Published in final edited form as:

J Am Chem Soc. 2023 October 25; 145(42): 22890–22895. doi:10.1021/jacs.3c09876.

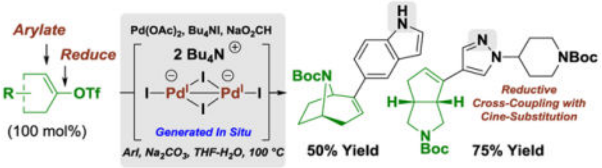
Palladium(I)-Iodide Catalyzed Deoxygenative Heck Reaction of Vinyl Triflates: A Formate-Mediated Cross-Electrophile Reductive Coupling with *cine*-Substitution

Yu-Hsiang Chang,
Weijia Shen[§],
Jonathan Z. Shezaf[§],
Eliezer Ortiz,
Michael J. Krische
Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States

Abstract

The first deoxygenative Heck reactions are described, as illustrated by formate-mediated *cine*-substitutions of vinyl triflates with aryl iodides. The collective data corroborate a mechanism in which $Pd(OAc)_2$ and Bu_4NI form the dianionic iodide-bridged dimer $[Pd_2I_6][NBu_4]_2$, which, under reducing conditions, serves as a precursor to the palladium(I) complex $[Pd_2I_4][NBu_4]_2$. Dinculear oxidative addition of aryl iodide forms $[Pd_2I_5(Ar)][NBu_4]_2$, which dissociates to the monometallic complex $[PdI_2(Ar)][NBu_4]$. Vinyl triflate migratory insertion-sulfonate elimination delivers a palladium(IV) carbene, which upon β-hydride elimination-C-H reductive elimination gives the product of *cine*-substitution. These processes are the first efficient formate-mediated cross-electrophile reductive couplings beyond carbonyl addition.

Graphical Abstract



Our laboratory has developed diverse metal-catalyzed carbonyl reductive couplings mediated by the feedstock reductants (hydrogen, 2-propanol, formic acid),[1,2] as well as related hydrogen auto-transfer reactions in which alcohols serve dually as reductant

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Corresponding Author: mkrische@mail.utexas.edu.

[§] W.S. and J. Z. S. contributed equally to this work.

Supporting Information. Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), including images of NMR spectra. Single-crystal X-ray diffraction data for $[Pd_2I_6][NBu_4]_2$ and compounds **3j** and **3k**.

Accession Codes. CCDC 2290442, 2293685 and 2289930 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

The authors declare no competing financial interest.

and carbonyl proelectrophile.[2] Such methods bypass use of premetalated *C*-nucleophiles, which are often hazardous and expensive. In an outgrowth of this work, the first carbonyl reductive couplings of aryl halides beyond discrete arylmetal nucleophiles or metallic reductants were discovered,[3a] along with related formate-mediated reactions of vinyl halides or triflates.[3b,c] The ability to exploit sp^2-halides as aryl- and vinylmetal pronucleophiles in formate-mediated carbonyl addition impelled investigations into "cross-electrophile reductive couplings" – an emerging class of C-C couplings that typically require elemental zinc or manganese as the terminal reductants.[4,5,6,7] Here, we report formate-mediated reductive cross-couplings of vinyl triflates with aryl iodides, which, unlike longstanding palladium(0)-catalyzed cross-couplings of vinyl triflates,[8,9] result in *cine*-substitution through a deoxygenative Heck-type pathway (Figure 1).[10,11,12] Our collective data corroborate a mechanism in which $Pd(OAc)_2$ and Bu_4NI form the dianionic iodide-bridged dimer $[Pd_2I_6][NBu_4]_2$, which, under reducing conditions, serves as a reservoir for the active palladium(I) complex $[Pd_2I_4][NBu_4]_2$. Our data also corroborate the key role of iodide counterions *vis-á-vis* stabilization of palladium(I) under reductive coupling conditions.[13,14,15] These transformations represent the first non-photochemical reductive C-C couplings via palladium(I)-catalysis, and highlight the distinct reactivity of dinuclear iodide-bridged palladium(I) complexes.[16,17,18]

Optimal conditions identified for palladium(I)-iodide-catalyzed deoxygenative Heck reaction represent the culmination of numerous experiments. For the sake of brevity, key features of the catalytic system are highlighted by deviation from ideal conditions (Table 1). The most efficient conditions involved exposure of iodoanisole **1a** (160 mol%) and vinyl triflate **2a** (100 mol%) to $Pd(OAc)_2$ (5 mol%) and Bu_4NI (20 mol%) in the presence of NaO_2CH (200 mol%) and Na_2CO_3 (100 mol%) in THF-H_2O (0.2 M, 40:1) at 100 °C. The product of deoxygenative Heck reaction **3a** was obtained in 88% yield along with a small quantity of *iso*-**3a** (Table 1, entry 1). The structural assignment of **3a** was verified by its conversion to a reported compound (see Supporting Information). The presence of Bu_4NI was found to be essential (Table 1, entries 2–4). As documented by Schoenebeck, iodide counterions stabilize palladium(I) species.[13,14] Indeed, the unique influence of iodide counterions in ruthenium-catalyzed C-C coupling via hydrogen transfer is what led us to palladium(I) catalysis.[14,15] The ammonium cation of Bu_4NI is also necessary, as other iodide sources failed to animate the catalytic process (Table 1, entry 5). Bu_4NI and $Pd(OAc)_2$ form the dianionic iodide-bridged dimer $[Pd_2I_6][NBu_4]_2$, which, in the presence of NaO_2CH, is a latent source of the palladium(I) complex $[Pd_2I_4][NBu_4]_2$ (*vide supra*), which is a competent catalyst for the reaction (Table 1, entry 6). Palladium(0) precatalysts diminish efficiency (Table 1, entry 7), and phosphine ligands completely suppress catalysis (Table 1, entries 8 and 9). Consistent with intervention of palladium(I) species, aryl iodides react with significantly greater efficiency than aryl bromides (Table 1, entry 10).[11,12] Finally, water is required (Table 1, entry 11), presumably to solubilize NaO_2CH and Na_2CO_3. Other enol derivatives (tosylates, phosphates, vinyl halides) were less efficient partners for C-C coupling (not shown).

To assess reaction scope, optimal conditions developed for formation of **3a** were applied to a diverse combination of reactants (Table 2). Both *para*- and *ortho*-iodoanisoles **1a** and **1b** are competent partners for C-C coupling, as are the corresponding unprotected phenols **1c** and **1d**. Notably, as illustrated by the formation of **3f**, aldehyde functional groups are tolerated under the conditions of formate-mediated reductive coupling. Other vinyl triflates, including the spirocyclic ketal-containing vinyl triflate **2b**, and the steroidal vinyl triflates **2c** and **2d**, which are derived from estrone and cholestanone, respectively, engage in C-C coupling. Tolerance of acidic residues is evident in formation of salicylate adduct **3i**. In the case of the estrone-derived vinyl triflate, the presence of a quaternary carbon center adjacent to the vinylic C-O bond does not preclude formation of adduct **3j**. Finally, the *N*-heterocyclic fused vinyl triflate **2e**, and bridged bicyclic triflate **2f** derived from tropinone, deliver products of C-C coupling in good yield, as demonstrated by formation of adducts **3l**-**3n** and **3o**-**3q**, respectively. As shown in formation of **3m** and **3p**, Lewis basic nitrogen atoms are tolerated. The presence of unprotected NH indoles is demonstrated by formation of adducts **3n** and **3q**. Fully substituted vinyl triflates are not competent partners for the deoxygenative Heck reaction, presumably due to inefficient **π**-complexation/carbopalladation.

A series of experiments and observations from the literature provide insight into the reaction mechanism (Scheme 1).. Exposure of aryl iodide **1a** to standard reaction conditions in the absence of vinyl triflate followed by filtration through Celite with the aid of THF and diffusion of hexane into the liquor led to the formation of the crystalline dianionic iodide-bridged dimer $[Pd_2I_6][NBu_4]_2$ (Scheme 1, eq. 1).[19] At longer reaction times under the conditions of formate-mediated reduction, we believe $[Pd_2I_6][NBu_4]_2$ slowly releases the palladium(I) complex $[Pd_2I_4][NBu_4]_2$. The formation of the palladium(I) complex $[Pd_2I_4][NBu_4]_2$ is corroborated by ^{31}P NMR studies in which $[Pd_2I_6][NBu_4]_2$ is exposed to $^{t}Bu_3P{\bullet}HBF_4$ in the presence of formate (Scheme 1, eq. 2). The signal corresponding to the known palladium(I) dimer $[Pd_2(^{t}Bu_3P)_2(I)_2]$ is the only signal observed in the ^{31}P NMR (See Supporting Information). In the absence of formate, the palladium(I) dimer $[Pd_2(^{t}Bu_3P)_2(I)_2]$ is not observed. Similarly, exposure of $Pd(OAc)_2$ to $^{t}Bu_3P{\bullet}HBF_4$ in the presence formate and Bu_4NI leads to clean formation of the palladium(I) dimer $[Pd_2(^{t}Bu_3P)_2(I)_2]$ (Scheme 1, eq. 3). Again, in the absence of formate, $[Pd_2(^{t}Bu_3P)_2(I)_2]$ is not observed. These data corroborate intervention of the dianionic palladium(I) complex $[Pd_2I_4][NBu_4]_2$ under catalytically relevant conditions. In the absence of $^{t}Bu_3P$, $[Pd_2I_4][NBu_4]_2$ and $[Pd_2I_6][NBu_4]_2$ may exist in equilibrium with higher polynuclear palladium-iodide complexes (including nanoparticles)[20] that may or may not be catalytically relevant. DFT calculations by Schoenebeck[13b] support the feasibility of aryl iodide oxidative addition by the dinuclear palladium(I) complex $[Pd_2(^{t}Bu_3P)_2(Br)_2]$ in the catalytic conversion of aryl iodides to aryl bromides (Scheme 1, eq. 4). Finally, exposure of *deuterio*-**2b** to iodoanisole **1a** under standard conditions provides *deuterio*-**3g**, demonstrating deuterium transfer from the vinylic position of the triflate to the vicinal vinylic carbon atom of the product (Scheme 1, eq. 5).

Based on these data, the following mechanism for the deoxygenative Heck reaction of vinyl triflates is proposed (Scheme 2). Entry into the catalytic cycle occurs via conversion of $Pd(OAc)_2$ to the iodide-bridged palladium(II) dimer $[Pd_2I_6][NBu_4]_2$. Formate-mediated reduction of $[Pd_2I_6][NBu_4]_2$ provides the palladium(I) dimer $[Pd_2I_4][NBu_4]_2$. Oxidative addition of aryl iodide generates the arylpalladium(II) complex $[Pd_2I_5(Ar)][NBu_4]_2$,[13b] which exists in equilibria with the monometallic complexes [PdI$_3$][NBu$_4$] and [PdI$_2$(Ar)][NBu$_4$]. The latter complex reversibly coordinates the vinyl triflate, which triggers migratory insertion. Carbopalladation occurs with concomitant elimination of triflate to form the palladium(IV) carbene.[21] β-Hydride elimination followed by C-H reductive elimination releases the product and generates PdI$_2$, which combines with [PdI$_3$][NBu$_4$] and Bu$_4$NI to close the catalytic cycle. The absence of palladium(0) species is consistent with the requirement of aryl iodides (and tolerance of aryl bromides) in this process. This mechanism illustrates an important and distinctive feature of the bimetallic palladium(I) catalyst: conventional formate-mediated transfer hydrogenolysis of reactant C-I bonds (i.e. hydrodehalogenation)[22] is suppressed as the hydride and aryl/vinyl moieties do not cohabit the metal.

In conclusion, we report a new catalytic transformation; the deoxygenative Heck reaction of vinyl triflates. Notably, these processes represent the first efficient cross-electrophile reductive couplings mediated by an inexpensive feedstock reductant, sodium formate. Additionally, the ability to affect vinylic cross-coupling with *cine*-substitution unlocks access to products that would otherwise require more circumlocutious methods of preparation. Most importantly, the present data add to a growing body of work[16] in which the distinctive structural-interactional features of dinuclear iodide-bridged palladium(I) complexes unlock unique catalytic pathways. Specifically, in the context of reductive coupling, the bimetallic nature of the palladium(I) species assists in suppressing competing hydrodehalogenation,[22] as the aryl and hydride ligands do not simultaneously reside on the metal center. Reductive biaryl cross-couplings will be disclosed shortly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) are acknowledged for partial support of this research. We thank Serhii Vasylevskyi for the acquisition and interpretation of single crystal X-ray diffraction data.

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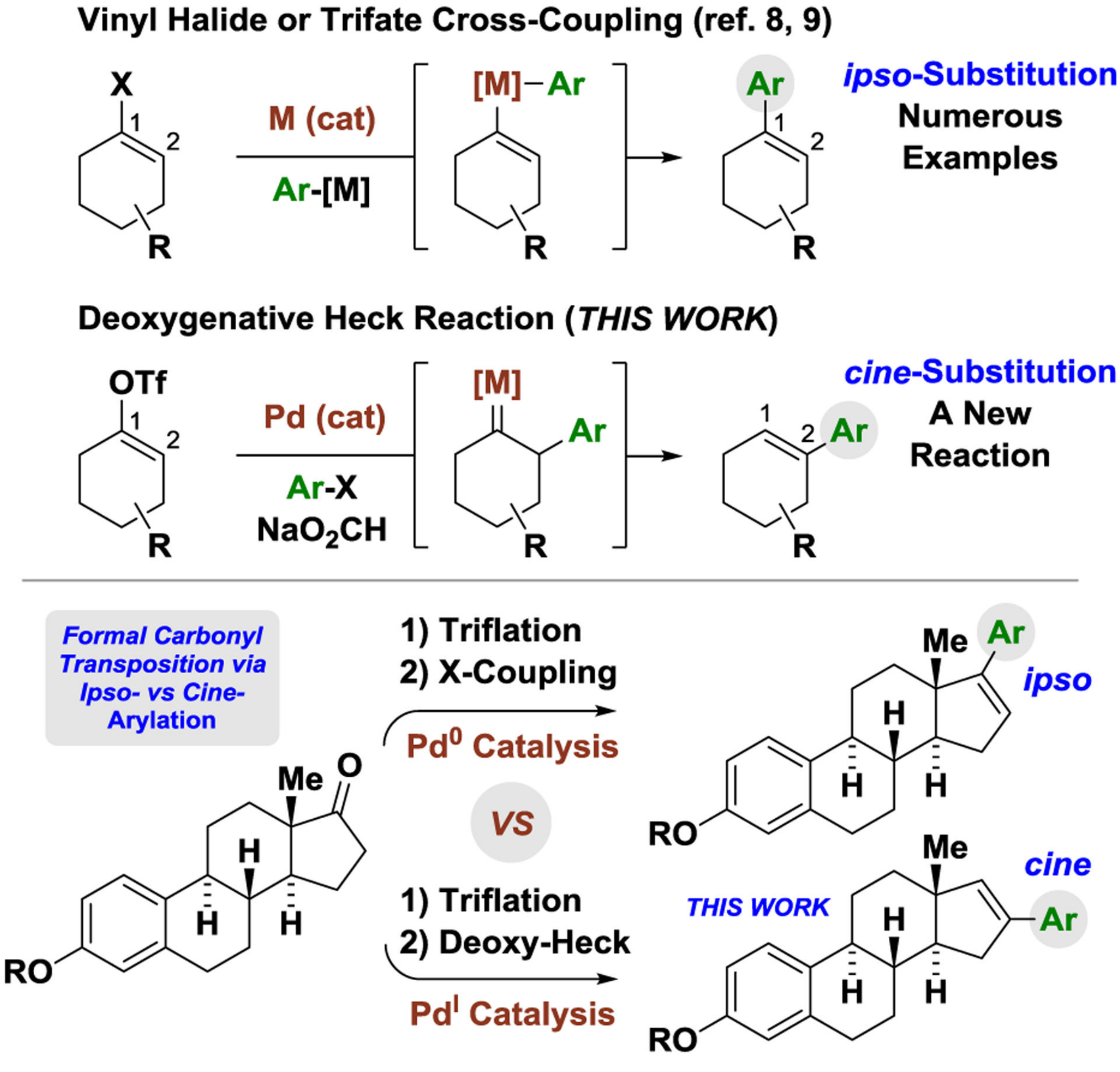
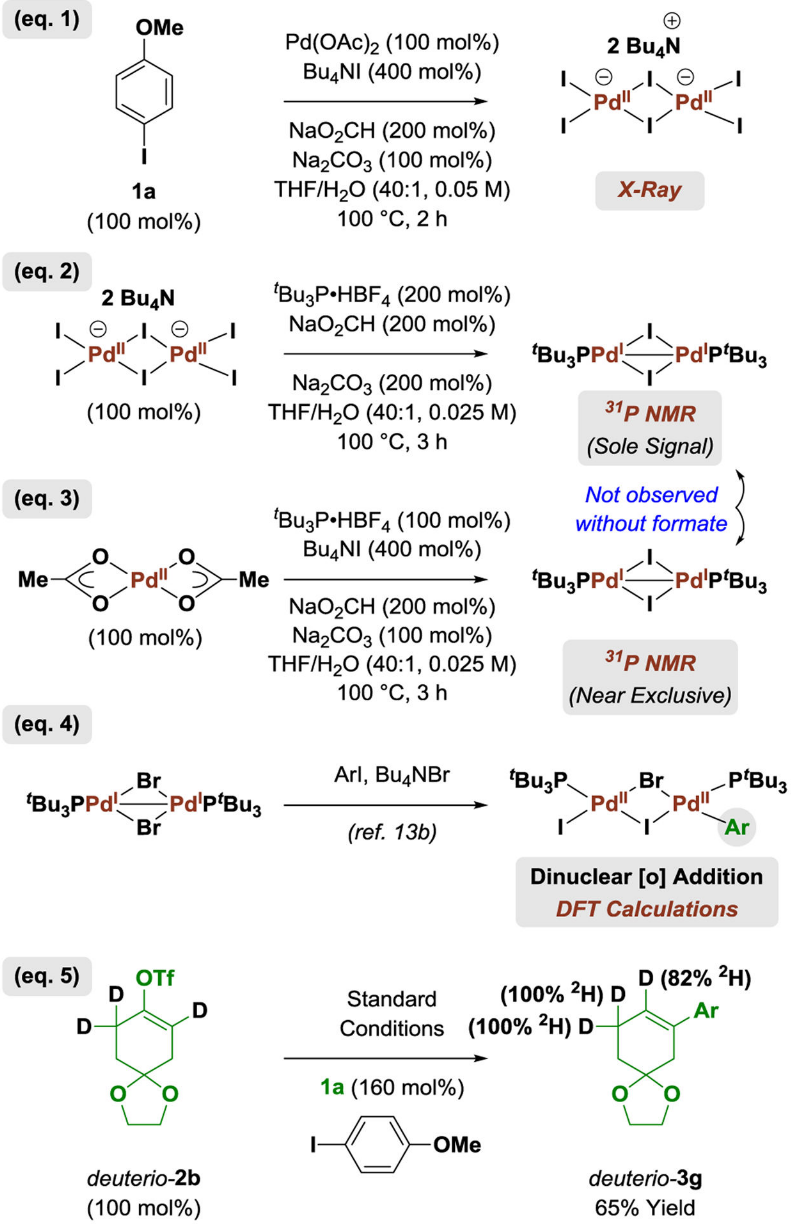


Figure 1.

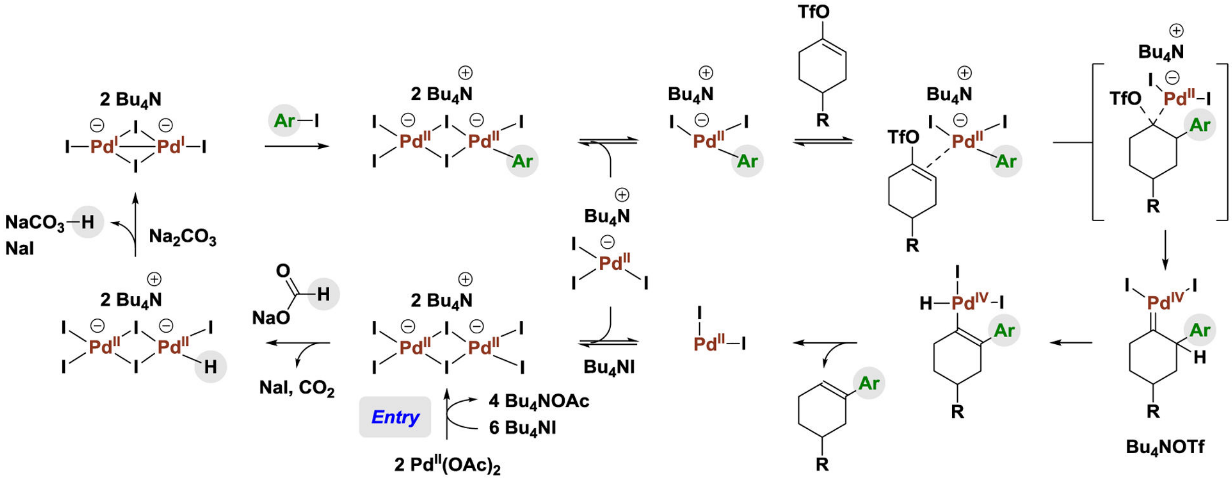
Cross-coupling with *ipso*- vs *cine*-substitution.



Scheme 1.

Mechanistic studies.[a]

[a]See Supporting Information for experimental details.

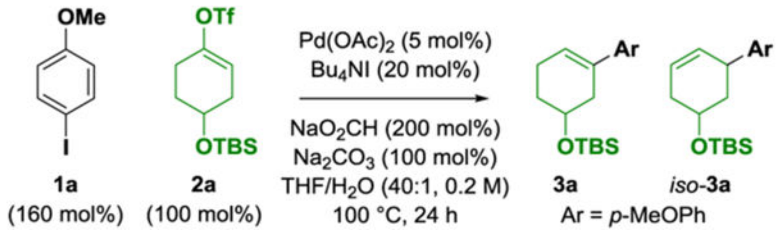


Scheme 2.

Proposed catalytic cycle for palladium(I)-catalyzed deoxygenative Heck reaction of vinyl triflates.

Table 1.

Palladium(I)-iodide-catalyzed deoxygenative Heck reaction of aryl iodide **1a** with vinyl triflate **2a**: Deviation from optimal conditions.[a]

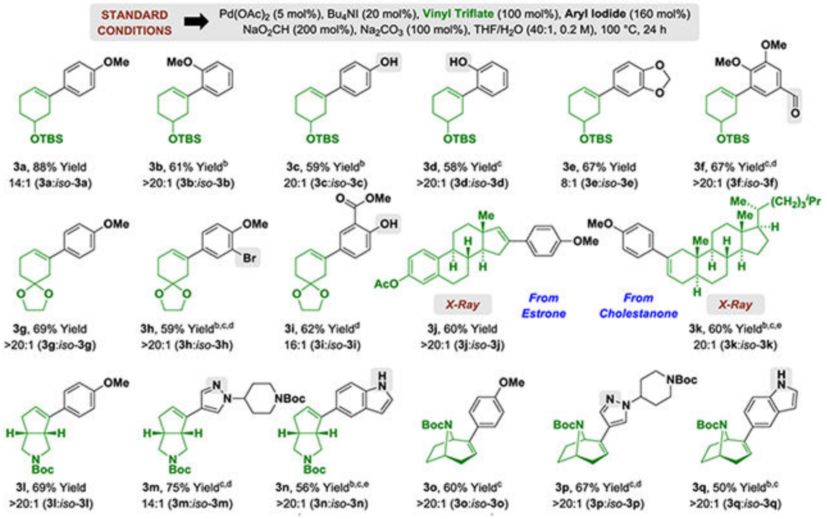


Entry	*Deviation from Optimal Conditions*	3a Yield (%)	3a:*iso*-3a
→1	None	88	14:1
2	Without Bu_4Nl	<5	---
3	Bu_4NCl *vs* Bu_4Nl	<5	---
4	Bu_4NBr *vs* Bu_4Nl	<5	---
5	Nal *vs* Bu_4Nl	<5	---
6	$[Pd_2|_6]|TBA]_2$ (2.5 mol%) *vs* $Pd(OAc)_2$	65	>20:1
7	$Pd_2(dba)_3$ (2.5 mol%) *vs* $Pd(OAc)_2$	40	8:1
8	$[Pd(l)(^tBu_3P)]_2$ (2.5 mol%) *vs* $Pd(OAc)_2$	<5	---
9	$^tBu_3P$●HBF_4 (5 mol%)	<5	---
10	Ar-Br vs Ar-I	15	>20:1
11	Without H_2O	<5	---

[a] Yields of isomeric mixtures isolated by silica gel chromatography.

Table 2.

Palladium(I)-iodide-catalyzed deoxygenative Heck reaction of aryl iodides **1a-1j** with vinyl triflates **2a-2f**.[a]



[a] Yields of material isolated by silica gel chromatography. bPd(OAc)2 (10 mol%). c105 ^{o}C. dArI (200 mol%). e48 Hr.