Simultaneous Catalysis

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Harnessing Reversible Oxidative Addition: Application of Diiodinated Aromatic Compounds in the Carboiodination Process**

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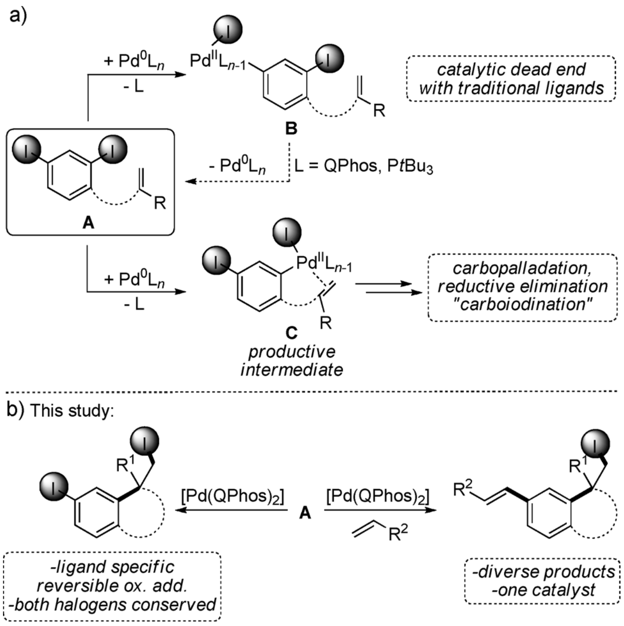
Transition-metal-mediated couplings of halogenated aromatics have been extensively studied since the 1960s.[1] Notwithstanding the success of recent aromatic functionalization strategies such as directed *ortho* metalation[2] and C–H functionalization,[3–5] Pd-catalyzed aromatic carbon–halogen bond functionalization remains a central strategy. In this regard, the application of polyhalogenated aromatic compounds in site-selective transformations is one of the remaining challenges in this field,[6] due to overcoupling[6h] and chemoselectivity issues.[7] Methods that take advantage of the intrinsic steric and electronic differences between different carbon–halogen bonds have been developed.[6a,i] However, most of these strategies remain limited, requiring difficult substrate prefunctionalization to enforce the desired selectivity. Under traditional catalytic conditions, irreversible oxidative addition to a carbon–halogen bond of **A** occurs to give **B** (Scheme 1 a), which lacks a productive reaction pathway. The presence of intermolecular Heck acceptors, or the addition of nucleophiles, is a strategy used to promote a catalytic cycle, as it allows catalytic dead ends to be avoided while increasing product complexity.[6b,f]

A more general and attractive solution would be to use catalysts capable of undergoing reversible oxidative addition.[8] Building on the stoichiometric experiments on reductive elimination from $ArPd^{II}X$ complexes conducted by Hartwig et al.,[9] and the contributions of Buchwald et al., which afford aromatic C–F[10a] and C–Br bonds;[10b] our group has developed Pd^0-catalyzed transformations exhibiting reversible oxidative addition as a key to catalysis.[8,11] To this end, the application of our carboiodination method to diiodinated substrates would highlight the unique capabilities of the Pd/QPhos combination: the ability to oxidatively add reversibly to carbon–halogen bonds, and to promote sp^3 carbon–iodine reductive elimination. Herein, we report both the carboiodination, and the sequential intramolecular carboiodination/intermolecular Heck reaction of diiodinated aromatic substrates (Scheme 1 b).



Scheme 1. a) Catalyst deactivation by irreversible oxidative addition; b) Strategy to overcome catalyst deactivation (when $R \neq H$). QPhos = 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene.

We began by optimizing the intramolecular carboiodination of **1a** (Table 1). Although 5 mol% of $[Pd(PtBu_3)_2]$ in toluene at 100 °C led to full conversion, the desired product (**2a**) was obtained in only 30% isolated yield after 18 h.[12] The yield of **2a** depended on the Pd^0 precatalyst used, as well as the presence of both additional QPhos and base.[13] Based on previous synthetic reports[8,11] and computational evidence,[14a] we believe that the steric bulk of QPhos make it ideal for promoting carbon-iodine reductive elimination.[14b] The optimized conditions were found to be $[Pd(QPhos)_2]$ (**Pd-1**; 5 mol%), additional QPhos (10 mol%), and 1,2,2,6,6-pentamethylpiperidine (PMP; 2 equiv) in toluene at 110 °C.[15] Under these conditions, **2a** was isolated in 74% yield. With the optimized reaction conditions in hand, we examined a series of diiodinated compounds, **1b–1f.**

Varying the location of the halogen substituent did not affect the transformation as **1b** could be efficiently cyclized to **2b** in 76% yield (Table 1, entry 2). Six-membered rings could be accessed, as **1c** cyclized to afford chroman **2c** in 74% yield (entry 3). Dihydrobenzofuran **2d** and oxindole **2f** were isolated in 60% and 68% yield when the reaction times

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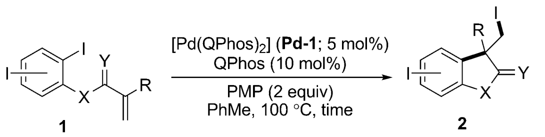
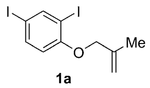
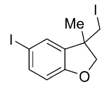
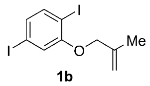
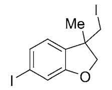
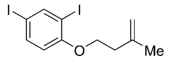
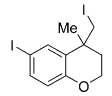
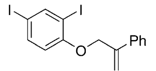
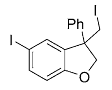
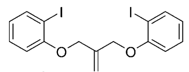
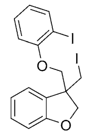
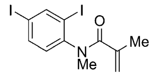
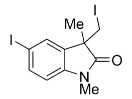
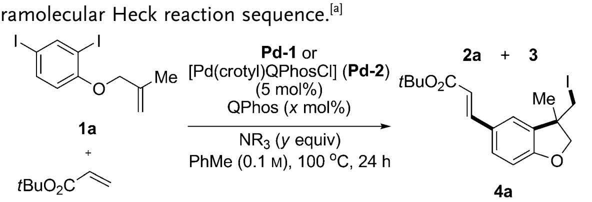
Table 1: Scope of the intramolecular carboiodination of diiodoarenes.[a]



Entry	Substrate **1**	Product **2**	*t* [h]	Yield [%][b]
1	 **1a**	 **2a**	5	74 (67)[c]
2	 **1b**	 **2b**	7	76
3	 **1c**	 **2c**	8	74
4	 **1d**	 **2d**	20	60
5	 **1e**	 **2e**	11	58
6	 **1f**	 **2f**	30	68

[a] Reactions conditions: diiodoarene (0.1–0.2 mmol), [Pd(QPhos)$_2$], (5 mol%), QPhos (10 mol%), PMP (2 equiv), PhMe, 110°C. [b] Yield of isolated product. [c] Reaction run on 2.5 mmol scale.

Table 2: Optimization of the orthogonal intramolecular carboiodination/intramolecular Heck reaction sequence.[a]

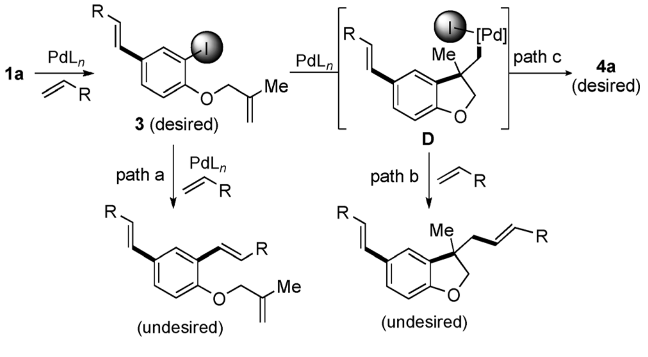


Entry	Pd Source	QPhos (*x* mol%)	NR$_3$ (*y* equiv)	Yield [%][b] **2a**	**3a**	**4a**
1	**Pd-1**	–	NEt$_3$ (2)	16	16	40
2	**Pd-1**	–	NEt$_3$ (4)	18	18	21
3[c]	**Pd-1**	–	NEt$_3$ (4)	8	5	55
4	**Pd-1**	10	NEt$_3$ (2)	10	7	57
5[c]	**Pd-1**	10	NEt$_3$ (2)	14	8	57
6[c]	**Pd-1**	10	PMP (2)	4	–	86
7[c]	**Pd-1**	5	PMP (2)	5	16	62
8[c,d]	**Pd-2**	10	PMP (2)	–	–	86
9[c–f]	**Pd-2**	**8**	**PMP (2)**	**–**	**–**	**88[g] (80)[h]**

[a] 0.2 mmol scale, 0.1 M in toluene. [b] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] TBA (1.5 equiv). [d] KO*t*Bu (20 mol%) used. [e] **Pd-2** (4 mol%). [f] **1a** (0.125 M). [g] Yield of isolated product. [h] Reaction run on a 2.5 mmol scale.

were increased to 20 h and 30 h, respectively (entries 4 and 6). Substrate **1e** contains iodides on different aryl rings, but gave **2e** in 58% yield after 11 h (entry 5).

We next sought to apply diiodinated compounds in an orthogonal intramolecular carboiodination/intermolecular Heck reaction sequence. Among the challenges are (Scheme 2): 1) starting material homo-dimerization; 2) undesired Heck reactions occurring either prior to or after the desired intermolecular Heck reaction (path a); 3) reactive neopentyl Pd^{II} intermediate[16] **D** could undergo an intermolecular Heck reaction (path b) instead of reductive elimination to form **4a** (path c).

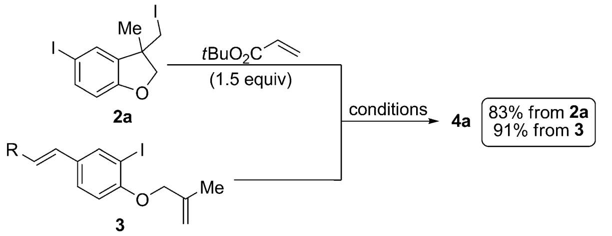


Scheme 2. Challenges of the reaction sequence (R = CO$_2$*t*Bu).

We began by optimizing the reaction between **1a** and *tert*-butyl acrylate (TBA; Table 2). With **Pd-1** (5 mol%) and NEt$_3$ (2 equiv) in toluene at 100°C for 24 h, **4a** was obtained as the major product in 40% yield along with 16% of both **2a** and **3a** (entry 1). The reaction was completely chemoselective, as no undesired Heck products were observed. Increasing the amount of NEt$_3$ to 4 equiv led to a decrease in the yield of **4a** to 21% (entry 2). However, increasing the amount of olefin to 1.5 equiv, or adding an additional 10 mol% of QPhos increased the yield of **4a** to 55% and 57%, respectively, while simultaneously decreasing the amount of **2a** and **3a** (entries 3 and 4). When PMP was used, **4a** was furnished in 86% yield, with only 4% of **2a** and no trace of **3a** (entry 6). The complex [Pd(crotyl)QPhosCl] (**Pd-2**) was an equally effective Pd^0 precursor,[17] and employing 5 mol%, while maintaining all established conditions, gave rise to **4a** in 86% yield (entry 8). Using this catalyst is ideal, as it is air stable and allows the ligand loading to be decreased. The final optimized conditions were TBA (1.5 equiv), **Pd-2** (4 mol%), QPhos (8 mol%), and PMP (2 equiv) in toluene at 100°C for 24 h, where **4a** was isolated in 88% yield with no observed **2a** or **3a** (entry 9).

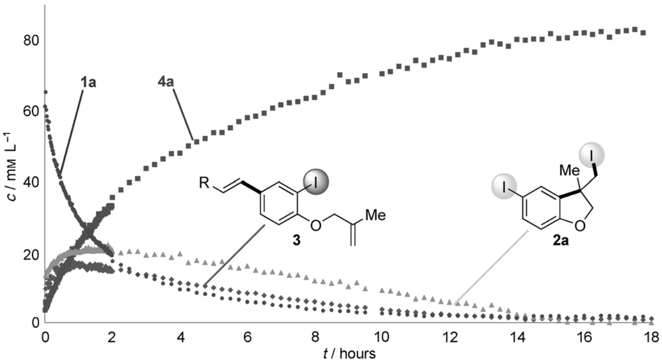
Control experiments were then conducted to determine if all proposed intermediate products could ultimately convert into the desired adducts (Scheme 3). We found that both **2a** and **3a** could be converted into **4a** in 83% and 91% yield, respectively. These experiments suggest that either intermediate could proceed towards the desired product, and that both pathways could be occurring simultaneously.

We tested this proposal using ^{1}H NMR spectroscopy to monitor the reaction between **1a** and TBA in situ



Scheme 3. Control experiments concerning reaction intermediates. Conditions: **Pd-2** (4 mol%), QPhos (8 mol%), KOtBu (20 mol%), PMP (2 equiv), toluene, 100 °C, 12 h. R = CO_2tBu.

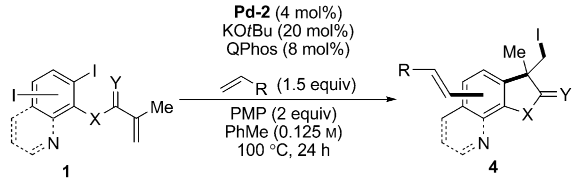
(Scheme 4).[18] We observed similar increases in the concentration of both products **2a** and **3a**, from the intramolecular carboiodination and the intermolecular Heck reaction, respectively. In contrast to Table 1 where selective *ortho* coupling occurs, this experiment strongly suggests that the Pd^0 catalyst can oxidatively add reversibly into both carbon–iodine bonds of **1a**, allowing both reactions to proceed simultaneously. Additionally, there are similar decreases in the concentrations of **2a** and **3a**, thus highlighting that both intermediates can converge to **4a**.

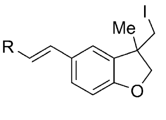
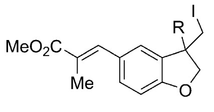
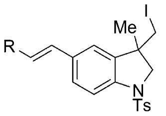
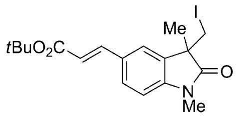
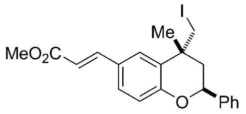
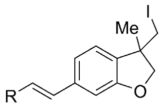
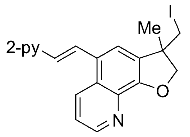


Scheme 4. In situ monitoring of the reaction of **1a** and TBA. Conditions: **Pd-2** (0.04 equiv), QPhos (0.08 equiv), KOtBu (0.2 equiv), **1a** (0.087 M), TBA (0.122 M), PMP (0.216 M), [D$_8$]toluene, 373 K, 700 MHz.

Finally, the optimized conditions were applied to a series of Heck acceptors and diiodoarenes (Table 3). When the reaction time was doubled to 48 h, the loadings of **Pd-2** and QPhos could be decreased to 2 mol% and 4 mol%, respectively, when the reaction was run on a 2.5 mmol scale. This combination allowed the isolation of **4a** in 79% yield (entry 1). Methyl acrylate and *N,N*-dimethyl acrylamide were well tolerated as acceptors, and their adducts, **4b** and **4c,** were isolated in 83% and 73% yield, respectively (entries 2 and 3). Subjecting styrene and acrylonitrile to the standard conditions delivered the desired products **4d** and **4e** in 82% and 90% yield, respectively (entries 4 and 5). Methyl methacrylate reacted selectively to form **4f** in 77% yield (entry 6) in the presence of 5 equiv of olefin. *N*-tosyl indolines could also be obtained as **4g** and **4h** were afforded in 86% and 84% (entries 8 and 9). Electron-deficient olefins were tolerated in the intramolecular carboiodination component, as *N*-methyl oxindole **4i** could be synthesized in 87% yield (entry 10). Switching to a *para*-iodo substitution pattern had no effect (entries 12–14). A nitrogen-containing polycycle **4n** could also be obtained in 70% yield (entry 15).

Table 3: Reaction scope.[a]



Entry	Product	4	Yield [%][b]
1	R = CO_2tBu 	**4a**	88 (79)[c]
2	R = CO_2Me	**4b**	83
3[c]	R = CONMe_2	**4c**	73
4	R = Ph	**4d**	82
5	R = CN	**4e** (4:1 *E*/*Z*)	90[d]
6			
7		**4f** (R = Me)	77
		4f' (R = Ph)	25
8[e]	R = CO_2tBu 	**4g**	86
9	R = 2-py	**4h**	84
10[e]		**4i**	87
11		**4j**[f] (d.r. = 87:13)	86
12	R = CO_2tBu 	**4k**	91
13	R = CONMe_2	**4l**	88
14	R = 2-py	**4m**	74
15[e]		**4n**	70

[a] 0.2 mmol scale. [b] Yield of isolated product. [c] **1a** (2.5 mmol, 0.25 M), **Pd-2** (2 mol%), QPhos (4 mol%), KOtBu (10 mol%), toluene, 48 h. [d] Combined yield of both isomers. [e] Reaction heated for 48 h. [f] Stereochemistry assigned based on analogy to a previous report, see Ref. [11c]. 2-py = 2-pyridyl.

In conclusion, we have shown the utility of diiodinated aromatic compounds in a Pd^0-catalyzed intramolecular carboiodination. These two complementary reactions allow access to a diverse range of cross-coupling substrates and olefin containing heterocycles. Commonly encountered problems associated with this important class of compounds are effectively avoided by carefully selecting a ligand that allows reductive elimination from unproductive catalytic intermediates.

Experimental Section

KO*t*Bu (4.5 mg, 0.04 mmol, 20 mol %), [Pd(crotyl)QPhosCl] (7.3 mg, 0.008 mmol, 4 mol %), and QPhos (11.4 mg, 0.016 mmol, 8 mol %) were added to a dry screw cap vial equipped with a stir bar, which was purged with dry argon. The contents were taken up in toluene (0.8 mL) and stirred at room temperature for 15 min. A toluene solution (0.8 mL) of **1a** (79.9 mg, 0.2 mmol, 1 equiv), *tert*-butyl acrylate (44 μL, 0.3 mmol, 1.5 equiv), and PMP (72 μL, 0.4 mmol, 2 equiv) was then added to the pre-mixed catalyst solution. The vial was sealed and placed into a preheated oil bath (100 °C). After 24 h, the reaction was filtered through silica, and concentrated. The crude product was purified by column chromatography using hexanes/EtOAc (100:0–100:3 v/v) to give a clear, colourless oil (70.4 mg, 0.176 mmol, 88 %).

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[15] For a thorough discussion on the optimization, see the Supporting Information.

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[18] The optimized [**1a**] was not suitable for this experiment, owing to severe peak broadening.

Communications

Simultaneous Catalysis

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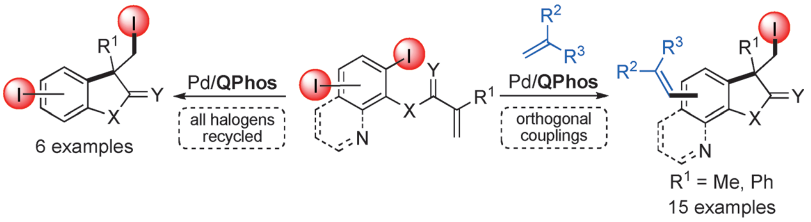
Harnessing Reversible Oxidative Addition: Application of Diiodinated Aromatic Compounds in the Carboiodination Process



An I for an I: Conditions for the intramolecular carboiodination and the simultaneous convergent intramolecular carboiodination/intermolecular Heck reaction of various diiodoarenes were developed. The ability of the Pd^0/QPhos catalyst/ligand combination to undergo reversible oxidative addition allows these reactions to proceed well, thus increasing both the appeal and utility of this class of substrates in site-selective cross-coupling reactions.