

Letter

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ACS Catal., Just Accepted Manuscript • Publication Date (Web): 03 Sep 2019

Downloaded from pubs.acs.org on September 3, 2019

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# Pd-Catalyzed Dearomative Three-Component Reaction of Bromoarenes with Diazo Compounds and Allylborates.

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**ABSTRACT:** A catalytic dearomative three-component reaction of bromoarenes with TMS-diazomethane and allyl borate was developed. The key of this assembling reaction is the use of a diazo compound to generate a Pd- $\pi$ -benzyl intermediate through a Pd-carbene species. This method allowed for a dearomative functionalization using arenes as limiting reagents. Heteroaryl bromides were also applicable to give dearomatized structures under the reaction conditions.

### Keywords: Dearomatization, Palladium, Alicyclic compounds, Diazo compounds, (Hetero)arenes

Dearomatization is a powerful method to construct structurally complex alicyclic scaffolds from simple and abundant aromatic molecules. Examples of Birch reduction and metal-catalyzed hydrogenation of arenes have found wide use in organic synthesis.<sup>[1]</sup> Meanwhile, dearomative functionalization, which combines the molecular assembling with dearomatization, is recently attracting much attention.<sup>[2]</sup> Several dearomative functionalizations of arenes have been reported, mainly using electronically biased arenes such as phenols,<sup>[3]</sup> indoles,<sup>[4]</sup> and azines.<sup>[5]</sup> In contrast, more general but electronically unbiased arenes such as benzenes are still underdeveloped substrates.<sup>[6]</sup> Existing methods for benzenes often require the use of stoichiometric amounts of metal reagents as well as excess amounts of Recently, substrates. catalytic dearomative functionalizations using arenes as limiting agents have been emerging. For example, the reactions using nitrobenzenes<sup>[7]</sup> as well as phenyl malonates <sup>[8]</sup> were achieved by Trost and You, respectively.

As another catalytic method, the dearomative functionalization of electronically non-biased arenes through a  $\pi$ -benzyl complex<sup>[9]</sup> generated by benzylic bond cleavages is known. In this context, Yamamoto, Bao, and our group have developed dearomative allylation of benzyl chlorides and phosphates (Figure 1A).<sup>[10,11]</sup> These methods hold several benefits: arenes can be used as the limiting reagent, and the reactions can be conducted with catalytic amounts of palladium. The key for these reactions is the generation of a palladium  $\pi$ -benzyl complex as a catalytic intermediate. With this intermediate, allyl nucleophiles undergo transmetalation,

followed by remote C–C bond forming reductive elimination to afford dearomatized products.<sup>[12,13]</sup> However, this dearomatization strategy has so far necessitated benzylic bond cleavage, forming an exocyclic olefin in the product.

We targeted the use of haloarenes as the starting material for the dearomative reaction because they are abundant and also easy to prepare. In order to achieve dearomatization, we focused on the Pd-catalyzed reaction of haloarenes with diazo compounds developed by Van Vranken, Wang, and Barluenga.<sup>[14]</sup> These reactions are thought to proceed through a palladium carbene, which is known to allow for migratory insertion to generate a benzyl-palladium intermediate. We hypothesized that if allyl nucleophiles react with the benzyl complex, we could use haloarenes entry as ubiquitous starting materials for dearomative functionalization, initiated by aromatic C-halogen bond cleavage (Figure 1B). To achieve this reaction, the control of the reaction sequence (of diazo compound addition and then allyl nucleophiles addition) is required. We herein report a Pd-catalyzed dearomative C-C bond formation of bromoarenes.





Figure 1. Dearomative functionalization initiated by a bond cleavage.

We initiated the study by screening conditions using bromonaphthalene 1A with TMS-diazomethane (2) and allyl borates **3** (Table 1). An initial attempt using  $PPh_3$  as a ligand delivered the desired product 4A in low yield along with Suzuki-Miyaura coupling product 5A (entry 1). Encouraged by this result, we modified the ligand. To deliaht, the use electron-donating our of triarylphosphines as well as a trialkylphosphine improved both the reaction yield and reaction selectivity (entries 2-4). The sterically demanding monophosphines and bidentate phosphines dropped the yield of 4A but generated **5A** as a major product (entries 5–7). Increasing the reaction temperature and using 1,4dioxane gave a better result (entry 8). Pd<sub>2</sub>(dba)<sub>3</sub> was a better catalyst precursor than Pd(OAc)<sub>2</sub> (entry 9). Because further improvement was difficult by changing parameters,<sup>[15]</sup> we then tested the effect of additives. Among several inorganic and organic bases, we found that potassium fluoride had a positive effect, producing **4A** in good yield (entry 10).<sup>[16]</sup> Although sodium fluoride was also effective, cesium fluoride resulted in a poor product yield (entries 11 and 12). Furthermore, it was found that allyl-Bpin is also capable in this reaction to give 4Aa in 70% yield (entry 13). Finally, we identified the optimized conditions: Pd<sub>2</sub>(dba)<sub>3</sub>, L1, and KF in 1,4dioxane at 70 °C for 12 h. It is noteworthy that the reaction conditions give the desired product using eguimolar amounts of bromoarenes TMS-1, diazomethane (2), and allyl borate 3.

#### Table 1. Conditions screening



entr y	[Pd]	ligand	additive	<b>4A</b> /% <sup>a</sup>	<b>5A</b> /% <sup>a</sup>
1	Pd(OAc) <sub>2</sub>	$PPh_3$	-	18	16
2	Pd(OAc) <sub>2</sub>	P(p-anis) <sub>3</sub>	-	30	2
3	Pd(OAc) <sub>2</sub>	L1	-	35	0
4	Pd(OAc) <sub>2</sub>	P <sup>n</sup> Bu₃	-	25	0
5	Pd(OAc) <sub>2</sub>	Xphos	_	2	17
6	Pd(OAc) <sub>2</sub>	dppf <sup>b</sup>	-	5	15
7	Pd(OAc) <sub>2</sub>	DPEphos <sup>b</sup>	-	2	21
8 <sup>c,d</sup>	Pd(OAc) <sub>2</sub>	L1	-	46	0
9 <sup>c,d</sup>	Pd <sub>2</sub> (dba)	L1	-	48	0
10 <sup>c,d</sup>	3 Pd <sub>2</sub> (dba)	11	KF	81	0
	3				
11 <sup>c,d</sup>	Pd <sub>2</sub> (dba)	L1	NaF	65	0
12 <sup>c,d</sup>	3 Pd <sub>2</sub> (dba) 3	L1	CsF	7	0
13 <sup>c,d,</sup> e	Pd <sub>2</sub> (dba) <sup>3</sup>	u	KF	70	0

Conditions; 1A (0.20 mmol), 2A (0.20 mmol), 3a (0.20 mmol), [Pd] (5 mol%), ligand (20 mol%), additive (2.0 equiv), solvent (1 mL), 60 °C, 12 h. [a] NMR yield [b] 10 mol% of ligand [c] 70 °C [d] 1,4-dioxane instead of toluene [e] Allyl-Bpin was used instead of 2. K<sub>2</sub>CO<sub>3</sub> (3.0 equiv) was added.

With the optimized conditions in hand, the substrate scope of the reaction was examined (Scheme 1). Owing to the instability of some of the products, <sup>1</sup>H NMR yields are shown in Scheme 1.<sup>[15]</sup> Both guaternary and tertiary carbons could be constructed on naphthyl bromides (4A-4C). Several functional groups such as ether (4D), acetate (4E), amines (4F) were tolerated in the reaction. An acenaphthene core was also smoothly dearomatized to afford the corresponding product 4G in good yield. Because of the higher aromatic stability of benzenes compared with naphthalenes, benzenes have been recognized as challenging substrates for the dearomative functionalizations. Previously, our dearomative reaction of benzyl phosphates was also suffered from this limitation.<sup>[11]</sup> However, pleasingly, the present

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methodology was exceptional, as a wide variety of bromobenzenes were applicable. C4-alkylated bromobenzenes were able to be converted to the corresponding products in moderate to good yields (4H, 4I), however, bulky substituents at the C4 position resulted in low yields. We also observed good functional group tolerance for bromobenzenes, as nitrile (4J), ester (4K), indoles (4L) and acetal (4N) were compatible. Even a hydroxy group was tolerated to form 40 in 40% yield. meta-Disubstituted molecules were also transformed to alicyclic compounds (4P, 4Q) in good yields.[17] The reaction of 2-fluoro bromotoluene generated dearomatized compound 4R in good yield in a 78:22 diastereoisomeric ratio. At this stage, unfortunately only simple allyl borates can be used, and other substituted allyl boron species gave low yield of products.

Delightfully, it was found that this method was applicable to five-membered heteroaryl bromides as well. For thiophene bromides, the products were generated as a mixture of diastereoisomers in an approximate 1:1 ratio (**4S–4V**). A pyridine-bearing bromothiophene **1U** could also be dearomatized smoothly. Moreover, furans were found to be amenable to the reaction conditions to form dihydrofuran cores in **Scheme 1.** Substrate scope<sup>*a*</sup> good yield with good diastereoselectivity (**4W** and **4X**). It is noteworthy that these heterocyclic products were more stable compared to dearomatized compounds derived from benzenes.

In order to showcase the utility of the Pd-catalyzed method, we conducted a one-pot reaction<sup>[18]</sup> starting from simple arenes (Scheme 2A). NBS bromination of thiophene 6 quantitatively proceeded to give **1S** with exclusive regioselectivity. After removing the solvent, the dearomative reaction successfully provided heterocycle 4S in 55% yield over two steps. Furthermore, we succeeded in demonstrating the viability of the method by functionalizing a drug-molecule (Scheme 2B). To this end, brominated ticlopidine<sup>[19]</sup> 7 was subjected to the present reaction to generate the corresponding dearomatized compound 8 in 49% isolated yield, albeit with low diastereoselectivity. This ticlopidine derivative 7 possesses highly reactive functional groups such as a tertiary amine and aryl chloride, but they did not influence the reaction efficiency. With these results, we expect that the further applications of the method to access otherwise novel chemical space would accelerate drug discovery.



Conditions; **1** (0.40 mmol), **2** (1.0 equiv), **3** (1.0 equiv), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.5 mol %), **L1** (20 mol %), KF (2.0 equiv), 1,4-dioxane (2 mL), 70 °C, 12 h. <sup>*a*</sup> <sup>1</sup>H NMR yields are shown because of the instability of products during purification process. <sup>*b*</sup> 5 mol % of Pd(OAc)<sub>2</sub> was used instead of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. <sup>*c*</sup> **2** (1.3 equiv), **3** (1.3 equiv).

**Scheme 2.** (A) A one-pot operation and (B) the reaction of a pharmaceutical substrate



After this catalytic dearomatization method, we could perform further functionalizations of the cyclic core (Scheme 3). For example, a crude mixture of **4M** was directly subjected to the diimide reduction conditions to give **1**,4-cyclohexadiene **9** in good yield over two steps. In this reaction, the allyl moiety was also reduced to propyl. The obtained compound **9** was further converted by *m*CPBA to furnish epoxide **10** in 28% yield, along with another diastereoisomer in 23% yield. Furthermore, oxidation of sulfur containing heterocycle **4S** generated the corresponding alkenyl sulfone **11** in 49% yield (2 steps).

#### Scheme 3. Derivatization of products



In summary, we have developed a dearomative threecomponent reaction of bromoarenes. This method could be applied to a variety of aromatic systems ranging from simple benzenes to five-membered heteroarenes. Of note, the protocol is catalytic, and aromatic substrates can be used as a limiting reagent. This allows the derivatization of drug molecules by late-stage structural modifications. Further studies to expand the generality of this dearomative functionalization utilizing other diazo compounds as well as nucleophilic participants are ongoing in our laboratory.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectroscopic data for compounds including  $^1\text{H-},\,^{13}\text{C}$  NMR spectra (PDF)

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#### ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP19H02726 (to J.Y.), JP18H04661 (Hybrid Catalysis), and JP19K15573 (to K.M.). The Materials Characterization Central Laboratory in Waseda University is acknowledged for the support of HRMS measurement. We would like to thank National Institute of Health Sciences in Japan for the support of NMR measurement.

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(15) For details, see Supporting Information.

(16) Although the exact effect is still unclear yet, ligand exchanging of Pd–Br species to Pd–F to accelerate transmetalation of allyl borate is supposed to be one of the factors for the improvement.

(17) These two products were detected by crude NMR, however, it was found that they smoothly rearomatized. For details, see Supporting Information.

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