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Direct C–H bond arylation of arenes with aryltin reagents catalysed by palladium complexes†

Hiroshi Kawai, Yasuhiro Kobayashi, Shuichi Oi* and Yoshio Inoue*

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Direct C–H bond arylation of simple arenes with aryltin reagents has been successfully catalysed by $PdCl_2$ in the presence of $CuCl_2$. $CuCl_2$ proved to be an activator for a palladium intermediate as well as an oxidant.

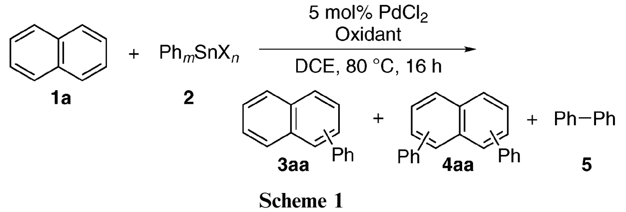
The direct C–H bond arylation of aromatic compounds in the presence of transition metal catalysts has recently gained significant attention as an efficient and useful method of biaryl synthesis.[1] In recent years, significant progress has been made toward the development of direct arylation of a wide variety of substrates using Pd,[2,3] Rh,[4] Ru,[5] and Ir[6] catalysts. For these reactions, the critical step is the C–H bond cleavage and metalation of the aromatic ring with the transition metal complex. Among the several mechanisms that can be proposed for this step, the electrophilic aromatic substitution with a transition metal intermediate can be considered as one of the very effective processes. Accordingly, electrophilic metalations with several transition metal complexes have been proposed in the direct coupling reaction of aromatic compounds.[7] In these reactions, however, the substrates are limited to electron-rich heteroarenes or arenes that possess directing groups in many cases. For substrates that do not possess such features, harsher reaction conditions and/or loading of a large excess of arene substrate are required to obtain satisfactory results. One possible solution to these limitations is to enhance the electrophilicity of the transition metal intermediate. Herein, we describe the direct C–H bond arylation of simple arenes with aryltin reagents in the presence of a palladium catalyst and $CuCl_2$ as the oxidant. Stoichiometric experiments on the reaction mechanism suggested that certain electrophilic active species were generated from $PdCl_2$ and $CuCl_2$.

Initially, using naphthalene (**1a**) as the arene substrate, reactions were carried out to determine the optimal combination of catalyst precursor, aryltin reagent, and oxidant (Scheme 1). Using a combination of $PdCl_2$, tetraphenylstannane, and $CuCl_2$ (Table 1, entry 1), a small amount of the desired α-phenylnaphthalene (**3aa**) was obtained together with a large amount of biphenyl (**5**). Interestingly, substitution of the phenyl groups of tetraphenylstannane with chlorides improved the yields and the cross-coupling selectivities (entries 2–4). In the case of phenyltintrichloride (**2a**, entry 4), the total yield of the cross-coupling products increased to 60% (40% yield of 1 : 1 coupling product **3aa** and 20% yield of 1 : 2 coupling product **4aa**), whereas formation of by-product **5** decreased to 12%. Addition of ligands, such as phosphines or amines, for the palladium catalyst decreased the yield of the cross-coupling products (20–40% yield). In the absence of $CuCl_2$ (entry 5), the reaction did not result in any products, proving that $CuCl_2$ is essential. Other oxidants, such as $Cu(OAc)_2$, $PhI(OAc)_2$, and oxone (entries 6–8 respectively), are not effective for the present reaction. The predominant formation of the α-coupling product strongly suggests that the reaction pathway involves the electrophilic substitution process on the naphthalene ring.

Using the optimized reaction conditions (Table 1, entry 4), phenanthrene (**1b**) was reacted with aryltintrichlorides that possess both electron-donating and -withdrawing groups (**2a–e**) to afford the corresponding 9-arylphenanthrenes **3ba–be** in good yields (Scheme 2). In the case of **1b**, the regioisomer and 1 : 2 coupling products were not observed.

Next, the direct arylations of various arenes with phenyltintrichloride (**2a**) were examined (Table 2). Phenylation of fluoranthene **1c** successfully gave the 1 : 1 (56% yield) and 1 : 2 (38% yield) coupling products as a mixture of regioisomers (entry 1). For the alkyl benzenes, the yields were lower than those of the polycyclic arenes (**1a–c**). Using the same reaction conditions as entry 1, the reaction between tetraline (**1d**) and **2a** afforded the 1 : 1 coupling product **3da** with a yield of merely 20% (entry 2), which can be attributed to the lower electronic density of the aromatic ring. Modifying the reaction conditions (doubling the amounts of **2a** and $CuCl_2$, and dropwise addition of **2a** over 11 h) improved the formations of **3da** (47%) and 1 : 2 coupling product **4da** (14%, entry 3). The reaction of 1,2,3-trimethylbenzene (**1e**) with **2a** gave coupling product **3ea** in a moderate yield of 44% (entry 4). Among the xylene isomers (entries 5–7), meta-isomer **1g** gave product **3ga** in the highest yield as a single regioisomer.

Subsequently, several experiments were carried out in attempt to gain insight into the reaction mechanism. As stated



Scheme 1

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan. E-mail: oishu@aporg.che.tohoku.ac.jp; Fax: +81 (0)22 795 5876; Tel: +81 (0)22 795 5876

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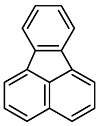
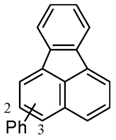
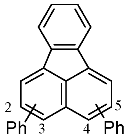
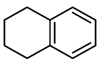
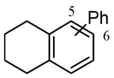
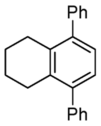
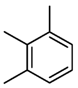
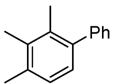
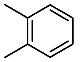
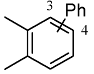
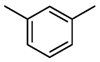
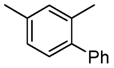
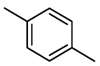
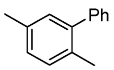
Table 1 Optimization of reaction conditions[a]

Entry	Ph_mSnX_n **2**	Oxidant (mmol)	Yield (%)[b] **3aa** ($\alpha:\beta$)	**4aa**	**5**[c]
1	Ph_4Sn	$CuCl_2$ (2.0)	4 (100 : 0)	0	106
2	Ph_3SnCl	$CuCl_2$ (2.0)	5 (100 : 0)	0	64
3	Ph_2SnCl_2	$CuCl_2$ (2.0)	37 (78 : 22)	13	74
4	$PhSnCl_3$ (**2a**)	$CuCl_2$ (2.0)	40 (78 : 22)	20	12
5	$PhSnCl_3$	None	0	0	0
6	$PhSnCl_3$	$Cu(OAc)_2$ (2.0)	6 (100 : 0)	0	56
7	$PhSnCl_3$	$PhI(OAc)_2$ (1.0)	1 (100 : 0)	0	8
8	$PhSnCl_3$	Oxone (1.0)	0	0	2

[a] Conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $PdCl_2$ (0.025 mmol) in 1,2-dichloroethane (1.0 ml) at 80 °C for 16 h. [b] Determined by GC using internal standard. [c] Based on Sn.

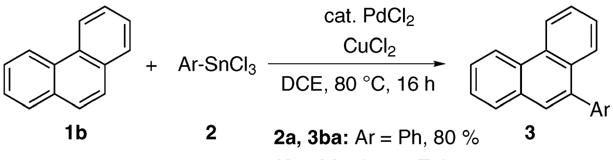
Table 2 Direct C–H phenylation of arenes with phenyltintrichlorides (**2a**)[a]

Entry	Arene (**1**)		Product, yield (%)[b] Mono (**3**)		Di (**4**)	
1		(**1c**)		56 (**3ca**)[d]		38 (**4ca**)[e]
2		(**1d**)		20 (**3da**)[f]		0
3[c]				47 (**3da**)[g]		14 (**4da**)
4[c]		(**1e**)		44 (**3ea**)	—	0
5[c]		(**1f**)		26 (**3fa**)[h]	—	0
6[c]		(**1g**)		38 (**3ga**)	—	0
7[c]		(**1h**)		14 (**3ha**)	—	0

[a] Conditions: arenes (0.5 mmol), $PhSnCl_3$ (**2a**, 1.0 mmol), $PdCl_2$ (0.025 mmol), $CuCl_2$ (2.0 mmol) in 1,2-dichloroethane (1.0 ml) at 80 °C for 16 h. [b] Isolated yield. [c] Modified conditions: **2a** (2.0 mmol, dropwise addition over 11 h), $CuCl_2$ (4.0 mmol). [d] 2- : 3-Ph = 17 : 83. [e] 2,5- : 3,4- : 3,5-Ph = 8 : 44 : 48. [f] 5- : 6-Ph = 100 : 0. [g] 5- : 6-Ph = 86 : 14. [h] 3- : 4-Ph = 76 : 24.

above, in the absence of $CuCl_2$, the reaction between **1a** and **2a** did not result in any coupling products, even when a stoichiometric amount of $PdCl_2$ was employed, which indicates that Pd^{II}/Pd^0 mechanisms including the divalent phenylpalladium and naphthylpalladium complexes shown in Scheme 3 can be ruled out. Secondly, the stoichiometric reaction between $PhPdCl(PPh_3)_2$ and **1a** in the presence of $CuCl_2$ did not afford any coupling product, and therefore the interaction and generation of an active species from the divalent phenylpalladium complex with $CuCl_2$ is unlikely (Scheme 4).[8] Third, addition of TEMPO (20 mol%) as a radical scavenger to the catalytic reaction of **1a** with **2a** did not affect the yield, indicating that the participation of radical species in the catalytic cycle is unlikely. Finally, because the reactions between **1a** and **2a** in the presence of a stoichiometric amount of palladium(0) complexes, such as $Pd(PPh_3)_4$ and $Pd(dba)_2$, did not yield any coupling products, the contribution of $PhPd(SnCl_3)L_2$ formed *via* oxidative addition of **2a** to a palladium(0) complex[9] is also unlikely. From these experimental results, it can be reasoned that $PdCl_2$ reacts with $CuCl_2$ prior to the reaction with **1a** or **2a**. Unfortunately, we do not have clear information about the active species at present, however, chloride-bridged Pd–Cu heterometallic clusters[10] or higher oxidized palladium(IV) species[11,12] can be assumed as possible intermediates. Scheme 5 shows a possible reaction mechanism, in which a palladium(IV) species is assumed as the active species and indicated as $PdCl_4$ for clarity. The resulting active species would be highly electrophilic, and should react with **2a** to give an arylpalladium intermediate **6**. Subsequent electrophilic substitution of **1a** with **6** would form diaryl intermediate **7**, which would then undergo reductive elimination to afford the coupling product and $PdCl_2$. The reaction pathway in the opposite direction, in which electrophilic substitution of **1a** with the palladium(IV) species takes place first and then transmetalation with **2a**, cannot be ruled out. However, homo-coupling products of arene substrates **1**, such as binaphthalene, was not observed in all cases but a small amount of biphenyl was always observed as the by-product, suggesting that the reaction pathway would not involve monoarylpalladium species corresponded to arene substrates.

It is known that arylpalladium(IV) species can be formed *via* reaction of palladium(II) complexes with diaryliodonium salts.[13] Accordingly, the reaction of $[Ph_2I]PF_6$ with **1a** in the presence of a catalytic amount of $PdCl_2$ gave the coupling products with a ratio of regioisomers that is comparable to that of the present reaction (Scheme 6). These results suggest the contribution of the arylpalladium(IV) intermediate to the reaction pathway.



2a, 3ba: Ar = Ph, 80 %
2b, 3bb: Ar = 4-Tol, 80 %
2c, 3bc: Ar = 2-Tol, 76 %
2d, 3bd: Ar = 4-F-C_6H_4, 82 %
2e, 3be: Ar = 4-F_3C-C_6H_4, 82%

Scheme 2 Arylation of phenanthrene with aryltintrichlorides.

$$Pd^{II}Cl_2 \xrightarrow{Ph\text{-}SnCl_3} Ph\text{-}Pd^{II}\text{-}Cl \xrightarrow{ArH} Ph\text{-}Pd^{II}\text{-}Ar \xrightarrow{-Pd^0} Ph\text{-}Ar$$

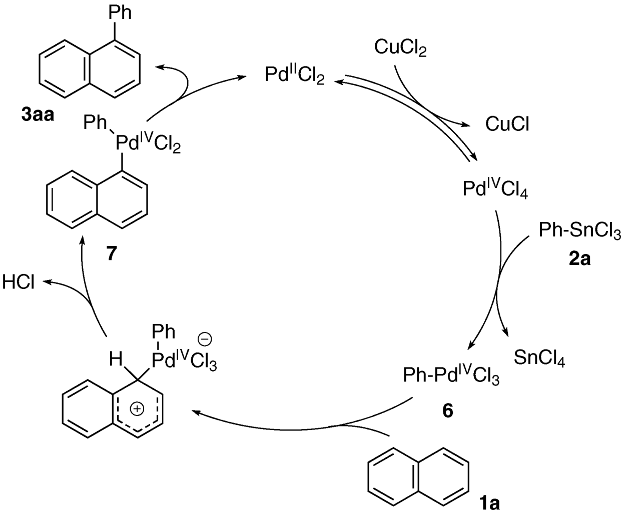
$$Pd^{II}Cl_2 \xrightarrow{ArH} Ar\text{-}Pd^{II}\text{-}Cl \xrightarrow{Ph\text{-}SnCl_3} Ar\text{-}Pd^{II}\text{-}Ph \xrightarrow{-Pd^0} Ar\text{-}Ph$$

Scheme 3

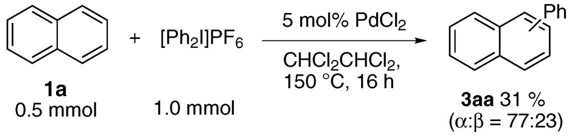
$$Pd^{II}Cl_2 \xrightarrow{Ph\text{-}SnCl_3} Ph\text{-}Pd^{II}\text{-}Cl \xrightarrow[CuCl_2]{ArH} Ph\text{-}[Pd]\text{-}Ar \xrightarrow{-[Pd]} Ph\text{-}Ar$$

[Pd] = active palladium species

Scheme 4



Scheme 5 A possible reaction mechanism.



Scheme 6

In conclusion, we have demonstrated the direct C–H bond arylation of simple arenes with aryltin reagents catalysed by a palladium complex. Although direct evidence for the reaction mechanism has not been obtained, we proposed the contribution of an electrophilic arylpalladium species formed by the combination of aryltintrichlorides, $\mathrm{CuCl_2}$ and $\mathrm{PdCl_2}$.

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7 For example, ref. 2*b*, *c*, *g*, *h*, *n*, *p*, 3*b*, *e*, *g*, *k*, *l*, 5*a*, *b* and *c*.

8 $\mathrm{PhPdCl(PPh_3)_2}$ was used because phosphine-free arylpalladium complexes could not be prepared. The catalytic reaction of **1a** with **2a** (5 mol% of $\mathrm{PdCl_2}$) with $\mathrm{PPh_3}$ (10 mol%) gave the cross-coupling product in 20% (400% based on Pd) yield.

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