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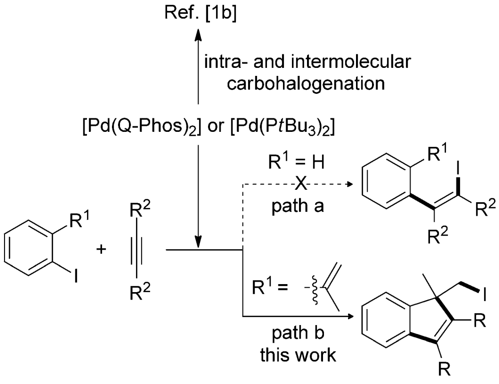
Carbohalogenation

A Conjunctive Carboiodination: Indenes by a Double Carbopalladation–Reductive Elimination Domino Process**

*Xiaodong Jia, David A. Petrone, and Mark Lautens**

We recently developed a novel Pd^0-catalyzed carbon–halogen bond forming reaction based on reversible oxidative addition. This reaction was highlighted in various intra- and intermolecular processes.[1] These formal carboiodinations were facilitated by the carbon–iodine reductive elimination proceeding through alkene carbopalladation (Scheme 1). Tong et al. also described interesting variants of this concept towards the synthesis of substituted bicyclic[2a] and heterocyclic[2b] frameworks. Our observed reactivity is strictly dependent on a bulky P-ligand, such as Q-Phos being present during catalysis. Since all previous reports highlight the formation of sp^3 carbon–iodine bonds, we hoped to extend the scope of this transformation to the synthesis of vinyl iodides using this ligand class. We attempted an intermolecular carboiodination reaction between an aryl iodide and an internal alkyne, but failed to isolate any of the desired product (Scheme 1, path a). Despite previous accounts of this ligand's unique ability to induce reductive elimination to form sp^2-hybridized C–Br bonds, the analogous sp^2-hybridized C–I bond formation was unsuccessful.

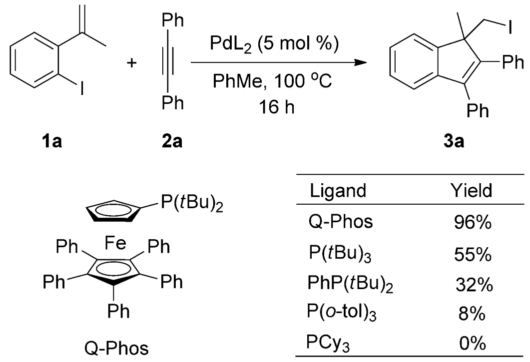


Scheme 1. Intramolecular and intermolecular carboiodination.

This prompted us to design a 2-iodo-α-methyl styrene substrate, which in the presence of an alkyne, would allow us to test the feasibility of an intermolecular–intramolecular domino reaction (Scheme 1, path b).[3,4] If compatible, we could still harness the reactivity of the vinyl Pd^{II} intermediate as means to access a new class of carboiodination products.

Herein, we report the development of a palladium-catalyzed domino intermolecular alkyne insertion/intramolecular alkene insertion terminated by a C–I reductive elimination. This methodology allows access to racemic polysubstituted indenes through the formation of two new carbon–carbon bonds and one new carbon–iodine bond.

We initially chose **1a** and **2a** to optimize the reaction conditions, and to test the effect of using different ligands (Scheme 2). At 100 °C in toluene, the carboiodinated indene product **3a** could be isolated in 96 % yield when 5 mol % [Pd(Q-Phos)$_2$] was used. Only 8 % of **3a** was obtained when P(o-tol)$_3$ was used as the ligand, and PCy$_3$ gave no detectable product.



Ligand	Yield
Q-Phos	96%
P(tBu)$_3$	55%
PhP(tBu)$_2$	32%
P(o-tol)$_3$	8%
PCy$_3$	0%

Scheme 2. Optimization of the reaction conditions.

The optimized reaction conditions were then applied to various alkynes to explore the scope of this transformation (Table 1). Symmetrical diaryl alkynes gave excellent yields of the desired indenes (entries 1–8). When dialkyl alkynes were used, the yields were generally lower, which may be a result of the presence of β-hydrogens in the vinyl Pd^{II} intermediate (entries 9 and 10). We also attempted the reactions of **1a** and various terminal alkynes, but no reaction was observed, and the starting materials remained unchanged. Dibromo alkyne **2g** gave only 32 % yield, which could be increased to 57 % by the addition of 1 equivalent of Et$_3$N (entry 7). The effect of added amine base remains unclear, but may be related to the regeneration of the active Pd^0 species.[6] No reaction occurred

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[*] Dr. X.-D. Jia, D. A. Petrone, Prof. Dr. M. Lautens
Davenport Laboratories, Department of Chemistry
University of Toronto
80 St. George Street, Toronto, ON, M5S 3H6 (Canada)
E-mail: mlautens@chem.utoronto.ca

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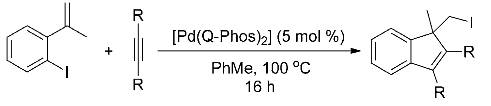
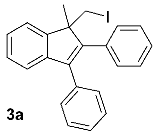
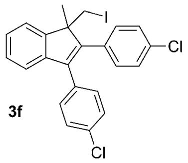
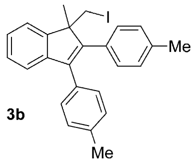
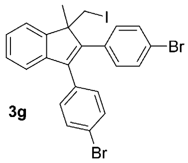
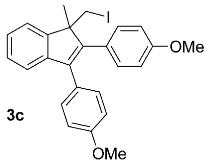
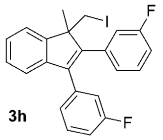
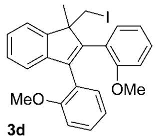
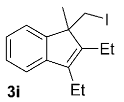
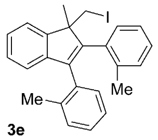
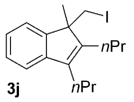
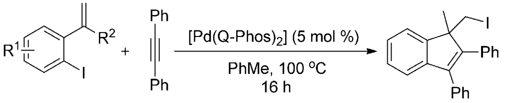
Table 1: Scope of alkynes.[a]

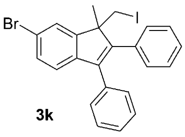
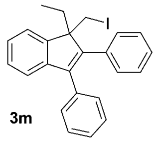
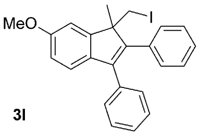
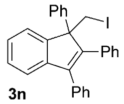


Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	 **3a**	96	6	 **3f**	92
2	 **3b**	93	7	 **3g**	57[b]
3	 **3c**	94	8	 **3h**	84
4	 **3d**	87	9	 **3i**	67[c]
5	 **3e**	N.R.[d]	10	 **3j**	68[c]

[a] Reaction conditions: Substrate **1** (0.1 mmol), alkyne **2** (0.12 mmol), [Pd(Q-Phos)$_2$] (5 mol%), 0.2 M in toluene, 100°C for 16 h. [b] Reaction ran in the presence of 1 equiv of Et$_3$N. [c] 3 Equiv of alkynes were used. [d] No reaction.

Table 2: Scope of 2-iodo-α-methyl styrene.[a]

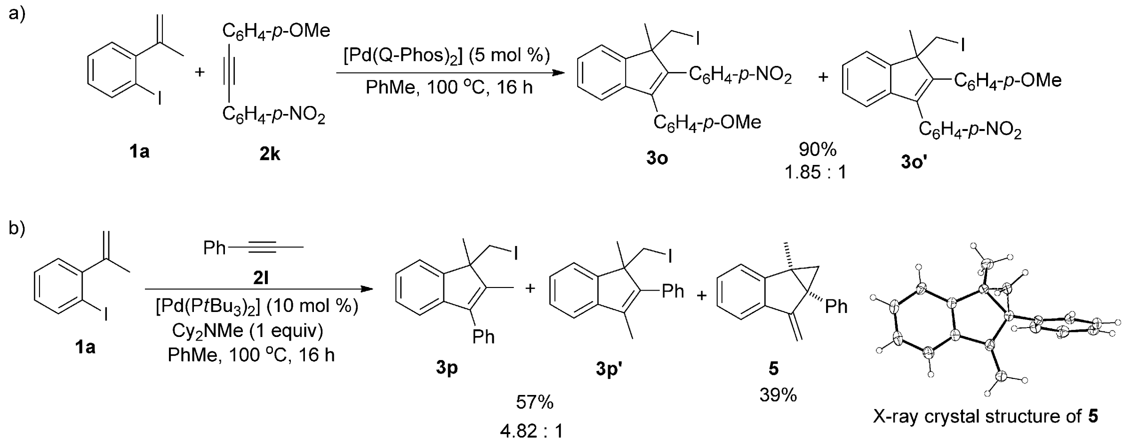


Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	 **3k**	75[b]	3	 **3m**	89
2	 **3l**	88	4	 **3n**	N.R.

[a] Reaction conditions: Substrate **1** (0.1 mmol), alkyne **2a** (0.12 mmol), [Pd(Q-Phos)$_2$] (5 mol%), 0.2 M in toluene, 100°C for 16 h. [b] Reaction ran in the presence of 1 equiv of Et$_3$N.

when bulky alkynes were used, presumably due to steric reasons (entry 5). When electronically polarized alkyne **2k** was used, a 1.85:1 ratio of regioisomers was observed (Scheme 3a). Interestingly, the major isomer was derived from Pd^{II} insertion to the more electron-rich carbon atom. When 1-phenyl-1-propyne **2l** was used in this reaction, the product ratio was increased to 4.82:1. However, by-product **5** was isolated in 39% yield in the presence of *N*-methyldicyclohexyl amine base. Cyclopropane **5** is presumed to be derived from intermediate neopentyl Pd^{II} species **D** (see Scheme 5) undergoing intermolecular cyclization and subsequent β-hydride elimination, instead of C−I reductive elimination (Scheme 3b).[6,7,9] Further studies concerning the improvement of regioselectivity are ongoing in our laboratory and will be reported in due course.

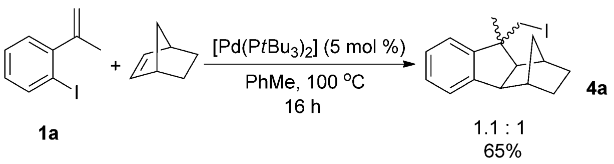
Iodinated styrene derivatives **1** bearing additional functionality were also investigated. Generally, the reactions proceeded smoothly to furnish the desired indenes in good yields (Table 2). 2-Iodo-5-bromo α-methyl styrene was well tolerated in this reaction when 1 equivalent of Et$_3$N was added highlighting the concept of reversible oxidative addition at remote sites (entry 1).[1a] Electron-rich aryl iodide **1l** was converted to the corresponding indene in 88% yield



Scheme 3. Preliminary regioselectivity results.

(entry 2). Alkene **1d** was used to test olefin steric effects, and appeared to have no effect on reaction efficiency (entry 3). However, iodinated 1,1-diaryl alkene does not react under the standard conditions, presumably due to increased steric effects preventing efficient carbopalladation (entry 4).

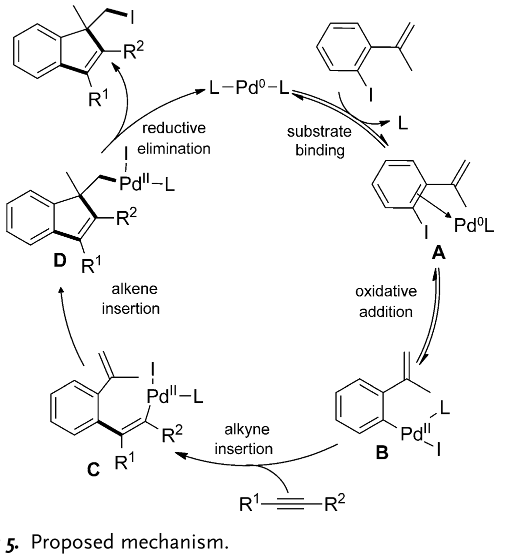
We extended this methodology to include reaction with strained, bicyclic norbornene (Scheme 4), in which the palladium intermediate cannot undergo *syn*-β-hydride elimination.[1b] Reoptimization of the reaction conditions showed [Pd(P*t*Bu$_3$)$_2$] to be the best catalyst.[8] Styrene **1a** gave 65 % of tetracycle **4a** as a 1.1:1 mixture of diastereomers.



Scheme 4. Reaction with norbornene.

A possible mechanism is proposed to rationalize the product formation (Scheme 5). Substrate binding first occurs[10] to generate Pd^0 complex **A**. This then undergoes a reversible oxidative addition which generates Pd^{II} intermediate **B**. Intermolecular alkyne insertion occurs to produce **C**, which can undergo cyclic alkene carbopalladation to form **D.** The indene product is formed once intermediate **D** undergoes C–I reductive elimination.

In summary, we have developed an efficient palladium-catalyzed domino carboiodination process between iodoaryl alkenes and internal alkynes en route to substituted indenes. In addition, norbornene participates in this reaction, affording the corresponding polycyclic indene in synthetically useful yield. We are currently focusing on expanding the scope of this transformation and further exploring its use in construction of complex molecular architectures. Mechanistic and computational studies concerning this type of transformation are also underway in our laboratory.



Scheme 5. Proposed mechanism.

Experimental Section

To a 0.5–2 mL biotage microwave vial equipped with a magnetic stir bar was added the compounds **1** (24.4 mg, 0.1 mmol) and **2** (21.4 mg, 0.12 mmol). The vial was purged with argon for 5 min, after which [Pd(Q-Phos)$_2$] (7.6 mg, 5 mol %) and toluene (0.5 mL) were added. The vial was capped and immersed to an oil bath pre-heated to 100 °C. After stirring for 16 h, the vial was cooled and the solution was filtered over a pad of silica gel eluting with Et$_2$O. The products were purified by flash chromatography using hexanes or 1 % Et$_2$O/hexane as eluent.

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[5] For a review concerning the Tollman angle of phosphine lingands, see: C. A. Tolman, *Chem. Rev.* **1997**, *97*, 313 – 348.

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[7] For a review of cyclic carbopalladations, see: E. Negishi, C. Copéret, S. Ma, S. Y. Liou, L. Fang, *Chem. Rev.* **1996**, *96*, 365 – 393.

[8] Our previous results also show that [Pd(P*t*Bu$_3$)$_2$] is more efficient than [Pd(Q-Phos)$_2$] in the intermolecular reaction with norbornene. See Ref. [1b] for details.

[9] CCDC 885982 (**5**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] The mechanism of Pd^0-catalyzed carbohalogenation of alkenes was investigated by computation, see: Y. Lan, P. Liu, S. G. Newman, M. Lautens, K. N. Houk, *Chem. Sci.* **2012**, *3*, 1987 – 1995.