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# Palladium-catalyzed arylation of aldehydes with bromo-substituted 1,3-diaryl-imidazoline carbene ligand

Tetsuya Yamamoto [a,b,*], Takuma Furusawa [a], Azamat Zhumagazin [a], Tetsu Yamakawa [a,*], Yohei Oe [b], Tetsuo Ohta [b,*]

[a] Catalysis Group, Sagami Chemical Research Institute, Hayakawa 2743-1, Ayase, Kanagawa 252-1193, Japan
[b] Department of Biomedical Information, Faculty of Life and Medical Sciences, Doshisha University, Kyotanabe, Kyoto 610-0394, Japan

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ABSTRACT

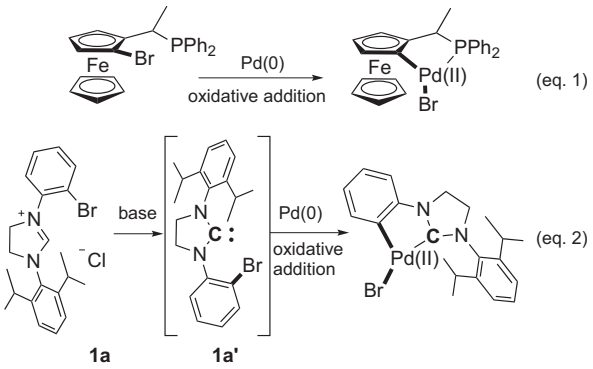
The combination of 0 valent palladium precursor and bromo-substituted 1,3-diaryl-imidazoline carbene ligand precursor such as 1-(2-bromophenyl)-3-(2,6-diisopropylphenyl)-imidazolinium chloride **1a** exhibited high catalytic activity for the 1,2-addition of arylboronic acids to aldehydes including aqueous formaldehyde.



## 1. Introduction

Functionalized benzylic alcohols are important intermediates for bioactive compounds[1] and functionalized materials.[2] So far, these alcohols were synthesized through the nucleophilic addition using aryllithium or magnesium reagents.[3] Recent development in the catalytic 1,2-addition of arylboron compounds to carbonyl compounds with the transition metals such as Rh,[4,5] Pd,[6] Ni,[7] Ru,[8] Pt,[9] Co,[10] Cu[11] or Fe[12] has made possible the preparation of these alcohols with wide range of functional groups. Therefore, this catalytic 1,2-addition is one of the most useful methods for the preparation of various substituted benzylic alcohols, which are difficult to synthesize from the classical nucleophilic addition. Rh catalysts have been chiefly used in this 1,2-addition and various ligands and complexes were developed. In contrast, the reports of other metal catalysts including palladium are relatively rare.

Previously, we demonstrated that the combination of Pd(0) precursors and chiral [2-(2-bromoferrocenyl)ethyl] diphenyphosphine as a ligand catalyzed the asymmetric 1,2-addition of arylboronic acids to aldehydes with moderate catalytic activity, while (2-ferrocenyl)ethyldiphenylphosphine that have no bromine atom was ineffective as a ligand.[6g] This indicates the phosphapalladacycle generated via oxidative addition of C–Br bond to Pd(0) would be catalytically active Pd(II) complex (Scheme 1, eq. 1), as Hu and co-workers independently reported Pd-catalyzed addition using the similar racemic phosphapalladacycle catalyst.[6o] On the other hand, most of NHCs are stronger electron-donating ligands than phosphine ligands.[13] This suggests that replacing the phosphorous ligand with *N*-heterocyclic carbene (NHC) ligand improves the




**Scheme 1.** Strategy of in situ generation of palladacycle catalyst.

* Corresponding authors. Tel.: +81 467 77 4112; fax: +81 467 77 4113 (T.Y.); tel.: +81 467 76 9268 (T.Y.); tel.: +81 774 65 6548; fax: +81 774 65 6789 (T.O.); e-mail addresses: t-yamamoto@sagami.or.jp (T. Yamamoto), t_yamakawa@sagami.or.jp (T. Yamakawa), tota@mail.doshisha.ac.jp (T. Ohta).

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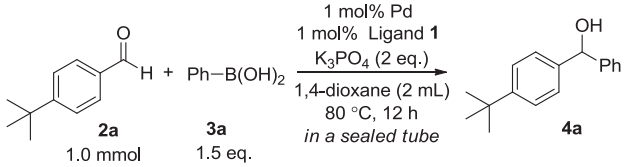
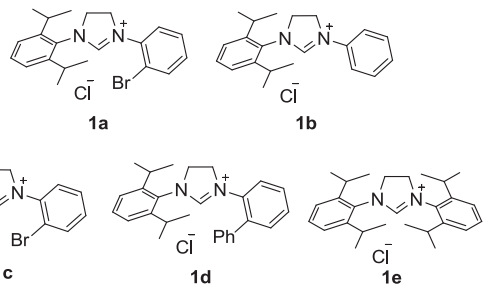
catalytic activity of the phosphapalladacycle-catalyzed 1,2-addition. Therefore, we have envisaged that the cyclometallated NHC Pd(II) complex generates from Pd(0)precursor with imidazolinium salt with bromo-substituted aryl moiety in the side chain such as 1-(2-bromophenyl)-3-(2,6-diisopropylphenyl)-imidazolinium chloride **1a** and this Pd(II) complex must act as a catalyst in the addition (Scheme 1, eq. 2). Herein, we report the Pd-catalyzed 1,2-addition of (hetero)arylboronic acids to aldehydes with imidazolinium salt **1a** as an imidazoline carbene ligand precursor.

## 2. Results and discussion

Table 1 shows the results of Pd-catalyzed 1,2-addition of phenylboronic acid **3a** to 4-*tert*-butylbenzaldehyde **2a** using Pd(0) precursors and imidazolinium salts as NHC ligand precursor. Predictably, the combination of [CpPd($\eta^3$-allyl)] as Pd(0) precursor and imidazolinium salt **1a** provided the corresponding alcohol **4a** in 86% yield (entry 1). In contrast, the replacement of **1a** with **1b**–**e** afforded very low activity (entries 2–5). As for **1b**, **1d** and **1e**, the formed amount of the catalytically active cyclometallated NHC palladium complex is very small due to the difficulty of the insertion of Pd(0) to $sp^2$ and $sp^3$-C–H bond in this reaction condition. Low activity of entry 3 suggests that the bulky phenyl group on NHC is important for the catalysis. $Pd_2(dba)_3$ showed similar effect to [CpPd($\eta^3$-allyl)] (entry 6). Moreover, the combination of [PdCl($\eta^3$-allyl)]$_2$ that acted as Pd(0) precursor and **1a** also exhibited excellent yield (entry 7). Interestingly, the combination of **1b** and [PdCl($\eta^3$-allyl)]$_2$ showed good catalytic activity (entry 8). In this case, [PdCl($\eta^3$-allyl)]$_2$ probably acted not only as Pd(0) precursor but also as Pd(II) species. Thus, the reasonable amount of the catalytically active cyclometallated NHC palladium complex for this reaction would have generated via the insertion of Pd(II) to C–H bond.[14] On the other hand, the combination of **1d** and [PdCl($\eta^3$-allyl)]$_2$ afforded moderate catalytic activity (entry 9): this yield is higher than that with the combination of **1d** and [CpPd($\eta^3$-allyl)] (entry 9). In this reaction condition, there was a possibility that the bromine atom on **1a** is reacted with a phenylboronic acid **3a** to give **1d**. The results in entries 4 and 9 indicates that the Pd species formed with **1d** is not essential active species in the reaction with **1a** though **1d** form in this way. Therefore, the generation of the cyclometallated NHC palladium species through the insertion of C–Br bond would be an important step in this catalytic reaction. The other Pd source, $Pd(acac)_2$, afforded very small yield (entry 10). Hereinafter, all the reactions under various conditions were carried out using the combination of [PdCl($\eta^3$-allyl)]$_2$ and imidazolinium salt **1a** as catalyst.

**Table 1**
Survey of Pd source and NHC ligand in the phenylation of 4-*tert*-butylbenzaldehyde **3a**



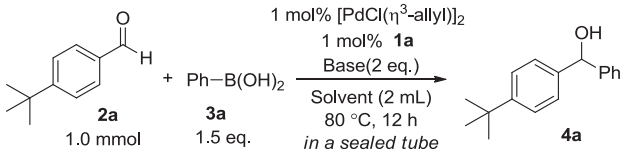




| Entry | Pd(0) precursor | Ligand | Yield (%)[a] |
|---|---|---|---|
| 1 | [CpPd($\eta^3$-allyl)] | **1a** | 86 |
| 2 | [CpPd($\eta^3$-allyl)] | **1b** | 6 |
| 3 | [CpPd($\eta^3$-allyl)] | **1c** | 18 |
| 4 | [CpPd($\eta^3$-allyl)] | **1d** | 19 |
| 5 | [CpPd($\eta^3$-allyl)] | **1e** | <5 |
| 6 | $Pd_2(dba)_3$ | **1a** | 83 |
| 7 | [PdCl($\eta^3$-allyl)]$_2$ | **1a** | 95 |
| 8 | [PdCl($\eta^3$-allyl)]$_2$ | **1b** | 73 |
| 9 | [PdCl($\eta^3$-allyl)]$_2$ | **1d** | 38 |
| 10 | $Pd(acac)_2$ | **1a** | <5 |

[a] Yields were determined by $^1$H NMR.

The optimization of reaction condition of Pd-catalyzed phenylation of 4-*tert*-butylbenzaldehyde **2a** is summarized in Table 2. By the use of $Cs_2CO_3$, CsF and $K_2CO_3$, the corresponding product **4a** was obtained in excellent yields (entries 1–3), while KF and $Na_2CO_3$ were less effective for this addition (entries 4 and 5). THF as a solvent provided a similar yield as 1,4-dioxane (entry 6). The yield was declined in toluene solvent (entry 7) and polar solvents such as *tert*-butyl alcohol and acetonitrile (entries 8 and 9).

**Table 2**
The optimization of reaction condition of Pd-catalyzed phenylation of 4-*tert*-butylbenzaldehyde **2a**




| Entry | Base | Solvent | Yield (%)[a] |
|---|---|---|---|
| 1 | $Cs_2CO_3$ | 1,4-Dioxane | 96 (89)[b] |
| 2 | CsF | 1,4-Dioxane | 96 |
| 3 | $K_2CO_3$ | 1,4-Dioxane | 94 |
| 4 | KF | 1,4-Dioxane | 37 |
| 5 | $Na_2CO_3$ | 1,4-Dioxane | <5 |
| 6 | $Cs_2CO_3$ | THF | 94 |
| 7 | $Cs_2CO_3$ | Toluene | 69 |
| 8 | $Cs_2CO_3$ | *tert*-Butyl alcohol | 51 |
| 9 | $Cs_2CO_3$ | Acetonitrile | 15 |

[a] Yields were determined by $^1$H NMR.
[b] Isolated yield.

The scope and limitation of the Pd-catalyzed phenylation of various aldehydes are listed in Table 3. The reactions proceeded smoothly with aryl aldehydes having various functional groups such as alkyl, alkoxy, alkoxycarbonyl, cyano and chloro groups in excellent yields (entries 1–8). The reaction with 4-bromobenzaldehyde **2j** afforded a mixture of desired alcohol **4j**, benzhydrol and 4-phenylbenzhydrol probably due to the Pd(0) precursor catalyzed side reactions such as Suzuki-Miyaura coupling and debromination before the generation of the palladacycle species (entry 9). Heteroaryl aldehydes such as thiophenecarboxyaldehydes **2k** and **2l** reacted cleanly in satisfactory yields (entries 10 and 11). Also the phenylation of aliphatic aldehyde such as cyclohexanecarbaldehyde **2m** obtained desired alcohol **4m** in 92% yield (entry 12).

The metal catalyzed addition of arylboron compounds to formaldehyde provides the various functionalized mono-arylmethanols, which are key intermediates for bioactive compounds including natural products. Very recently, we reported the first instance of the dinuclear palladacycle catalyzed hydroxymethylation of (hetero)arylboronic acids using aqueous formaldehyde.[6s] Therefore, we examined the present catalyst system of the combination of [PdCl($\eta^3$-allyl)]$_2$ and imidazolinium salt **1a** to the addition of arylboronic acids to aqueous formaldehyde. Table 4 shows the results of the hydroxymethylation of naphthalen-2-