Pd-Catalyzed 1,4-Carboamination of Bromoarenes with Diazo Compounds and Amines

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ABSTRACT: A palladium-catalyzed 1,4-carboamination of bromoarenes with diazo compounds and amines was developed. This reaction proceeds through a palladium-carbene that then generates a π-benzylpalladium intermediate, forming *ipso* C–C and *para* C–N bonds on haloarenes in a regioselective manner. The nature of this reaction as a multi-component reaction and its high regioselectivity can lead to a rapid construction of a range of *para*-substituted anilines. The successful application of this transformation to the rapid synthesis of an antitumor agent demonstrates its synthetic utility.

Aryl amines are often embedded in a wide range of functional molecules such as bioactive compounds and π-electron organic materials. *para*-Substituted aryl amines are particularly important because a *para*-amino group can often influences the electronic and physical properties of molecules. Metal-catalyzed C–N bond formations of haloarenes[1,2] or aryl borons[3] with amines are representative methods to access *para*-substituted anilines. However, *para*-selective preparation of the corresponding arene starting material is often problematic, resulting in a mixture of isomers. Although *para*-selective C–H functionalization of arenes has been recently developed, the site selectivity depends on the existence of a bulky or a directing group.[4]

A C–C and C–N bond-forming difunctionalization, namely carboamination, of aromatic molecules is an additional option enabling the rapid synthesis of densely functionalized aryl amines.[5,6] A Catellani-type reaction is the most popular example, achieving carboamination of haloarenes in a catalytic manner (Figure 1A).[5] For instance, a Pd/norbornene catalyst can promote the three-component reaction of haloarenes with hydroxylamine derivatives and alkenes to give 1,2-carboaminated arenes (*ipso* C–C and *ortho* C–N formation). Apart from this 1,2-carboamination, the other positional carboaminations of haloarenes are currently unknown.[7] Based on the mechanism of known 1,2-carboaminations, the development of the other carboaminations of arenes would require a conceptually novel reaction design.

On the other hand, the unique reactivity of π-benzyl palladium species has been unveiled over the past two decades, achieving various bond formations at the C4 position on the aromatic ring.[8,9] Among these examples, Bao and Tian have independently developed the C4 amination of benzyl chlorides and ammoniums, where a π-benzyl–Pd intermediate reacts with amines to form C–N bonds at the C4 position of arenes (Figure 1B).[10] In this context, our group recently reported a dearomative 1,4-difunctionalization of bromoarenes with diazo species and carbon nucleophiles.[11] Merging the C4 C–N bond formation of π-benzyl–Pd species and our three-component reaction, we envisaged that a 1,4-carboamination of bromoarenes with diazo species and amines could be realized (Figure 1C). Our mechanistic hypothesis is as follows: a bromoarene reacts with a diazo species and a palladium catalyst to generate an aryl–Pd^{II}-carbene[12] followed by a π-benzyl–Pd^{II} intermediate, which in turn reacts with an amine to afford a 1,4-carboaminated arene. In this mechanistic scenario, it is required to suppress the undesired Buchwald–Hartwig amination as well as the N–H bond insertion of the amines with the carbene species.[13] With these considerations in mind, we herein report the development of a Pd-catalyzed 1,4-carboamination of bromoarenes with diazo compounds and amines.

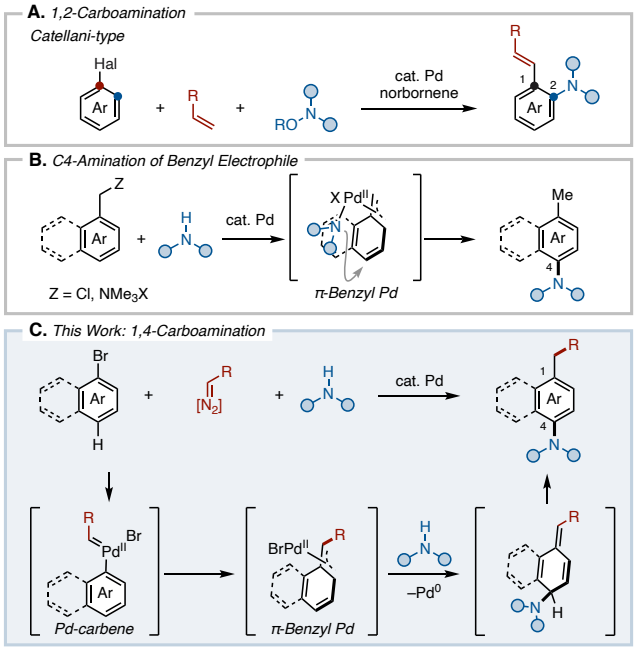
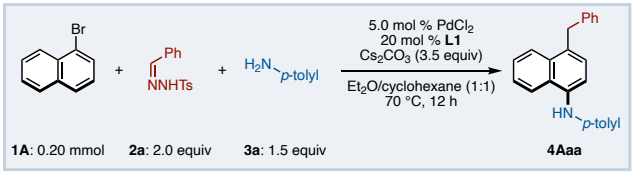


Figure 1. Carboamination of haloarenes. (A) 1,4-Carboamination (B) C4-Amination of benzyl electrophiles (C) 1,4-Carboamination.

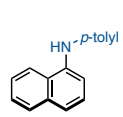
Our study commenced by screening conditions using 1-bromonaphthalene (**1A**), *N*-tosylhydrazone **2a**, and *p*-toluidine

(**3a**) under the influence of a palladium catalyst (Table 1). In our previous studies, Pd/DPEphos as well as Pd/**L1** (**L1**: 4-dimethylaminophenyl)diphenylphosphine) efficiently catalyzed the dearomative 1,4-difunctionalization of bromoarenes.[11] Therefore, as our initial attempt, we conducted the reaction of **1A**, **2a**, and **3a** in the presence of Pd/DPEphos catalyst and Cs_2CO_3 in toluene at 70 °C. However, we obtained only the undesired Buchwald–Hartwig amination product **5Aa** (Table 1, Entry 1). In contrast, Pd/**L1** catalyst completely changed this chemoselectivity, delivering the desired carboamination product **4Aaa** in 43% yield (Table 1, Entry 2). With this finding, we evaluated various solvents using the Pd/**L1** catalyst. A change to THF resulted in 4% yield of **4Aaa** (Table 1, Entry 3). Cyclohexane (*c*-hex) and Et_2O were applicable solvents, however, they were found to be poorly reproducible (Table 1, Entries 4 and 5). When we employed a mixed solvent system using Et_2O/cyclohexane, 65% yield of **4Aaa** was obtained with good reproducibility (Table 1, Entry 6). An Et_2O/toluene system did not improve the yield of **4Aaa** (Table 1, Entry 7). Using this Et_2O/cyclohexane mixed-solvent system, the effect of base was next examined. Cs_2CO_3 was found to be the best base in this reaction (Table 1, Entry 6). The use of K_2CO_3 did not afford **4Aaa**

Table 1. Condition screening



Entry	ligand	base	solvent	**4Aaa**/%	**5**/%
1	DPEphos	Cs_2CO_3	toluene	0	59
2	**L1**	Cs_2CO_3	toluene	43	0
3	**L1**	Cs_2CO_3	THF	4	0
4	**L1**	Cs_2CO_3	*c*-hex	20–32	0
5	**L1**	Cs_2CO_3	Et_2O	48–59	0
6	**L1**	Cs_2CO_3	Et_2O/*c*-hex	61–65	0
7	**L1**	Cs_2CO_3	Et_2O/toluene	40	0
8	**L1**	K_2CO_3	Et_2O/*c*-hex	0	0
9	**L1**	KOH	Et_2O/*c*-hex	42	0
10	**L1**	NaH	Et_2O/*c*-hex	0	0
11	PPh_3	Cs_2CO_3	Et_2O/*c*-hex	61	0
12	**L2**	Cs_2CO_3	Et_2O/*c*-hex	61	0
13	P^nBu_3	Cs_2CO_3	Et_2O/*c*-hex	1	0
14	SIPr[b]	Cs_2CO_3	Et_2O/*c*-hex	25	3



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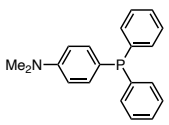
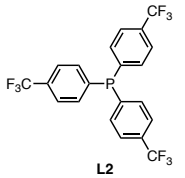


L1



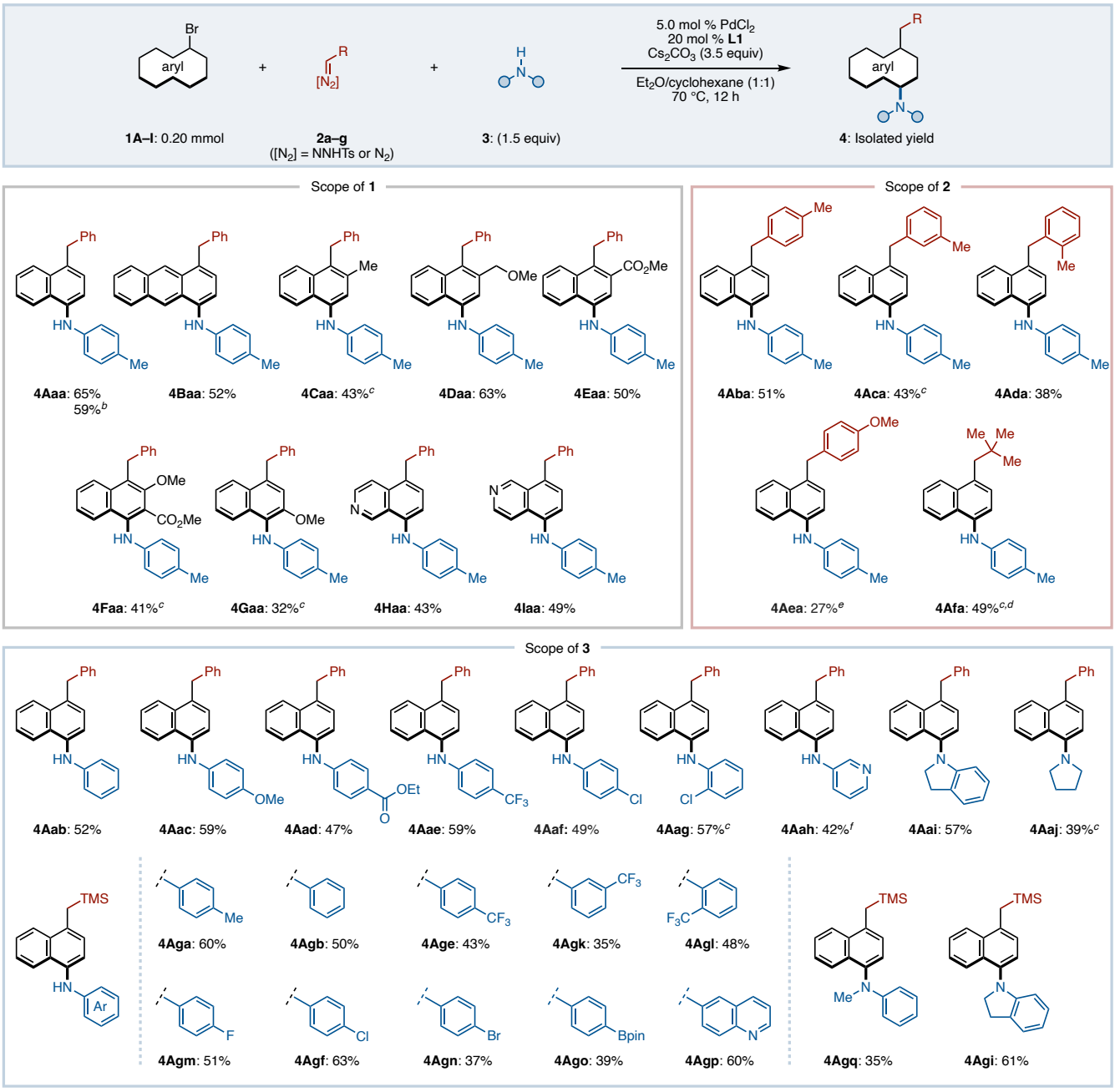
L2

[a] Conditions: **1A** (0.20 mmol), **2a** (0.40 mmol), **3a** (0.30 mmol), $PdCl_2$ (5.0 mol %), ligand (20 mol %), base (0.70 mmol), solvent (2.0 mL), 70 °C, 12 h. [b] SIPr–Pd-PEPPSI was used instead of $PdCl_2$.

(Table 1, Entry 8). Inexpensive KOH was an applicable base to produce **4Aaa** (Table 1, Entry 9). NaH afforded many byproducts and no desired product **4Aaa** (Table 1, Entry 10).[11b] Finally, the influence of the ligand was examined. PPh_3 as well as less electron-donating triarylphosphine **L2** gave **4Aaa** in comparable yields to **L1** (Table 1, Entries 11 and 12). Highly electron-donating ligands such as tributylphosphine resulted in poor yields of **4Aaa** and recovery of **1A** (Table 1, Entry 13). *N*-Heterocyclic carbene ligand delivered **4Aaa** in 25% yield together with 3% yield of **5Aa** (Table 1, Entry 14). Through this survey, we identified the conditions using $PdCl_2$, **L1**, and Cs_2CO_3 in Et_2O/cyclohexane at 70 °C as optimized conditions. Of note, varying these conditions did not affect the site-selectivity, obtaining no other positional isomers in each entry.

With these optimized conditions in hand, the substrate scope of this reaction was explored (Scheme 1). These reaction conditions were found to be applicable to π-extended aromatic systems. 1-Bromonaphthalene and anthracene were smoothly reacted to produce the corresponding 1,4-carboaminated products (**4Aaa**, **4Baa**).[14] This catalytic system also allowed for naphthyl triflate instead of bromide, affording **4Aaa** in a comparable yield. C2-Substituents on naphthalene such as methyl, methoxymethyl and methoxycarbonyl did not significantly influence the reaction progress, giving 1,4-carboaminated products **4Caa**, **4Daa**, and **4Eaa** in 43%, 63%, and 50% yields, respectively. Regarding substituents at the C3 position, desired 1,4-carboaminated products **4Faa** and **4Gaa** were generated with a perfect site selectivity, albeit in slightly lower yields. These results implied that the positional pattern of substituents does not influence on this 1,4-selectivity. Isoquinolines were also carboaminated in moderate yields (**4Haa**, **4Iaa**). Next, the scope of *N*-tosylhydrazones were surveyed: *para*-, *meta*-, and *ortho*-tolyl groups were installed by using the corresponding *N*-tosylhydrazones (**4Aba**, **4Aca**, **4Ada**). However, the reaction using *N*-tosylhydrazone bearing a *p*-anisyl group (**2e**) resulted in poor yields of **4Aea**. In this case, self-insertion of **2e** occurred (See the SI for details). The use of the sodium salt of **2e** suppressed this undesired reaction, yielding **4Aea** in 27%. In addition to arylmethyl groups, a *t*-amyl group was successfully installed onto the naphthalene ring (**4Afa**). As for the scope of amines, a wide range of amines were found to be useful. Anilines bearing both electron-donating and electron-withdrawing substituents were smoothly assembled into their corresponding products **4Aab**, **4Aac**, **4Aad**, and **4Aae**. A C–Cl bond on aniline was tolerated (**4Aaf**, **4Aag**). 3-Aminopyridine was also reacted to give **4Aah** in 42% yield. Cyclic amines such as indoline and pyrrolidine were able to participate in this 1,4-carboamination, delivering **4Aai** and **4Aaj** in 57% and 39% yields, respectively. TMS-diazomethane (**2g**) was also applicable instead of *N*-tosylhydrazones under the modified conditions using K_3PO_4 as a base (see the SI for details). By using **2g**, the capability of amines was also investigated. The results of the synthesis of **4Aga** and **4Agb** indicate the comparable reactivity of **2g** to *N*-tosylhydrazones. Less nucleophilic anilines such as trifluoromethyl and fluoro-substituted anilines gave the corresponding products **4Age**, **4Agk**, **4Agl**, and **4Agm** in moderate yields. Chloro- and bromoanilines were applicable to the present conditions without the loss of the halogen atom (**4Agf**, **4Agn**). Moreover, boronate was tolerated, giving **4Ago** in 39% yield. In this case, no Suzuki–Miyaura coupling as well as catalyst-free coupling of aryl–Bpin with **2g**, (Barluenga–Valdés coupling),[15] occurred. 6-Aminoquinoline was successfully introduced on a naphthalene core in 60% yield (**4Agp**). For the reaction using **2g**, secondary anilines were also suitable substrates, as *N*-methylaniline and indoline were successfully coupled to give **4Agq** and **4Agb**.

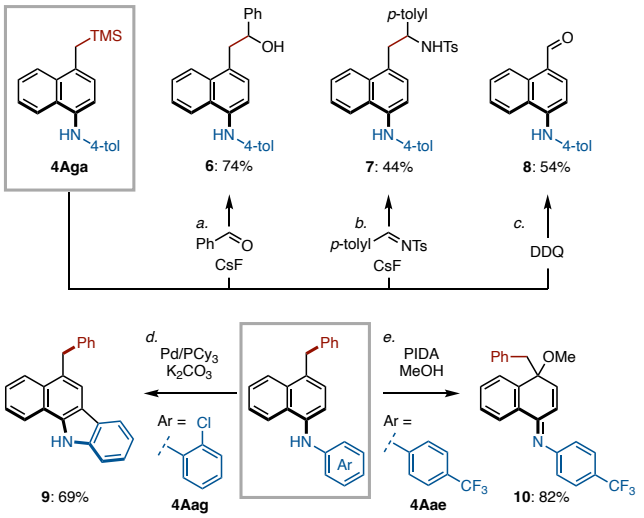
Scheme 1. Substrate scope[a]



[a] Conditions using *N*-tosylhydrazones **2a**–**2f**: **1** (0.20 mmol), **2** (0.40 mmol), **3** (0.30 mmol), $PdCl_2$ (5.0 mol %), **L1** (20 mol %), Cs_2CO_3 (0.70 mmol), Et_2O/cyclohexane (1.0 mL/1.0 mL), 70 °C, 12 h. Conditions using TMS-diazomethane **2g**: **1** (0.20 mmol), **2g** (0.20 mmol), **3** (0.30 mmol), $PdCl_2$ (5.0 mol %), **L1** (20 mol %), K_3PO_4 (0.70 mmol), Et_2O/cyclohexane (1.0 mL/1.0 mL), 70 °C, 36 h. [b] 1-Naphthyl–OTf was used instead of naphthyl bromide. [c] 80 °C. [d] Toluene (2.0 mL) as a solvent. [e] Sodium salt of **2e** was used. [f] 36 h.

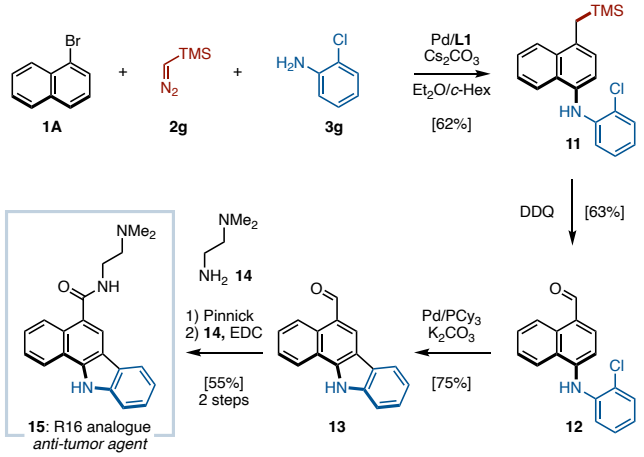
We then demonstrated that the carboaminated products can be converted into various functional groups. By using the nature of the benzylsilyl groups as a versatile synthetic platform, carboaminated product **4Aga** was assembled with various electrophilic components (Scheme 2). For example, in the presence of fluoride activator, **4Aga** was reacted with benzaldehyde to give homobenzyl alcohol **6** in 74% yield.[16] A similar transformation using *N*-tosylimine produced tosylamide **7**. Moreover, subjecting **4Aga** to DDQ oxidation conditions successfully delivered aldehyde **8** in an acceptable yield. Other types of derivatizations were also demonstrated by using **4Aag** and **4Aae**. Subjecting *o*-chloroaniline **4Aag** to Fagnou's intramolecular C–H arylation conditions[17] afforded benzocarbazole **9** in 69% yield. Furthermore, the aminonaphthalene core of **4Aae** was converted under oxidative dearomatization conditions using PIDA in methanol, giving **10** in a good yield.[18]

Scheme 2. Derivatization of carboaminated products **4.**



We next applied the developed reaction to the synthesis of an anti-tumor reagent, R16 analogues **15** (Scheme 3).[19] The synthesis started with the present 1,4-carboamination of bromoarenes **1A**, TMS-diazomethane (**2g**), and chloroaniline (**3g**) to give carboaminated product **11** in 62% yield. Oxidation of **11** by DDQ gave aldehyde **12**, followed by intramolecular C–H arylation to afford formylbenzocarbazole **13** in a good yield over 2 steps. Finally, Pinnick oxidation of **13**, followed by amide formation with **14** completed the synthesis of R16 analogue **15**. Compared to the previous synthesis of **15** which required over 10 steps, our carboamination strategy enabled for the rapid synthesis of **15** in 5 steps from commercially available starting materials.

Scheme 3. Rapid synthesis of anti-tumor agent 15.



In summary, we have developed a Pd-catalyzed 1,4-carboamination of bromoarenes with diazo compounds and amines. The site selectivity was remarkably high, producing 1,4-carboaminated products without depending on the substituent patterns and the electronic nature of the parent bromoarenes. The demonstration of various derivatization of products and rapid synthesis of an anti-tumor agent show this transformation's synthetic utility. Further studies to develop other 1,4-difunctionalizations based on the understanding of the reaction mechanism is currently undergoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available.

Experimental procedures and spectroscopic data for compounds including ^{1}H-, ^{13}C, and ^{19}F-NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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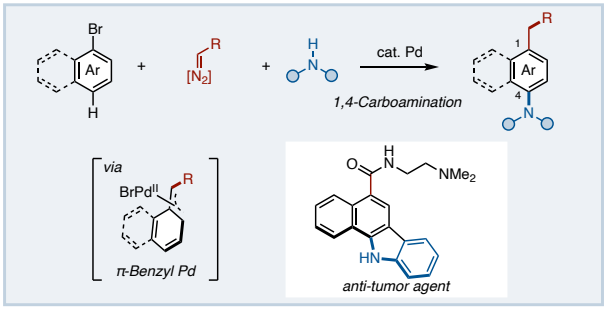
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