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Intermolecular Domino Reaction of Two Aryl Iodides Involving Two C–H Functionalizations**

*Marcel Sickert, Harald Weinstabl, Brendan Peters, Xiao Hou, and Mark Lautens**

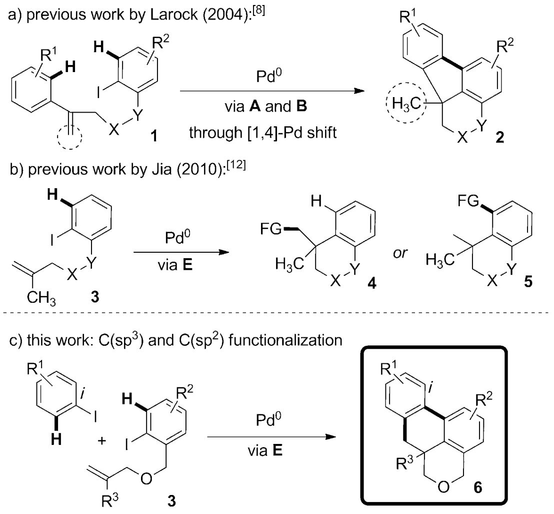
***Abstract:** A palladium-catalyzed intermolecular cross-coupling of two aryl iodides is reported, giving polycyclic ring systems with a high level of convergence and efficiency.*

The rapid construction of complex heteroatom-containing carbon frameworks has become an attractive challenge in the past years. For this reason, domino reactions represent a powerful strategy for the rapid formation of multiple bonds in a single flask.[1,2] In recent years, this class of reactions, involving transition-metal-catalyzed C–H bond activation, have emerged as an important field of research in organic synthesis. Metals, including palladium, rhodium, and iridium, have been used to access a variety of *ortho*- or *meta*-directed C–H activations.[3] For over a decade, our group[4] has used variants of the palladium-catalyzed Catellani reaction[5] to direct C–H functionalization by generating the directing group in situ and catalytically. This task has been accomplished by using norbornene as the shuttle to direct the desired C–H palladation. The power of this reaction was recently demonstrated in the total syntheses of two distinct classes of natural products.[6]

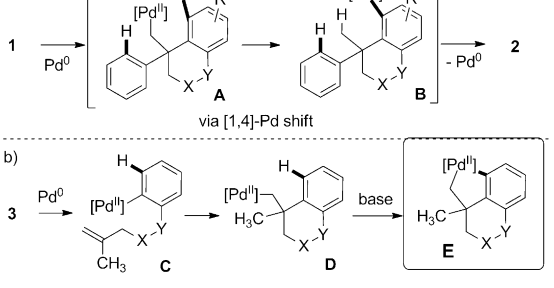
The key to success of the norbornene-facilitated transformation is the lack of suitable *syn*-β-hydrogen atoms in the carbopalladated intermediate, which prompts the C–H activation and initiates the subsequent steps. The utilization of other olefins following similar principles was rarely reported, and in most cases an incorporation of the double-bond scaffold in the final product structure was observed.[7,8] In a pioneering study, Larock and co-workers[8] illustrated the utility of an in situ generated neopentyl–Pd^{II} species **A** for the synthesis of complex fused biaryls **2** through a sequence of C–H activations, which is facilitated by a net 1,4-palladium shift to form intermediate **B** (Scheme 1 a and Scheme 2).

Related to Larock's report,[9–11] Jia and co-workers recently described the intermolecular functionalization of the palladacycle intermediate **E**, in which aryl, hetaryl, nitrile, and Heck acceptors may be introduced on either position ($C(sp^2)$ versus $C(sp^3)$, Scheme 1 b) depending on the reaction conditions.[12]

We now illustrate that both positions of the six-membered palladacycle **E** can be functionalized in a single step through



Scheme 1. a) Intramolecular arylation through [1,4]-Pd shift and final C–H activation by Larock (2004). b) $C(sp^2)$ or $C(sp^3)$ functionalization of σ-alkyl/Pd^{II} intermediate **E** by Jia (2010). c) This work: $C(sp^2)$ and $C(sp^3)$ arylation of intermediate **E** with an aryl iodide. FG = functional group.



Scheme 2. Proposed Pd^{II} intermediates **A** to **E** of transformations shown in Scheme 1.

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[*] Dr. M. Sickert, Dr. H. Weinstabl, B. Peters, X. Hou,
Prof. Dr. M. Lautens
Department of Chemistry, University of Toronto
80 St. George St. Toronto, Ontario, M5S 3H6 (Canada)
E-mail: mlautens@chem.utoronto.ca
Homepage: http://www.chem.utoronto.ca/staff/ML/index.php

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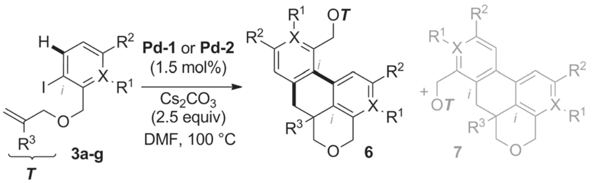
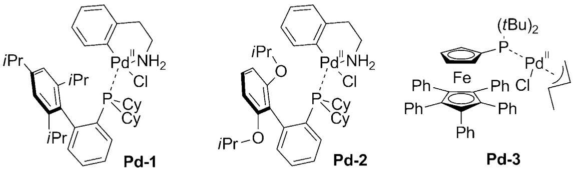
an intermolecular domino reaction of an aryl iodide. These positions react selectively in a sequence of carbopalladations and cross C–H activations, furnishing complex fused biaryls (Scheme 1c). Our interest in this particular area was driven by recent studies on the Pd^0-catalyzed carboiodination reaction.[13] We initially set out to capture intermediate **E** with an alkyl iodide,[14] however, we observed the formation of the dimerization product **6a** (see Scheme 4) in modest yields. Intrigued by the complexity of this product we set out to investigate the transformation in detail.

Upon optimization,[15] synthetically useful levels of dimer **6a** could be obtained. However, a by-product (**7a**) remained an issue and indicated the presence of an additional and competing reaction pathway.[16] Interestingly, the extent of by-product formation depended on the nature of the base, the Pd source, and the ligand.[15] By using Buchwald's palladacycle precatalyst **Pd-1** (Scheme 3) and Cs_2CO_3 in DMF, the highest selectivity for **6a**:**7a** was 7:1, and **6a** was isolated in 68% yield. With the optimized reaction conditions in hand, we began to explore the scope of the transformation.



3/6/7	R^1	R^2	R^3	(X)	Yield of **6** (**7**)[b]	Ratio **6**:**7**[c]	(notes)
a			CH_3	(C)	68% (9%) 54% (6%)	7:1 10:1	(**Pd-1**) (**Pd-2**)
b		CH_3	CH_3	(C)	69% (-)[d,e]	>8:1	(**Pd-1**)
c	-OCH_2O-		CH_3	(C)	53% (8%)	6:1	(**Pd-1**)
d		CF_3	CH_3	(C)	50% (9%)	5:1	(**Pd-1**)
e			Et	(C)	59% (8%)	5:1	(**Pd-2**)
f			*n*Bu	(C)	61% (9%)	5:1	(**Pd-2**)
g			CH_3	N	75%[f]	6:1	(**Pd-1**)

Scheme 4. Substrate scope of the dimerization of **3**.[a] [a] When R^1, R^2, or R^3 were H, they were omitted for clarity in the table. Yields are reported with respect to 0.30 mmol of **3**. Conditions: 0.60 mmol scale.[17] **Pd-1** or **Pd-2** (1.5 mol%), **3** (1.0 equiv), Cs_2CO_3 (2.5 equiv), DMF (0.4 M), 100°C, 18–22 h. [b] Yields of isolated products. [c] Ratio determined by ^1H NMR analysis of the crude reaction mixture. [d] 2.45 mmol scale (0.60 mmol scale resulted in 67% yield of **6b**). [e] Isolation of clean **7b** failed because of coeluting impurities [f] Combined yield of **6g** and **7g**.



Scheme 3. Privileged Pd precatalysts.

When the aromatic ring contained either an electron-donating or an electron-withdrawing group, a marginal impact on the yield was observed and yields higher than 50% were typically obtained (entries b–d, Scheme 4). The effect of varying the alkyl chain was also investigated. Both ethyl and butyl groups were tolerated, giving the corresponding products **6e** and **6f** in 59% and 61% yield, respectively; however, the application of **Pd-2** was necessary to achieve good selectivities in these cases (Scheme 4). The selectivity of the reaction (**6** vs. **7**) ranged between 5:1 and 7:1, and by-products **7a–f** were generally obtained in 8–9% yield (Scheme 4).

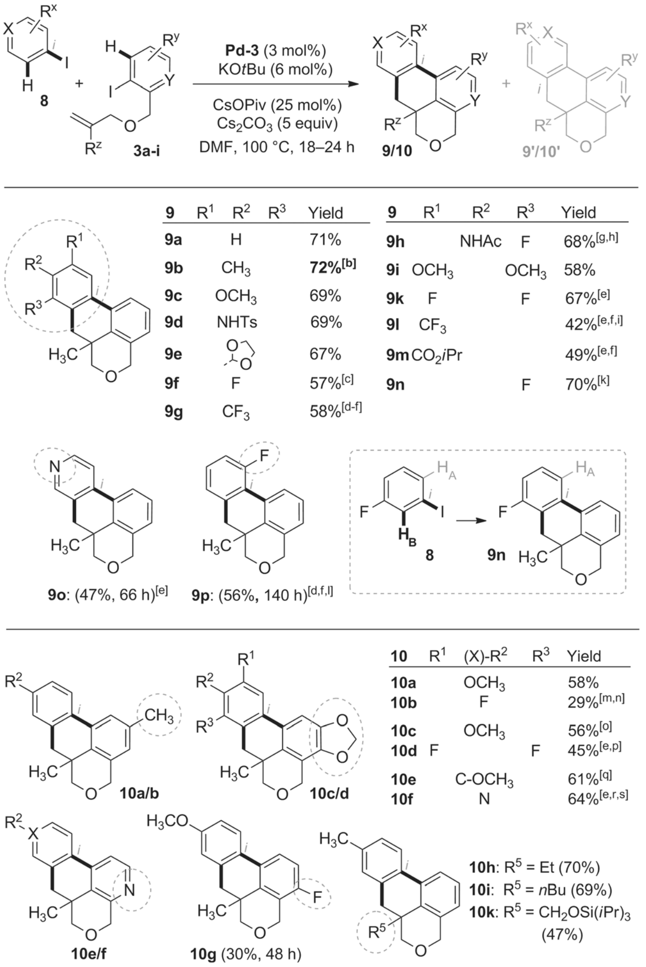
We next studied a heteroaryl cross-coupling (Scheme 5). We successfully obtained the desired product **9**, accompanied by smaller amounts of the dimerization product **6a**. The highest yields were obtained using Cs_2CO_3 in DMF, however, efficient suppression of **6a** was only observed when palladium precatalyst **Pd-3** was used.[15] An increase in the reaction rate was observed when a catalytic amount of CsOPiv was added, even with a catalyst loading of 3 mol%.[18]

Under the optimized reaction conditions, *para*-substituted aryl iodides formed the desired products in up to 71% yield. In general, electron-donating substituents on the aryl iodide, such as alkoxy groups, protected amines, or acetals, resulted in higher yields compared to their electron-deficient counterparts (Scheme 5). In the case of the electron-withdrawing CF_3-containing substrate, it was necessary to increase the catalyst loading to 6 mol%. Bis-*meta*-substituted aryl iodides were also tolerated and the products were afforded in synthetically useful yields (**9i**, **9k**). Aryl iodides substituted with sterically different groups on the *meta* position gave divergent selectivity. More sterically demanding electron-withdrawing groups, such as CF_3 (**9l**), favored the C–H activation in the *para* position ($\mathbf{H_A}$, Scheme 5), whereas a *meta*-fluoro substituent allowed the final C–C formation at the C–$\mathbf{H_B}$ position with a regioselectivity of 8:1 (**9n**). Although, substituents at the *ortho* position generally gave poor results,[20] a fluoro group at the *ortho* position was tolerated and the corresponding product **9p** and by-product **9n** were afforded in 56% and 6% yield, respectively.

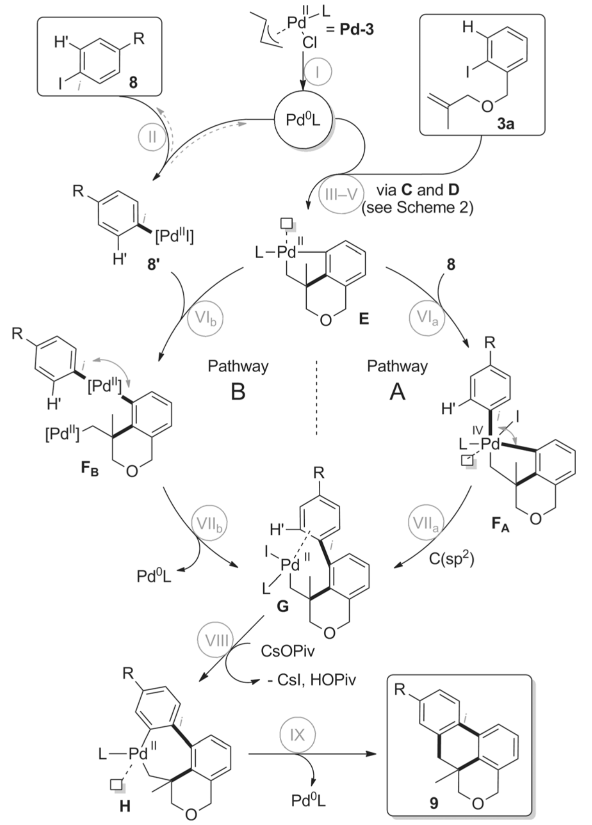
Variations on the aromatic ring of the methallyl ether were also studied (Scheme 5). The reaction of methyl- and dioxolane-substituted methallyl ethers with *para*-methoxy iodobenzene furnished products **10a** and **10c** in yields of 58% and 56% yield, respectively. Additionally, a fused bipyridyl structure was accessible by the reaction of electron-deficient pyridyl-substituted methallyl ether **3g** with the 4-iodopyridine, and **10f** was isolated in 64% yield. However, the introduction of **3g** enhanced both the by-product formation (up to 10%) and the dimerization process (up to 20%). Substitution of the vinylic methyl group with longer alkyl chains did not seem to affect the reaction. Similarly high yields of 70% and 69% were observed for both the ethyl- and the butyl-substituted systems (**10h** and **10i**). In order to have a handle for post-synthesis modification, a silyl ether was subjected to the reaction conditions and **10k** was obtained in 47% yield after 21 hours.

The scalability of the heterodimerization reaction was demonstrated for the reaction of **6a** with 4-methyl iodobenzene. When run on a 3.7 mmol scale, the desired product **9b** was obtained in 72% yield.

On the basis of these preliminary results, a proposed mechanism is outlined in Scheme 6, in which two reaction pathways (A: Pd^{IV} versus B: Pd^{II}–Pd^{II}) are considered in



Scheme 5. Substrate scope of domino reactions with aryl iodides.[a] [a] When R^1, R^2, or R^3 were H, they were omitted for clarity in the table. Conditions: 0.40–0.45 mmol scale, **Pd-3** (3 mol%), KO*t*Bu (6 mol%),[18b] CsOPiv (25 mol%), Cs_2CO_3 (5.0 equiv), **3** (1.0 equiv), **8** (1.3 equiv), DMF (0.2 M), 100 °C. [b] 3.70 mmol scale (0.40 mmol scale resulted in 65% yield). [c] 80 h. [d] 3–8% of **6a** observed. [e] **Pd-3** (6 mol%), KO*t*Bu (12 mol%). [f] **8** (1.5 equiv). [g] 48 h. [h] Combined yield; r.r. = 7:1. [i] 120 h. [k] Combined yield; r.r. = 8:1. [l] 6% of **9p′** (**9n**) was observed. [m] 13% of **6b** was observed. [n] 72 h. [o] 13 h. [p] 25% of **6c** was observed.[19] [q] 6% of **10e′** was isolated. [r] 10% of **10f′** was isolated. [s] 18% of **6g** was observed. r.r. = regioisomeric ratio.



Scheme 6. Proposed simplified mechanism: I) generation of active Pd^0 species; II) competitive oxidative addition; III) oxidative addition; IV) carbopalladation; V) C–H activation; VI_a) second oxidative addition; VII_a) reductive elimination; VI_b) transmetalation; VII_b) reductive elimination; VIII) second C–H activation; IX) second reductive elimination.

analogy to the proposed mechanisms of the Catellani reaction.[21,22] After oxidative addition, carbopalladation, and C–H activation of **3a** (steps III–V, Scheme 6), the palladacycle **E** may follow one of two pathways: The oxidative addition of **E** with a second aryl iodide **8** may form a Pd^{IV} complex $\mathbf{F_A}$, which upon aryl–aryl reductive elimination generates intermediate **G** (Scheme 6, pathway A). Another plausible sequence (pathway B) may occur by the reaction of **E** with an additional Pd^{II} species **8′**[23] through transmetalation between both Pd^{II} centers to form the dinuclear complex $\mathbf{F_B}$, which generates intermediate **G** following aryl–aryl reductive elimination (Scheme 6, pathway B). Finally, the 7-membered palladacycle **H** could be formed by a second intramolecular C–H activation of the alkyl Pd^{II} species **G**. Upon the final reductive elimination, the Pd^0 catalyst is regenerated and the fused bicycle **9** is formed.

Despite the similarities to the Catellani reaction, the selective formation of the fused biaryls **9**/**10** gave rise to intriguing questions regarding: 1) the apparent selectivity in oxidative addition in the presence of aryl iodides **3** and **8**;[23,24] 2) the origin of a selective heterodimerization to **9**/**10**, preventing dimerization to **6** with the QPhos ligand;[25] and 3) the mechanism leading to the formation of regioisomer **9′**/**10′**.[26]

In conclusion, we have developed a novel Pd^0-catalyzed intermolecular domino reaction, in which two structurally distinguishable aryl iodides react together through a carbopalladation and a sequence of C–H activations to form three new C–C bonds.[27] The reaction allows an efficient and convergent synthesis of fused biaryls with high complexity based on a dihydrodibenzoisochromene framework.

Experimental Section

Representative procedure for **9c**: [Pd(crotyl)QPhosCl] (**Pd-3**) (3.0 mol%), KO*t*Bu (6.0 mol%), cesium pivalate (25 mol%), and cesium carbonate (5.0 equiv) were weighed into a dry microwave vial and purged with argon for ten minutes. The contents were suspended in anhydrous DMF (0.4 mL) and after 10 min, a DMF solution (1.6 mL) of methallyl ether **3a** (0.40 mmol, 1.0 equiv) and 4-methoxy iodobenzene **8c** (1.3 equiv) was added. The vial was sealed, purged with argon for 5 min and heated for 18 h in a preheated oil bath at 100 °C. Following standard work-up procedures (see the Supporting Information), the crude product was purified by flash column chromatography on silica gel using a gradient of hexanes to EtOAc/hexanes (1:10, *v*:*v*) as eluent, and **9c** was isolated as white solid (73.5 mg, 0.276 mmol, 69 %).

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Keywords: carbopalladation · C–H activation · domino reactions · fused-ring systems · palladium

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[14] An *ortho* butylation accompanied by a reductive carbopalladation was observed by using *n*Bu-I, giving a yield of 30–40 % (see the Supporting Information).

[15] Detailed optimization studies are summarized in the Supporting Information.

[16] X-Ray structures of **6c**, **7c**, **9c**, and **10c** support the proposed assignment; see Supporting Information. CCDC 982746 (**7c**), 982747 (**9c**), 982748 (**10c**), and 982749 (**6c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] For selected examples, experiments were also conducted with **3** on a 0.40 and 0.80 mmol scale.

[18] a) By using 5 equiv of CsOPiv, an enhanced formation of by-product **9′** was observed (see the Supporting Information). b) The addition of KO*t*Bu leads to a more reproducible reaction.

[19] An enhanced formation of **6c** was detected in the final phase of the reaction.

[20] MeO, Me, and CF$_3$ groups at the *ortho* position of **8** led to complex product mixtures, including the formation of the dimer product **6a** as the main product.

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[25] The bulkiness of QPhos may cause the preferential reaction of **E** with less hindered **8**/**8′**, rather than **3**.

[26] The formation of **9′**/**10′** and **7**, respectively, can be rationalized by a C(sp^3) arylation step. The C(sp^3)–C(sp^2) reductive elimination from Pd^{IV} is proposed as an exceptional process in the Catellani reaction, see Ref. [11b].

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