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Palladium-Catalyzed Carbohalogenation: Bromide to Iodide Exchange and Domino Processes

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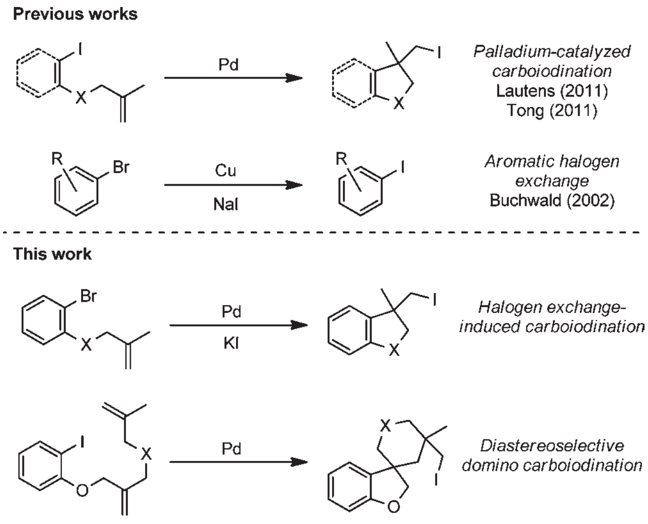
S Supporting Information

ABSTRACT: Aryl bromides have been used to prepare a variety of nitrogen- and oxygen-containing heterocycles featuring new carbon−carbon and carbon−iodine bonds. This palladium-catalyzed carbohalogenation requires potassium iodide for the reaction to proceed in high yields. Additionally, the first examples of domino carbohalogenation reactions have been demonstrated using both aryl iodide and aryl bromide starting materials. Complex products with multiple rings and stereogenic centers are generated in excellent yields with moderate to excellent diastereoselectivities.

Palladium-catalyzed coupling reactions are among the most important methods available for forming carbon−carbon bonds.[1] Well-established transformations such as the Suzuki−Miyaura and Mizoroki−Heck reactions remain of great importance, with recent advances in palladium catalysis focusing on improving efficiency, reducing waste, and introducing new modes of reactivity. For example, direct arylation reactions have become a remarkable method for C−C bond formation by allowing the use of unfunctionalized substrates.[2] Toward the goal of developing more efficient palladium-catalyzed carbon−carbon bond-forming reactions, we recently demonstrated that reversible oxidative addition into carbon−halogen bonds can lead to selective coupling of polyhalogenated substrates,[3] and we developed a carboiodination reaction of aryl iodides (Scheme 1).[4] Tong and co-workers have shown that vinyl iodides can also undergo carbohalogenation reactions, with catalyst loading, ligand, and reaction temperature being noteworthy differences between these complementary procedures.[5] These reactions form a new carbon−carbon bond and a new carbon−iodine bond, generating no stoichiometric waste in the process. The reaction is proposed to occur through oxidative addition of the aryl iodide to Pd(0), carbopalladation of the alkene, and carbon−halogen reductive elimination. Reductive elimination of carbon−halogen bonds from Pd(II) has only recently been recognized as a catalytically viable elementary step in catalysis and is opening up many new pathways in palladium-catalyzed transformations.[6,7]

To further the utility of the carbohalogenation reaction, we explored two new directions. Inspired by the work of Buchwald and co-workers on aromatic halogen exchange reactions,[6e,8] we sought relief from the constraint of using more expensive aryl iodide starting materials by pursuing the reactivity of aryl bromides in the presence of iodide sources. Second, we were interested in increasing the complexity of the products by developing domino reactions with polyunsaturated substrates. Herein we report our findings on how aryl bromides can be used in the carboiodination reaction and how polyunsaturated alkenes can be used to form polycyclic alkyl iodides containing multiple stereogenic centers. Finally, these two concepts have been united to allow domino reactions to occur starting from aryl bromides.

Scheme 1. Studies of Palladium-Catalyzed Carbohalogenation and Halogen Exchange



In our initial report on carbohalogenation, only aryl iodide starting materials were effective substrates. Aryl iodides are the most reactive of the aryl halides toward oxidative addition[9] and thus are very useful starting materials. Unfortunately, they are the least desirable from the standpoint of cost and availability. Thus, intense effort has been devoted to improving the scope of these coupling reactions, and a wide range of halides and pseudohalides can now be used.[10]

To increase the usefulness of our methodology, we explored carbohalogenation using aryl bromides. Despite screening a range of conditions and ligands, we could not obtain synthetically useful quantities of carbobromination products. Given the precedent that similar aryl bromides react with a wide range of Pd(0) catalysts,[11] we hypothesized that the oxidative addition and carbopalladation steps of the carbohalogenation were occurring but that the novel alkyl halide reductive elimination may be less

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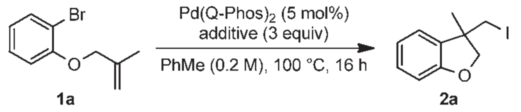
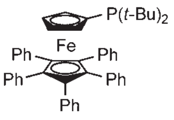
Scheme 2. Optimization of the Bromide to Iodide Exchange



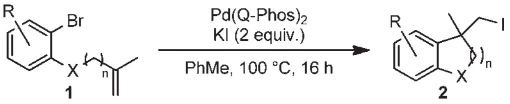
1a **2a**



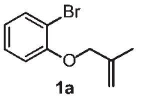
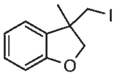
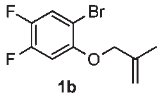
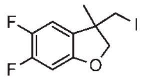
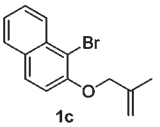
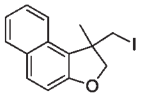
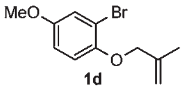
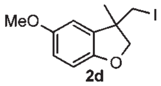
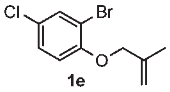
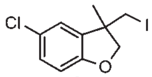
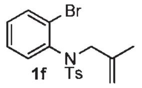
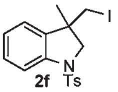
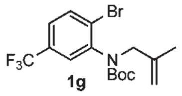
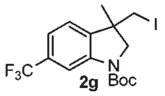
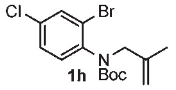
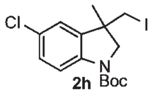
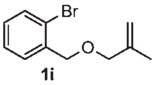
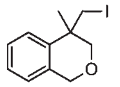
Q-Phos

additive	Yield
LiI	28%
NaI	37%
KI	66%
TBAI	<5%
KI + 18-crown-6	<5%
KI (2 equiv) (0.05 M)	95%

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



1 **2**

Entry	Substrate	Product	Mol% Pd	Yield [%]
1	 **1a**	 **2a**	5	89
2	 **1b**	 **2b**	5	83
3	 **1c**	 **2c**	7.5	87
4	 **1d**	 **2d**	5	92
5	 **1e**	 **2e**	5	90
6	 **1f**	 **2f**	7.5	91
7	 **1g**	 **2g**	5	93
8	 **1h**	 **2h**	5	91
9	 **1i**	 **2i**	5	71

[a] Reaction conditions: Substrate **1** (0.1 mmol), KI (0.2 mmol), Pd(Q-Phos)$_2$ (5 or 7.5 mol %), 0.05 M in toluene, 100 °C for 16 h.

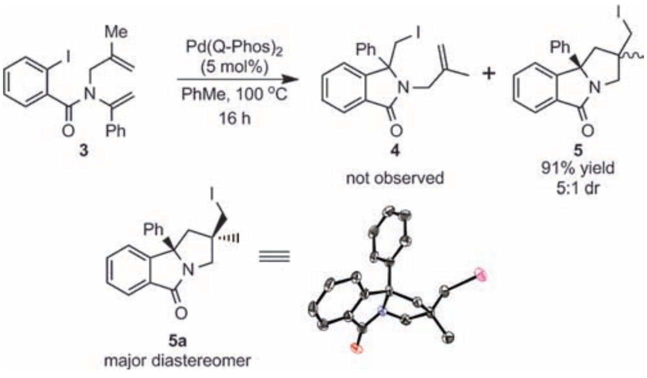
efficient with bromides than it is with iodides. Buchwald and co-workers previously showed that aromatic halogen and pseudo-halogen exchange can occur through the use of copper[8] and palladium[6e] catalysis. We hypothesized that the addition of a stoichiometric amount of iodide may displace the bromide and allow reductive elimination and catalyst turnover to take place (Scheme 2). Indeed, upon treatment of aryl bromide **1a** with catalytic Pd(Q-Phos)$_2$[12] and 3 equiv of lithium iodide, alkyl iodide **2a** was formed in 28% yield. Different iodide sources were tested, and KI was found to be superior at facilitating this transformation.[13] Interestingly, the addition of crown ether to increase the nucleophilicity of the iodide or the use of soluble TBAI completely inhibited the reaction, suggesting that the concentration of iodide in solution is an important variable.

Ultimately, running the reaction under higher dilution with 2 equiv of potassium iodide allowed us to isolate aryl iodide **2a** in 95% yield. Screening of other solvents, catalysts, and temperatures did not lead to improved reactivity. With these optimized conditions, the scope of the bromide to iodide exchange was further explored (Table 1) by preparing a number of useful functionalized dihydrobenzofurans (entries 1–5) and indolines (entries 6–8) and an isochroman (entry 9).[14]

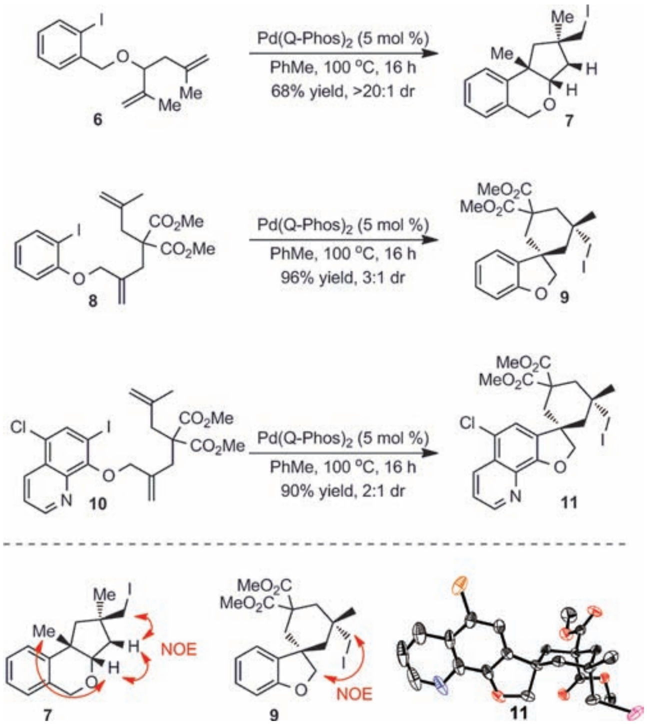
Concurrent with the development of our halogen exchange process, we sought to use polyunsaturated aryl iodides to form complex polycyclic products containing multiple stereogenic centers. Transition-metal-catalyzed domino reactions have found immense use in the synthesis of polycyclic carbo- and heterocycles.[15] Palladium-catalyzed "zipper"-type transformations, which involve oxidative addition, multiple carbopalladations, and a terminating event, are particularly effective at constructing complex ring systems from simple starting materials.[16] The extension of our methodology to domino substrates was nontrivial, as carbopalladation and reductive elimination are competing intramolecular processes that could lead to monocyclization as well as domino cyclization products. We chose as our test substrate amide **3**, which upon cyclization could provide either monocyclization product **4** or domino carbohalogenation product **5** (Scheme 3). Utilizing our typical reaction conditions, we observed the domino cyclization product in 91% yield as a 5:1 mixture of diastereomers, and no monocyclization product was observed. The stereochemistry of the major product was confirmed to be **5a** by single X-ray crystallography. A variety of other ligands were screened, but none were found to be more effective than Q-Phos. The reaction conditions developed by Tong and co-workers[5] were also tried, but only trace amounts of the domino carboiodination product were detected.[17]

To evaluate the domino carbohalogenation reaction further, diene **6** was subjected to the reaction conditions (Scheme 4), and [6.5.0] bicycle **7** containing three stereogenic centers was formed in 68% yield as a single diastereomer, the relative stereochemistry was established by nuclear Overhauser effect (NOE) analysis. Next, in an attempt to form spirocyclic products, compound **8** was employed in the cyclization, providing **9** in 96% yield and 3:1 dr; again, the stereochemistry was established by NOE analysis. The phenolic backbone was changed to quinoline **10**, which provided spirocycle **11** in 90% yield and 2:1 dr, and the stereochemistry was confirmed by single-crystal X-ray analysis. The preparation of **11** also demonstrates an expansion in functional group tolerance, being the first example of an

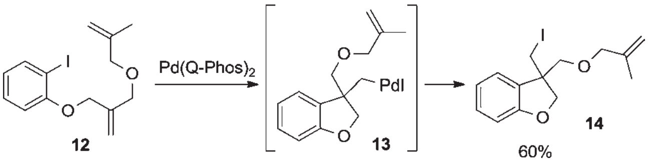
Scheme 3. Domino Synthesis of Polycyclic Alkyl Iodides



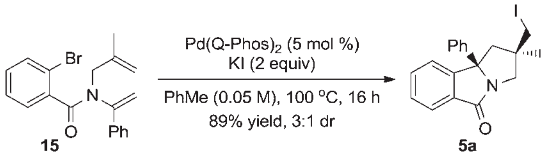
Scheme 4. Complex Molecule Synthesis via Carbohalogenation



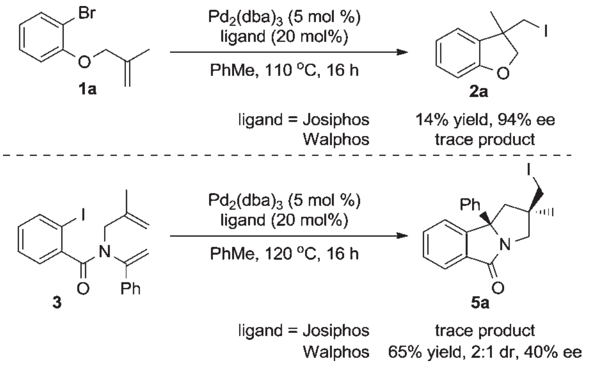
Scheme 5. Interrupted Domino Reaction



Scheme 6. Domino Cyclization Using an Aryl Bromide



Scheme 7. Preliminary Enantioselective Results



aromatic nitrogen-containing heterocycle undergoing cyclization. In substrates **3**, **6**, **8**, and **10**, only the domino cyclization products were ever observed.

We hypothesized that if carbopalladation of the monocyclized intermediate were slowed, the reductive elimination to the monounsaturated product could be observed. Ether **12**, which lacks the Thorpe−Ingold effect found in **8**, was subjected to the reaction conditions and provided monocyclized product **14** in 60% yield (Scheme 5). No evidence of domino cyclization arising from carbopalladation of intermediate **13** was observed. While further studies are necessary to make definitive conclusions about the rates of cyclization and reductive elimination, this experiment gives significant insight into the relative rates and practical information on potential synthetic applications of our methodology.

These two processes could ultimately be combined in an efficient halogen-exchange domino reaction. Substrate **15**, the bromide analogue of **3**, was prepared (Scheme 6). Utilizing our standard halogen exchange conditions, we observed cyclization to **5** in 89% yield and 3:1 dr.[18]

Lastly, in the interest of developing an enantioselective variant of this process, we explored a variety of chiral ligands. Preliminary results using the ligands Josiphos and Walphos were promising (Scheme 7). Cyclized iodide **2a** could be obtained in up 14% yield and 94% ee using Josiphos. Domino product **5a** could also be obtained in 65% yield, 2:1 dr, and 40% ee using Walphos. Further studies into this enantioselective process are underway.

In conclusion, we have demonstrated the first example of cyclization of aryl bromides in the presence of an iodide source to generate alkyl iodide products in excellent yields. In addition, polyunsaturated aryl iodide substrates are amenable to domino carbohalogenation reactions yielding complex bicyclic alkyl iodides containing multiple stereogenic centers in high yields with good diastereoselectivities. These concepts can be merged to allow polyunsaturated aryl bromide substrates to participate in domino chemistry, generating bicyclic alkyl iodide products. Finally, preliminary studies of asymmetric carboiodination have given promising results. These modifications significantly broaden the range of substrates that can be utilized for carbohalogenation.

■ ASSOCIATED CONTENT

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

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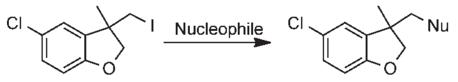
(13) Aryl chlorides gave much lower conversions under these reaction conditions. Aryl triflates gave no conversion.

(14) Substitution of the iodide using the nucleophilic species cyanide, thiophenolate, azide, and water was surprisingly efficient. See the Supporting Information for further details.



Nu	Yield
CN^-	98%
PhS^-	90%
N_3^-	86%
H_2O	45%

(15) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH, Weinheim, Germany, 2006. (b) Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Adv. Synth. Catal.* **2011**, *353*, 809.

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(17) For further details on ligand screens, see the Supporting Information.

(18) Subjection of **3** to cyclization in the presence of KI at 0.05 M in toluene also gave **5** in 3:1 dr.