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Palladium-Catalyzed Carboiodination of Alkenes: Carbon—Carbon Bond Formation with Retention of Reactive Functionality

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Supporting Information

ABSTRACT: We report a palladium-catalyzed carbon—carbon bond-forming reaction between aryl iodides and alkenes. In contrast to traditional cross-coupling reactions, two new bonds are formed, and all of the atoms in the starting materials are incorporated into the product. The use of a palladium catalyst with bulky phosphine ligands is found to be crucial for reactivity.

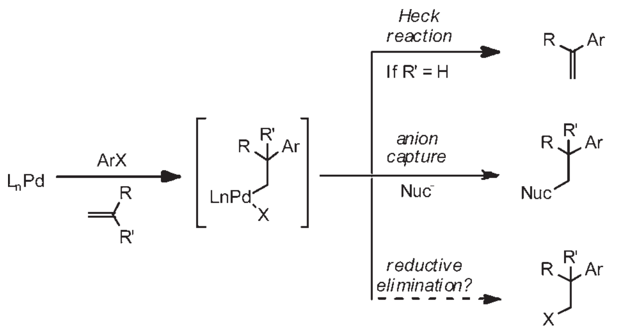
The efficient formation of carbon—carbon bonds is the most important and most challenging aspect of organic chemistry. Transformations such as the aldol, Friedel—Crafts, Diels—Alder, and Grignard reactions, all of which were developed over 80 years ago, still constitute the most useful reactions we have today for preparing the core of complex natural products, pharmaceuticals, and novel materials. Perhaps the dominant advance in carbon—carbon bond construction is the emergence of transition-metal catalysis.[1] By utilizing precious metals, new bonds can be made between readily accessible organic molecules efficiently and reliably.

Among transition metals, palladium has stood out due to its ability to catalyze diverse reactions and its applicability to practical synthesis.[2] The Mizoroki—Heck reaction is one such coupling transformation, which unites an aryl halide and an alkene with the loss of HX (X = halide or pseudohalide) (Scheme 1). Significant attention has been devoted to increasing the efficiency of coupling reactions by using domino processes. For example, the alkyl Pd(II) halide intermediate in the Heck reaction can undergo an anion capture event to form a second new bond.[3] This transformation typically requires an alkyl Pd(II) halide intermediate with no *syn*-*β*-hydrogens.

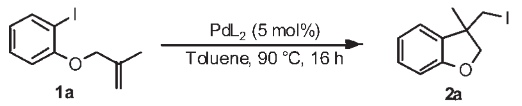
We speculated a direct reductive elimination of an alkyl palladium halide would be possible to provide an alkyl halide. The resulting reaction would provide a new carbon—carbon bond while retaining the reactive halide of the starting material. Similar processes have been explored by Heck[4] and more recently greatly improved by Sanford,[5] utilizing an organometallic reagent and stoichiometric oxidant. Other carbohalogenation reactions are known but are usually radical-type processes, which imparts limitations on the scope.[6]

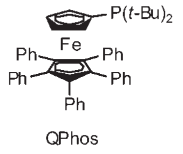
Carbon—halogen reductive elimination has only recently been identified as a plausible elementary step in Pd(0)/Pd(II) catalytic cycles, and no carbon—carbon bond-forming reaction has utilized this step.[7] Herein, we report the development of a palladium-catalyzed carboiodination reaction of alkenes with aryl iodides. Both intra- and intermolecular reactions take place when exceptionally bulky phosphine ligands are used. The products contain a new carbon—carbon and carbon—iodine bond, and no stoichiometric waste is formed in the reaction.

Scheme 1. Reaction Pathways of Alkyl Palladium Halides and Proposed Reductive Elimination



Scheme 2. Effect of Catalyst in Intramolecular Carboiodination of Alkenes





Ligand	Yield
Q-phos	82%
$P(t\text{-}Bu)_3$	61%
$PhP(t\text{-}Bu)_2$	76%
PCy_3	0%
$P(o\text{-}tol)_3$	0%

We began our studies by analyzing the use of well-defined Pd(0) catalysts with bulky phosphine ligands for the intramolecular cyclization of substrate **1a** (Scheme 2). At 90 °C in toluene, carboiodination complex **2a** could be obtained in up to 82% yield by using 5 mol % $Pd(Q\text{-}phos)_2$ as a Pd(0) source.[8] Other bulky ligands such as $P(t\text{-}Bu)_3$ and $PhP(t\text{-}Bu)_2$ gave lower conversion, while less bulky ligands such as PCy_3 and $P(o\text{-}tol)_3$ gave no detectable product.

Running the reaction at 100 °C with 2.5 mol % of $Pd(Q\text{-}phos)_2$ gave full conversion of starting material after 4 h and a 95% isolated yield of **2a**. With these optimized conditions, a number of intramolecular

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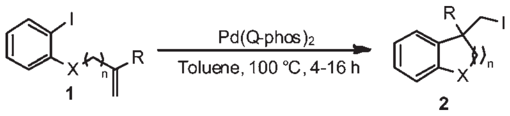
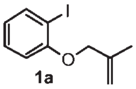
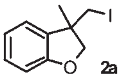
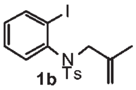
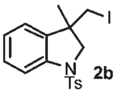
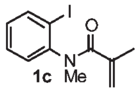
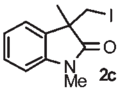
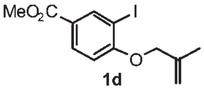
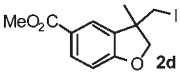
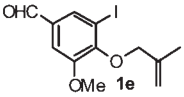
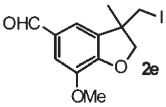
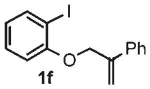
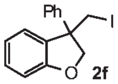
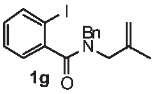
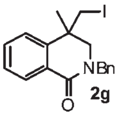
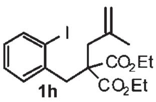
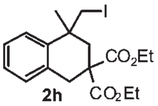
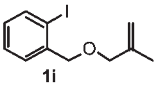
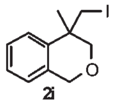
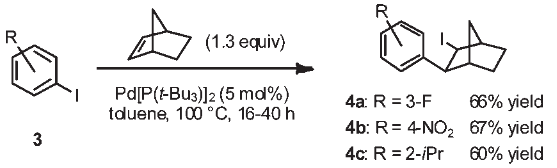
Table 1. Scope of Palladium-Catalyzed Intramolecular Carboiodination[a]



Entry	Substrate	Product	Mol% Pd	Yield
1	 1a	 2a	2.5	95
2	 1b	 2b	2.5	93
3	 1c	 2c	5	97
4	 1d	 2d	2.5	92
5	 1e	 2e	2.5	96
6[b]	 1f	 2f	5	94
7	 1g	 2g	5	93
8	 1h	 2h	5	78
9	 1i	 2i	2.5	86

[a] Reaction conditions: Substrate **1** (0.1 or 0.2 mmol scale), Pd(Q-Phos)$_2$ (2.5 or 5 mol %), 0.2 M in toluene, 100 °C, sealed tube. [b] 0.05 M in toluene.

Scheme 3. Intermolecular Carboiodination of Norbornene



4a: R = 3-F 66% yield
4b: R = 4-NO$_2$ 67% yield
4c: R = 2-*i*Pr 60% yield

cyclizations were explored (see Table 1). Both 5- and 6-membered rings could be formed to produce various oxygen- and nitrogen-containing heterocycles as well as a carbocycle in high yields. Reactions that formed 5-membered rings generally required lower catalyst loading and shorter times than those that formed 6-membered rings. The analogous reaction with an aryl bromide or chloride does not give the corresponding carbohalogenation product, suggesting the sp^3 C−Cl and C−Br reductive elimination may be more difficult than C−I reductive elimination. Thus far, the reaction does not work if *β*-hydrogens are present in the cyclized alkyl Pd(II) halide intermediate. Instead, olefin isomerization or Heck-type products are formed.

To investigate an intermolecular variant of this transformation, we chose norbornene as our model alkene, as the intermediate alkyl palladium halide species cannot undergo *syn-β*-hydride elimination. Reoptimization revealed Pd[P(t-Bu$_3$)]$_2$ to be the best catalyst. Treating 3-fluoroiodobenzene and 1.3 equivalents of norbornene with 5 mol % catalyst gave the carboiodination adduct **4a** in 66% yield as the major product, along with small quantities of unidentified side products (Scheme. 3). Similar reactivity was found for other aryl iodides. Product **4b**, derived from 4-nitroiodobenzene, was a crystalline solid, and single-crystal X-ray diffraction confirmed the *syn*, *exo* stereochemistry of the major product (see Supporting Information).

While it is premature to make strong mechanistic implications, an oxidative addition, carbopalladation, reductive elimination pathway seems most likely.[9] Reductive elimination of alkyl halides from Pd(II) has not been studied; however, oxidative addition of alkyl halides to Pd(0) has been investigated and is generally considered to occur by either an S$_N$2 or nonchain radical mechanism, depending on the catalyst, substrate, and conditions.[10] The intramolecular reaction is found to be uninhibited by radical scavengers such as TEMPO or galvinoxyl, while the intermolecular reaction was found to be partially inhibited by these species. Further mechanistic studies into the corresponding reductive elimination are currently underway. It is noteworthy that the catalytic cycle suggested was first proposed almost 30 years ago by Ban and co-workers in their palladium-catalyzed ene-halogenocyclization reactions.[11] This mechanism was subsequently shown by Curran and co-workers to actually be a radical atom transfer process.[12]

The ability of bulky phosphine ligands to induce reductive elimination of Pd(II) complexes has been frequently utilized in the past decade to increase the scope of many known C−C- and C−X-forming reactions. Further support for alkyl palladium halide reductive elimination as a novel elementary step for catalytic cycles will open a wide door for new coupling reactions. We are currently working to further our knowledge of the reaction mechanism and ligand requirements for carbohalogenation. Extensions to a diverse range of unsaturated substrates are also underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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