremely mild conditions (5 min to 24 h at 25 °C depending on the catalyst), show high selectivities for arylation at C-2 versus C-3, and are compatible with

(44) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563−1565.
(45) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2005**, *24*, 482−485.
(46) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523−2526.
(47) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483−11498.
(48) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134−7135.
(49) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112−2115.
(50) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330−7331.
(51) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046−4048.
(52) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972−4973.

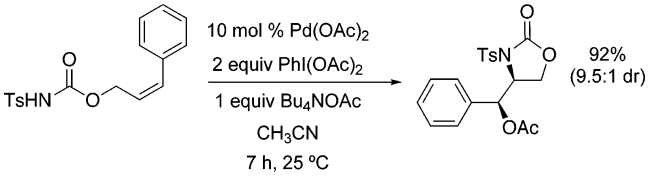
Scheme 28. Pd-Catalyzed Arylation of Indoles with $[Ar_2I]BF_4$



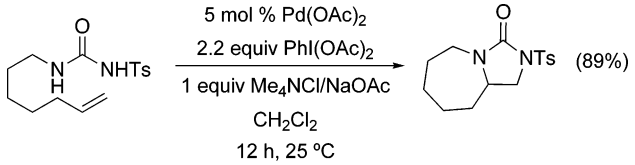
Scheme 29. Pd-Catalyzed Olefin Aminoacetoxylation with $PhI(OAc)_2$



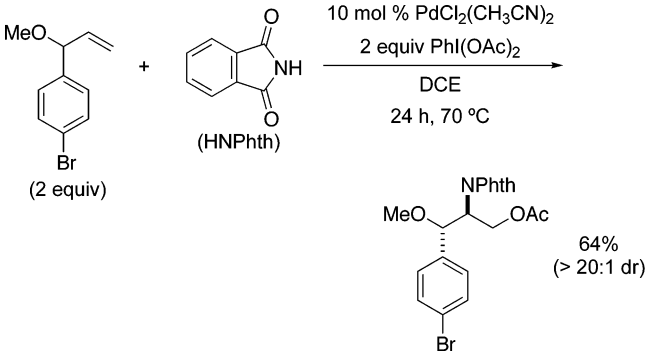
Scheme 30. Pd-Catalyzed Intramolecular Aminoacetoxylation of Olefins with $PhI(OAc)_2$



Scheme 31. Pd-Catalyzed Intramolecular Diamination of Olefins with $PhI(OAc)_2$



Scheme 32. Pd-Catalyzed Intermolecular Aminoacetoxylation of Olefins with $PhI(OAc)_2$/Phthalimide



unprotected indole and pyrrole substrates. These attractive features are believed to result from the $Pd^{II/IV}$ mechanism of these reactions, and current investigations are probing this possibility in detail. These transformations compare favorably to analogous heterocycle arylations with ArI, which typically require elevated temperatures (>120 °C), provide modest levels of C-2 versus C-3 selectivity, and require strong bases to "protect" the N−H bond of free indoles and pyrroles.[53]

The studies discussed above show that Pd^{II}−aryl and −alkyl intermediates formed via directed C−H activation can be intercepted and oxidatively functionalized using I^{III} reagents. On the basis of these results, several research groups reasoned that other Pd^{II} intermediates (formed by other fundamental organometallic transformations) might also be subject to oxidative functionalization with hypervalent iodine reagents. Initial work to test this idea has focused on β-aminoalkyl intermediates of the general structure **23** (Scheme 29) that are formed upon aminopalladation of olefinic substrates. The oxidation of β-aminoalkyl complex **23** to Pd^{IV} followed by C−O bond-forming reductive elimination could then be used to access valuable 1,2-aminoacetoxylated products. Importantly, for this sequence to be successful, the oxidation of intermediate **23** with $PhI(OAc)_2$ must be faster than competing β-hydride elimination processes. Furthermore, β-hydride elimination must not occur from the resulting Pd^{IV} intermediate prior to C−O coupling.

Sorensen and co-workers disclosed the first example of $Pd(OAc)_2$-catalyzed aminoacetoxylation in the intramolecular reaction of γ-aminoolefins with $PhI(OAc)_2$ (Scheme 30).[54] In these systems, intramolecular aminopalladation was followed by oxidative C−OAc bond formation, resulting in the stereoselective assembly of diverse heterocycles, including pyrrolidines, piperdines, cyclic carbamates, lactams, and oxazolidinones. A subsequent report by Muniz and coworkers demonstrated a related Pd^{II}-catalyzed intramolecular diamination of alkenylureas to afford substituted cyclic urea products (Scheme 31).[55] Muniz's procedure also used $PhI(OAc)_2$ as a terminal oxidant; however, in this reaction, the second amination was effected by an intramolecular amino group of the urea (Scheme 31). Finally, the Pd-catalyzed intermolecular aminoacetoxylation of alkenes with phthalimide/$PhI(OAc)_2$ was discovered in Stahl's laboratory[56] as well as by our group.[57] Liu and Stahl showed that this transformation is particularly effective for the aminoacetoxylation of allyl ether derivatives (Scheme 32), and the high diastereoselectivities of these reactions (typically >20:1) were rationalized based on chelation by the ether oxygen of these substrates.

Stahl's group has also studied the mechanism of these intermolecular aminoacetoxylation reactions.[56] On the basis of analysis of the stereochemistry of both the aminoacetoxylation and β-hydride elimination products in the reaction of a 1,2-disubstituted olefin, they concluded that these trans-

(53) For $Pd^{II/0}$-catalyzed arylation of indoles, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057. (b) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149. (c) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897−2900.

(54) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690−7691.

(55) Streuff, J.; Hovelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586−14587.

(56) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179−7181.

(57) Desai, L. V.; Sanford, M. S., manuscript in preparation, 2006.

formations take place via (i) cis-aminopalladation followed by (ii) oxidation to Pd^{IV} with $PhI(OAc)_2$ and finally (iii) C−O bond-forming reductive elimination with inversion of stereochemistry to afford the aminoacetoxylated products.

Conclusions

In summary, the unique reactivity of hypervalent iodine reagents with Pd complexes has been exploited for the development of a variety of synthetically useful organic transformations. For example, I^{III} reagents have been used in place of aryl halides for Pd-catalyzed C−C and C−heteroatom bond-forming cross-coupling reactions. In addition, these reagents have found application in Pd-catalyzed oxidation reactions, including the oxidative functionalization of C−H bonds and the 1,2-aminooxygenation of olefinic substrates. While the mechanisms of the cross-coupling reactions remain to be elucidated, the oxidation reactions are believed to proceed via $Pd^{II/IV}$ catalytic cycles, in which the key bond-forming step occurs from a Pd^{IV} center. Importantly, this mechanism facilitates bond constructions that would not be accessible in traditional $Pd^{0/II}$ catalysis, including the formation of both sp^2 and sp^3 C−OAc, $C-OCH_2CF_3$, C−I, and C−F bonds. Future work in this field will continue to probe the mechanisms of these transformations (particularly in the context of cross-coupling) and will seek to develop novel Pd-catalyzed reactions with hypervalent iodine reagents that take advantage of the unusual $Pd^{II/IV}$ pathways available in these systems.

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