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Pd-Catalyzed Intramolecular Chemoselective C(sp2)−H and C(sp3)−H Activation of *N*-Alkyl-*N*-arylanthranilic Acids

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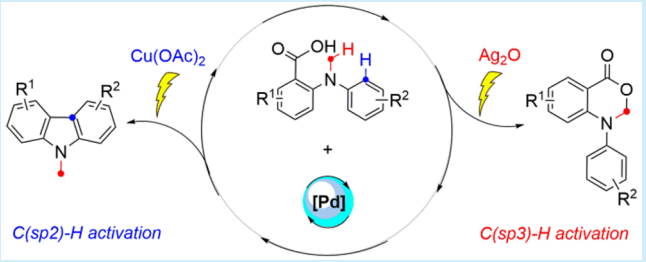
Supporting Information

ABSTRACT: A controllable palladium-catalyzed intramolecular C−H activation of *N*-alkyl-*N*-arylanthranilic acids has been developed. The methodology allows selective synthesis of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones and carbazoles from the same starting materials and palladium catalyst. The selectivity is controlled by the oxidant. Silver oxide promotes C(sp3)−H activation/C−O cyclization to provide 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones, while copper acetate contributes to C(sp2)−H activation/decarboxylative arylation to afford carbazoles. This protocol is demonstrated by its wide substrate scope and good functional group tolerance.

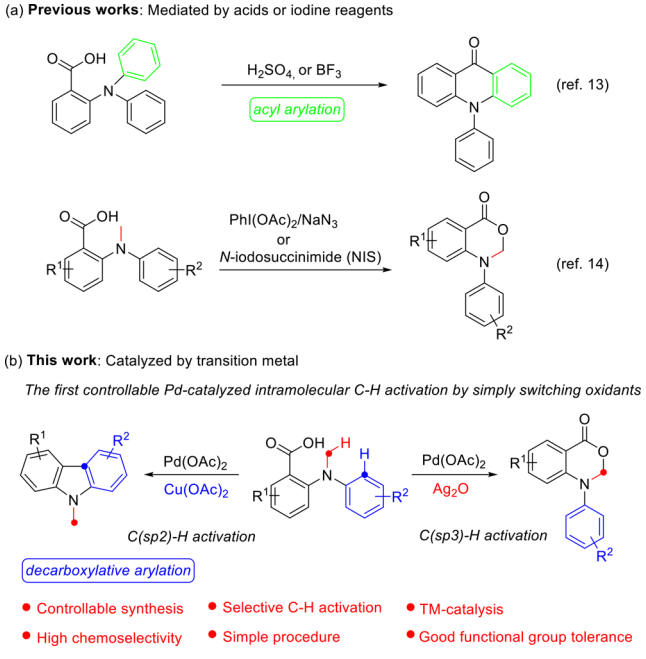


The development of efficient synthetic methodologies for the construction of heterocycles is one of the most important topics in organic synthesis. As one of the convenient and efficient synthetic protocols for the formation of complex molecules from simple starting materials, transition-metal-catalyzed C−H functionalization has received much attention, and many novel methodologies have been developed in the past decades.[1] Although significant achievements have been made, transition-metal-catalyzed controllably chemoselective C−H functionalization remains challenging.[2]

Carboxylic acids are versatile feedstock chemicals, which can be used for the preparation of numerous complex molecules.[3] Recently, considerable effort has been devoted to the development of catalytic strategies for the synthesis heterocycles by the intramolecular C−H functionalization of carboxylic acids. For example, Wang reported a Pd-catalyzed C−H activation of phenylacetic acids for the formation of benzofuranones.[4] Gilmour developed a photocascade catalysis method for the synthesis of coumarins from *E*-cinnamic acids.[5] In addition, the intramolecular C−H lactonization of 2-arylbenzoic acids has been investigated, and some efficient synthetic protocols, such as transition-metal catalysts including Pd,[6] Cu,[7] Ag,[8] and transition-metal-free catalysis,[9] photocatalysts,[10] and electrochemical synthesis[11] have been developed. However, the successful examples of carboxylic acids in the intramolecular C−H functionalization are very limited. The development of new types of carboxylic acids for the catalytic synthesis of heterocycles by intramolecular C−H functionalization is greatly desired.

As ones of important acids, anthranilic acids, which combined with an amino and a carboxyl functional group, have been widely used in organic synthesis.[12] However, the reactivity of the intramolecular C−H functionalization of *N*,*N*-disubstituted anthranilic acids is rarely investigated, possibly due to the difficulty in controlling the functionalization of multiple C−H bonds. The reported examples are shown in Scheme 1a. One is acid-mediated intramolecular acyl arylation of *N*,*N*-disubstituted anthranilic acids for the synthesis of *N*-arylacridones.[13]

Scheme 1. Strategies for Intramolecular C−H Functionalization of *N*,*N*-Disubstituted Anthranilic Acids



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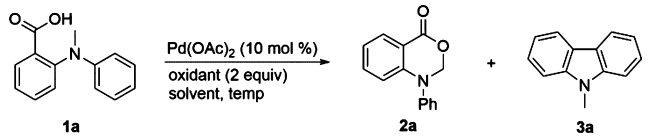
Another is the iodine reagent mediated intramolecular cyclization of *N*,*N*-disubstituted anthranilic acids for the preparation of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones,[14] but these reported reactions are limited to intramolecular C−H functionalization of *N*,*N*-disubstituted anthranilic acids, and transition-metal-catalyzed C−H activation remains undeveloped.

Given the structure of *N*,*N*-disubstituted anthranilic acids, we became interested in the *N*-alkyl-*N*-arylanthranilic acids, which contain both C(sp3)−H bonds and C(sp2)−H bonds in the same molecule.[15] We envisioned that the selective C(sp3)−H and C(sp2)−H activation might occur by choosing the suitable transition-metal catalysts. Furthermore, we might realize controllable synthesis of two completely different heterocycles from the same starting materials based on transition-metal-catalyzed intramolecular selective C−H activation. Therefore, the exploration of the controllable synthesis from transition-metal-catalyzed intramolecular selective C−H activation of *N*-alkyl-*N*-arylanthranilic acids is highly desirable but remains highly challenging.

Herein, we report a novel and efficient palladium-catalyzed intramolecular cyclization of *N*-alkyl-*N*-arylanthranilic acids for the synthesis of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones and carbazoles. To the best of our knowledge, this is the first transition-metal-catalyzed intramolecular C−H activation of *N*,*N*-disubstituted anthranilic acids and is also the first controllable palladium-catalyzed intramolecular chemoselective C−H activation of *N*-alkyl-*N*-arylanthranilic acids by simply switching the oxidants. The methodology allows highly selective synthesis of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones and carbazoles from the same starting materials and palladium catalyst (Scheme 1b).

In our initial study, we chose *N*-methyl-*N*-phenylanthranilic acid (**1a**) as the model starting material to examine the reaction. As shown in Table 1, the reaction of compound **1a** in the presence of 10 mol % of $Pd(OAc)_2$ with 2 equiv of BQ in DMAc at 120 °C for 24 h afforded the product **2a** and **3a** in 11% and 8% yield, respectively (Table 1, entry 1). Although the oxidants TBHP and $K_2S_2O_8$ provided the products **2a** and **3a** in low yields (Table 1, entries 2 and 3), AgOAc gave the product **2a** in 49% yield with 15% yield of **3a** (Table 1, entry 4). Further screening of silver salts revealed Ag_2O as the best one to selectively give **2a** in 45% yield as the major product with a very small amount of product **3a** (Table 1, entry 5). Interestingly, the use of $Cu(OAc)_2$ as an oxidant selectively provided **3a** as the major product with 40% yield under the same reaction conditions (Table 1, entry 6). We used $Cu(OAc)_2$ as the oxidant to optimize other reaction conditions. After optimization of the solvent and reaction temperature, it shows the optimal ones are DMAc and 130 °C, respectively (Table 1, entries 7−10). We found that 3 equiv of $Cu(OAc)_2$ improved the yield of product **3a** to 57% (Table 1, entry 11). Furthermore, extension of the reaction time to 72 h greatly improved the yield of **3a** to 71% (Table 1, entry 13). In order to obtain a high yield of **2a**, we used Ag_2O as an oxidant to optimize the reaction conditions. Although the product **2a** can be formed in a large range of reaction temperatures tested between 120 and 50 °C, the optimal reaction temperature is 70 °C, giving **2a** in 80% yield when the catalyst loading was decreased to 5 mol % (Table 1, entries 14−19). The solvent screening shows DMAc is the optimal one (Table 1, entries 19−21). To our delight, the yield of product **2a** was further improved to 85% when 4 mL of DMAc was used (Table 1, entry 22).

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

				yield[b] (%)	
entry	oxidant	solvent	temp (°C)	**2a**	**3a**
1	BQ	DMAc	120	11	8
2	TBHP	DMAc	120	9	16
3	$K_2S_2O_8$	DMAc	120	3	2
4	AgOAc	DMAc	120	49	15
5	Ag_2O	DMAc	120	45	2
6	$Cu(OAc)_2$	DMAc	120	3	40
7	$Cu(OAc)_2$	DMF	120	6	12
8	$Cu(OAc)_2$	DMSO	120	27	7
9	$Cu(OAc)_2$	DMAc	130	2	46
10	$Cu(OAc)_2$	DMAc	140	4	40
11[c]	$Cu(OAc)_2$	DMAc	130	3	57
12[c,d]	$Cu(OAc)_2$	DMAc	130	3	63
13[c,e]	**$Cu(OAc)_2$**	**DMAc**	**130**	**3**	**71**
14	Ag_2O	DMAc	100	58	6
15	Ag_2O	DMAc	80	67	6
16	Ag_2O	DMAc	60	79	trace
17	Ag_2O	DMAc	50	59	trace
18[f]	Ag_2O	DMAc	60	66	trace
19[f]	Ag_2O	DMAc	70	80	trace
20[f]	Ag_2O	DMF	70	53	3
21[f]	Ag_2O	dioxane	70	39	3
22[f,g]	**Ag_2O**	**DMAc**	**70**	**85**	**trace**

[a]Unless otherwise noted, the reactions were performed in a sealed tube with **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), and oxidant (0.4 mmol) in solvent (2.0 mL) at 120 °C for 24 h under N_2. [b]Isolated yields. [c]$Cu(OAc)_2$ (0.6 mmol) was used. [d]48 h. [e]72 h. [f]$Pd(OAc)_2$ (0.01 mmol) was used. [g]4 mL of DMAc was used.

With the optimized conditions in hand (entry 22), we explored the substrate scope of the C(sp3)−H activation/C−O cyclization process for the preparation of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones **2**. The results are summarized in Scheme 2. A variety of *N*-alkyl-*N*-arylanthranilic acids can be used in the present reaction to give the corresponding cyclization products in good to high yields. Both electron-donating groups and electron-withdrawing groups on the aryl rings are tolerated in this reaction. For example, it provided the product **2b** with a methyl group on the aryl ring in 83% yield when compound **1b** was treated in the presence of 5 mol % of $Pd(OAc)_2$ with 2 equiv of Ag_2O in DMAc at 70 °C for 24 h. Under the same reaction conditions, the product **2e** having a chloro group on the same position was formed in 81% yield. The steric effect of the substituent R^2 was observed. Although *meta*- and *para*-substituted cyclization products **2l** and **2m** were obtained in high yields, the *ortho*-substituted product **2k** was formed in 55% yield. It was found that the *N*-alkyl-*N*-arylanthranilic acids with a substituent on the two aryl rings proceeded well to give the corresponding cyclization products in high yields (Scheme 2, products **2q**−**u**). In addition, when the R^3 group was extended to other substituents except H, such as a methyl and a phenyl group, the reactions also afforded the corresponding product **2v** and **2w** in moderate to good yields.

We also examined the substrate scope of the C(sp2)−H activation/C−C cyclization process for the synthesis of

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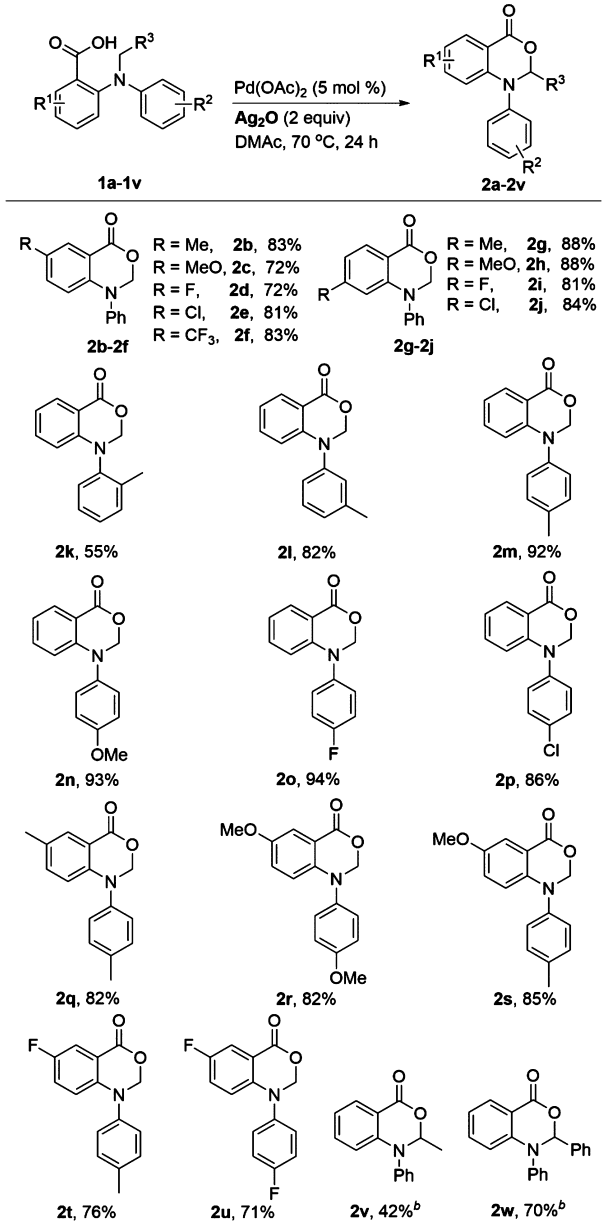
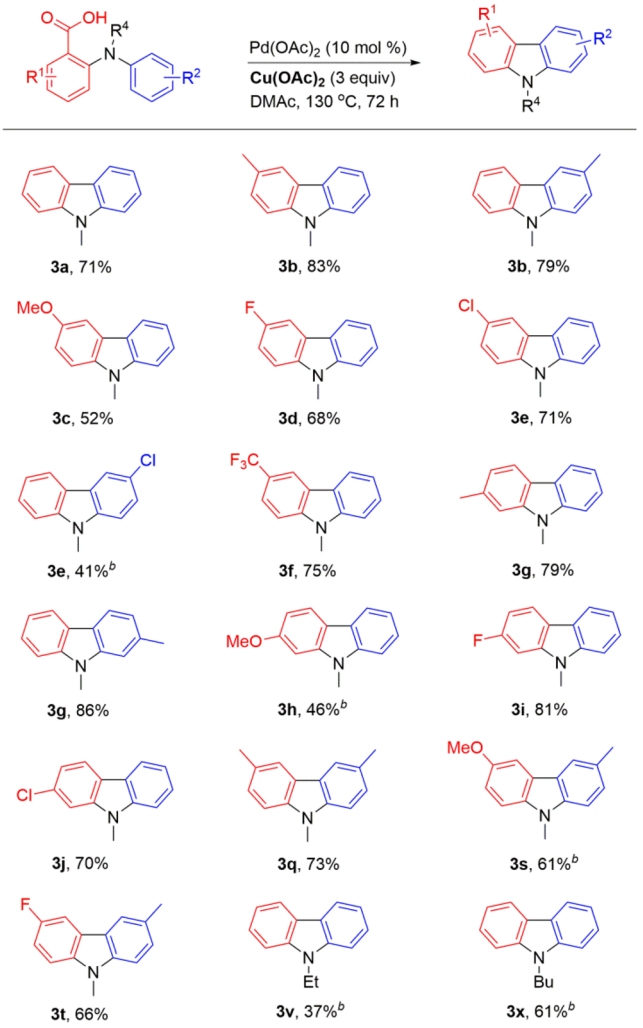
Scheme 2. Scope of 1,2-Dihydro-(4*H*)-3,1-benzoxazin-4-ones[a]



[a]The reactions were performed in a sealed tube with **1** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), and Ag_2O (0.4 mmol) in DMAc (4.0 mL) at 70 °C for 24 h under N_2. Isolated yields are shown. [b]100 °C.

carbazoles **3**. As shown in Scheme 3, various carbazoles were prepared in moderate to high yields by switching the oxidant from Ag_2O to $Cu(OAc)_2$. For example, the palladium-catalyzed intramolecular cyclization of compound **1a** with 3 equiv of $Cu(OAc)_2$ in DMAc at 130 °C for 72 h afforded carbazole **3a** in 71% yield. For the monosubstituted compounds, the substituent R^1 with the electron-donating groups and electron-withdrawing groups gave the corresponding carbazoles in moderate to high yields (Scheme 3, products **3b**−**j**). The substituent R^2 with an electron-withdrawing group provided lower yield compared to the compound with an electron-donating group (Scheme 3, product **3e** with 41% yield vs **3b** with 79% yield). We also tested the compounds with two substituents, and the present method gave the corresponding products in good yields (Scheme 3,

Scheme 3. Scope of Carbazoles[a]



[a]The reactions were performed in a sealed tube with **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), and $Cu(OAc)_2$ (0.6 mmol) in DMAc (2.0 mL) at 130 °C for 72 h under N_2. Isolated yields are shown. [b]$Pd(OAc)_2$ (0.03 mmol) was used.

products **3q**,**s**,**t**). Furthermore, we found that the carbazoles **3v** and **3x** were formed in moderate yields when the substituent R^4 was an ethyl and a butyl group, respectively.

Based on the above experimental results and related literature reports, a possible mechanism has been proposed in Scheme 4. Treatment compound **1a** with silver oxide forms a silver carboxylate complex **A**.[16] Transmetalation with a Pd^{II} complex generates species **B**, which gives a seven-membered cyclopalladated species **C** by an intramolecular C(sp3)−H activation.[6,17] Subsequently, reductive elimination takes place to afford product **2a** and a Pd^0 species. The Pd^{II} species is regenerated by oxidation of the Pd^0 species for the catalytic cycle. When copper acetate is used in the reaction, an arylcopper species **E** is generated by copper-mediated decarboxylation of compound **1a**.[18] Then transmetalation with a Pd^{II} complex followed by an intramolecular C(sp2)−H activation forms species **G**. Finally, reductive elimination occurs to provide product **3a** and a Pd^0 species, which can be reoxided to the Pd^{II} complex by copper acetate.

In conclusion, we demonstrate an efficient method for the controllable synthesis of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-

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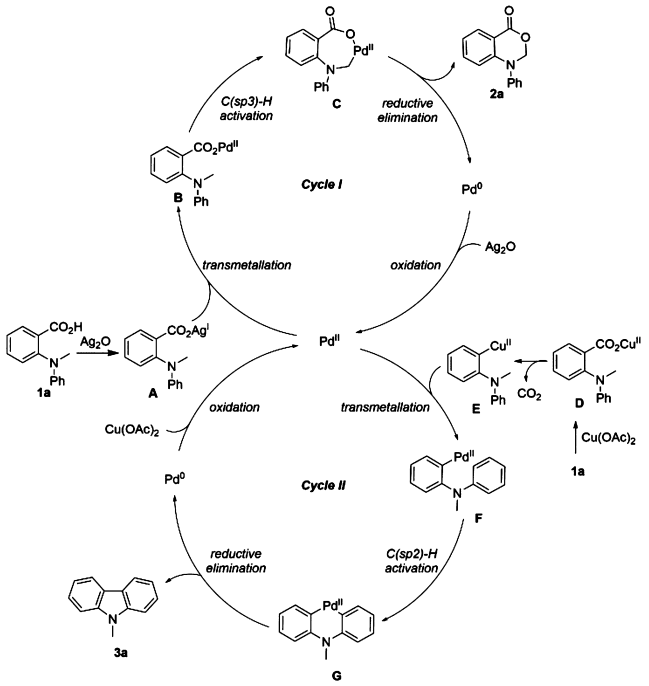
Scheme 4. Proposal Mechanism



ones and carbazoles by palladium-catalyzed intramolecular chemoselective C(sp2)−H and C(sp3)−H activation of *N*-alkyl-*N*-arylanthranilic acids. The high selectivity is controlled by simply switching the oxidants. This novel methodology shows wide substrate scope and good functional group tolerance and provides the corresponding 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones and carbazoles in good to high yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03976.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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