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Palladium-Catalyzed Intramolecular C–H Amination in Water

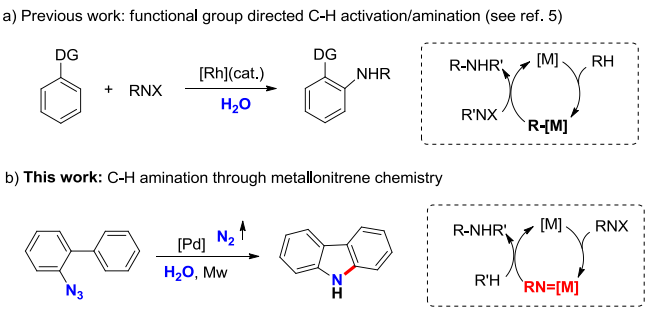
Lizheng Yang,[a] Hao Li,[a] Haifei Zhang[a] and Hongjian Lu*[a]

Dedication ((optional))

Abstract: Palladium (II) catalysis is effective for intramolecular C–H amination in water. With 2-azidobiphenyls as substrates, the reaction can efficiently provide various carbazoles with N_2 as the sole by-product. The reaction shows a high functional group tolerance and can be used in the synthesis of several natural carbazole alkaloids. The catalytic process is promoted by water and the reaction is inefficient in organic solvents that were investigated.

Water as a reagent has attracted much attention in organic synthesis owing to cost, safety, and environmental concerns.[1] It has unique physicochemical properties, such as polarity, amphiphilicity and hydrogen bonding capability, which influence the selectivity and reactivity of chemicals.[2] Water has been widely used as a solvent in organic reactions such as pericyclic, multicomponent, Wittig, olefin metathesis and bioorthogonal reactions.[1] Metal-catalyzed C−H functionalization, which allows simplification and abbreviation of synthetic procedures has become one of most powerful and facile approaches to construction of complex molecules.[3] Recently, methods of metal-catalyzed C−H functionalization using water as solvent have emerged as a research field of immense interest.[2a,4] Difficulties associated with such reactions are the poor solubility of the metal catalysts and substrates in water, and the inhibition of reactions by water, which are known to prevent many metal catalytic reactions.[2a] Despite these challenges, methods of metal catalyzed C–C, C–halogen or C–O bond formations *via* breaking of C–H bonds in aqueous systems have been developed.[4] Metal catalyzed C–H amination protocols with water as solvent are not currently well known (Scheme 1),[5] although in organic solvents such protocols have been proved to be a powerful approach to the construction of valuable amine derivatives from non-functionalized starting materials.[6,7]

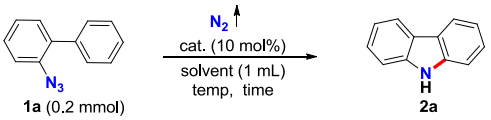
Recently, our group has studied the metal catalyzed C–H amination with water as a reagent.[5] We have developed Rh(III) catalyzed C–H activation/amination with aryl azides[5a] and *t*-butyl 2,4-dinitrophenoxycarbamate[5b] as sources of the amine (Scheme 1a). Water plays a key role in these reactions,[1d,1g,8] and the catalytic processes are inefficient in common organic solvents. Besides the C–H activation chemistry,[6] C–H amination through metallonitrene chemistry is another important direction for functionalization of C–H bonds.[7] These catalytic protocols however proceed in organic solvents and must avoid water and air because of the high reactivity of metallonitrene species. Herein we report intramolecular C–H amination reactions in water through a palladium-based metallonitrene chemistry (Scheme 1b).[9]



Scheme 1. Metal Catalyzed C–H Amination Using Water as the Solvent.

Following Driver's reports on Rh catalysis[10a] and Plietker's recent report on Fe-catalyzed[10b] carbazole and indole synthesis,[10,11] we began our investigation by screening reaction catalysts in water (Table 1). With 2-azidobiphenyls as the substrates, the reactions may proceed in non-oxidative conditions with N_2 as the sole byproduct,[12] forming functionalized carbazoles which are of interest due to their various biological activities.[13] Initial results with different metal catalysts using 2-azidobiphenyl (**1a**) as the substrate are shown in entries 1-15. With these catalysts, the desired carbazole (**2a**) was either not formed or produced in low yield. When commercially available $Pd(OAc)_2$ was used as the catalyst however, **2a** was obtained in moderate yield (entry 16). We speculated that microwave irradiation might accelerate the reaction rate through a more efficient energy transfer, and in fact a 56% yield of **2a** was achieved within 3 hours by 200 W microwave irradiation (entry 18). When the catalyst loading and the reaction time were increased, the yield of **2a** was enhanced to 90% (entry 19). The yield decreased at lower or higher reaction temperatures (entries 20 and 21), and no **2a** was produced in the absence of the palladium catalyst (entry 22). The reaction was inefficient in all common organic solvents investigated (entries 23-27). The yield of desired product increased when adding water to organic solvents (entries 28-31).

Table 1. Optimization of Reaction Conditions.[a]



entry	cat.	solvent	time (h)	temp (°C)	yield [a](%)
1	$Ni(OEt)_2Cl_2$	H_2O	24	110	<5
2	$NiCl_2$	H_2O	24	110	<5
3	$Ni(OTf)_2$	H_2O	24	110	<5
4	$Fe(acac)_3$	H_2O	24	110	0
5	$FeBr_2$	H_2O	24	110	<5
6	$Fe(OAc)_2$	H_2O	24	110	<5
7	$Cu(OTf)_2$	H_2O	24	110	<5

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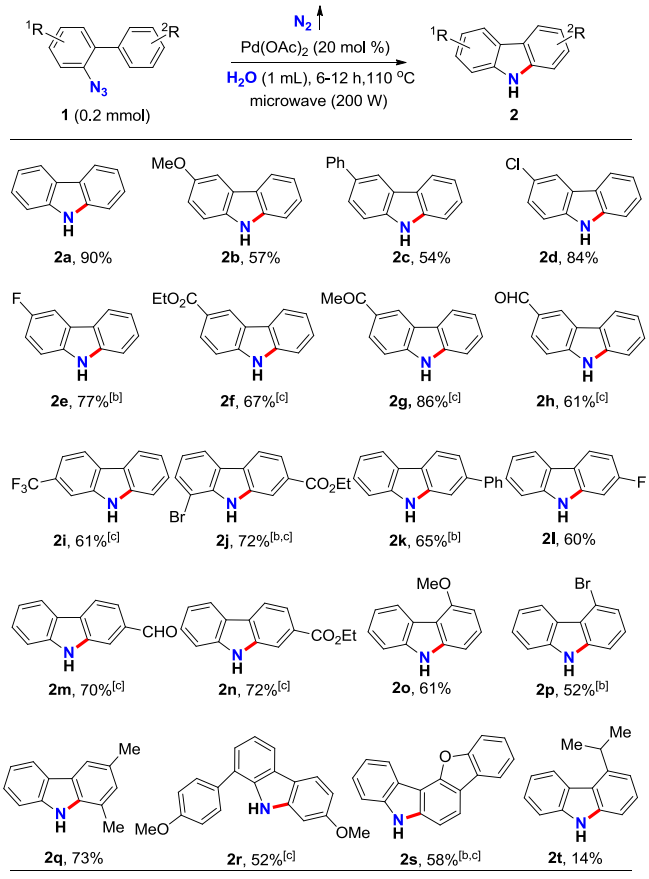
8	$Cu(OAc)_2$	H_2O	24	110	0
9	$CuBr_2$	H_2O	24	110	<5
10	$IrCl_3$	H_2O	24	110	<5
11	$[Ir^*CpCl_2]_2$	H_2O	24	110	18
12	$RuCl_3$	H_2O	24	110	<5
13	$Rh_2(OAc)_4$	H_2O	24	110	<5
14	$Pd(OTf)_2$	H_2O	24	110	10
15	$Pd(NO_3)_2$	H_2O	24	110	10
16	$Pd(OAc)_2$	H_2O	24	110	48
17	$Pd(OAc)_2$	H_2O	3	110	10
18[b]	$Pd(OAc)_2$	H_2O	3	110	56
19[b,c]	**$Pd(OAc)_2$**	**H_2O**	**6**	**110**	**90**
20[b]	$Pd(OAc)_2$	H_2O	6	120	61
21[b,c]	$Pd(OAc)_2$	H_2O	6	90	60
22[b]	/	H_2O	24	110	0
23[b]	$Pd(OAc)_2$	toluene	3	110	<5
24[b]	$Pd(OAc)_2$	DCE	3	110	10
25[b]	$Pd(OAc)_2$	DMF	3	110	<5
26[b]	$Pd(OAc)_2$	MeCN	3	110	<5
27[b]	$Pd(OAc)_2$	EtOH	3	110	<5
28	$Pd(OAc)_2$	CH_3CN/H_2O[d]	3	110	15
29	$Pd(OAc)_2$	$EtOH/H_2O$[d]	3	110	48
30	$Pd(OAc)_2$	DCE/H_2O[d]	3	110	42
31	$Pd(OAc)_2$	toluene $/H_2O$[d]	3	110	10

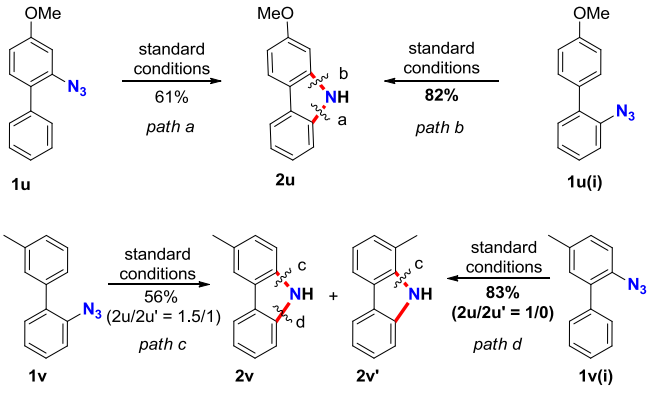
[a] Yield of **2a** was determined by crude ^{1}HNMR using CH_2Br_2 as the standard. [b] Using microwave (200 W). [c] Catalyst (20 mol%). [d] v/v = 1/1.

Table 2. Scope of 2-Azidobiphenyls **1**.[a]



[a] Isolated yield. [b] Azide **1** (0.15 mmol). [c] Time 12 h.

With the optimized reaction conditions, we explored the scope and generality of the reaction and obtained the results shown in Table 2. Various substrates with substituents in the azidophenyl ring of 2-azidobiphenyl (**1**) were examined. Azidophenyl groups bearing electron-donating and -withdrawing groups in the *para*-position are tolerated, forming the desired carbazoles in good to high yields (**2a-2h**). *Meta*- and *ortho*-substitution of the azidophenyl ring (**2i**-**2j**) failed to affect the efficiency of the reaction, and various functional groups such as alkoxy, halides, esters, ketone, and aldehyde are also well tolerated. Subsequently, we explored substrates with substituents in the phenyl ring of 2-azidobiphenyls (**1**). We found that *para*-substituted derivatives which contain functional groups commonly used in organic synthesis were successfully aminated, giving the desired products in good yield (**2j-n**), and compounds with *ortho*- and *meta-sub*stituents in the phenyl ring (**2o-q**) also reacted satisfactorily. The sterically hindered azide (**1r**) was an acceptable substrate, giving a moderate yield of the corresponding carbazole (**2r**) and a benzofuran-containing derivative could be converted to *5H*-benzofuro[3,2-c]carbazole (**2s**) in moderate yield. When 2-azido-2'-isopropyl-1,1'-biphenyl was used as substrate, the desired product **2t** was isolated in 14% yield and small amount of benzylic C−H amination product was also observed based on mixture ^{1}H NMR.[14]



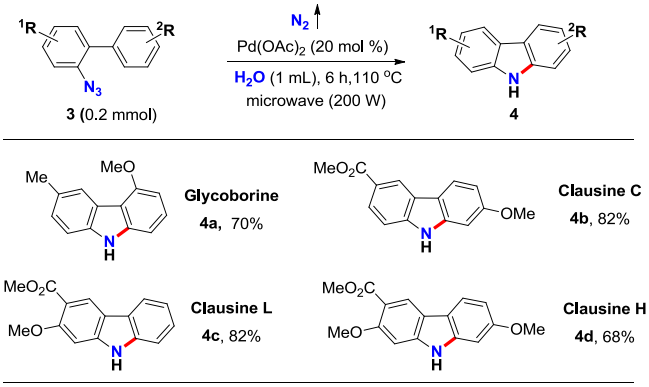
(Standard conditions: Azide **1** (0.2 mmol), $Pd(OAc)_2$ (20 mol %), microwave (200 W), H_2O (1 mL), 6 h,110 °C)

Scheme 2. Different Synthetic Pathways.

Carbazoles can be obtained efficiently by designed synthetic routes based on the reactivity and selectivity of different substrates (Scheme 2). For example, the azide **1u**, with a methoxyl group in the azidophenyl moiety produced under standard reaction conditions the desired carbazole (**2u**) in 61% yield (path a). In contrast, the azide **1u**(**i**), an isomer of **1u** bearing an unsubstituted azidophenyl moiety, gave the desired product **2u** in 82% yield (path b). For the substrates with *meta*-substituents in the phenyl moiety of 2-azidobiphenyls there are regioselectivity concerns. For example, the azide **1v** produces isomers **2v** and **2v'** with low regioselectivity (path c), but when the isomer **1v**(**i**) with *para* methyl groups substituted in the azidophenyl moiety, was used as the substrate, the desired product **2v** was formed exclusively (path d). These observations

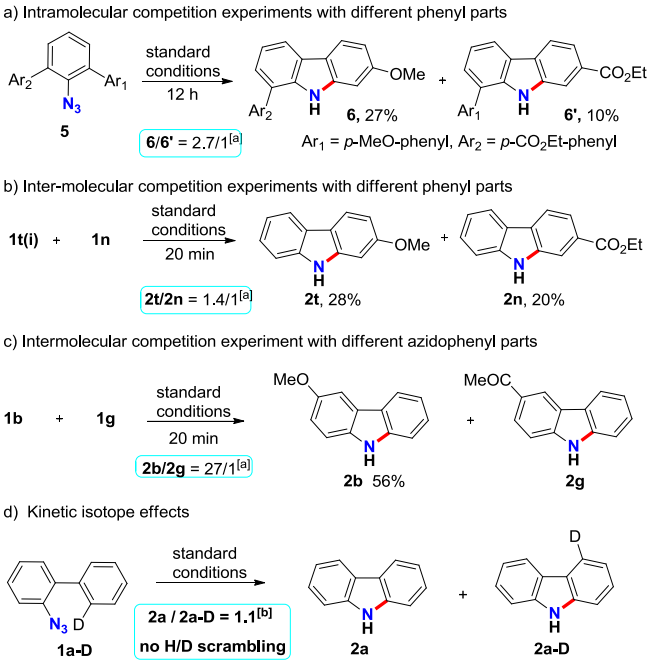
can be used to find suitable synthetic pathways to differently functionalized carbazoles.

Table 3. Synthesis of carbazole alkaloids **4**.[a]



[a] Isolated yield.

Since carbazole alkaloids exhibit a broad range of significant biological activities,[13] we applied this Pd catalysis to the synthesis of natural compounds (Table 3). Four natural carbazole alkaloids, glycoborine, and clausine **C**, **L** and **H** can be obtained in good to high yields from the appropriate substrates (**4a**-**d**).



[a] The ratio of products was determinated by mixture 1H NMR. [b] P_H/P_D was determinated by both ^{1}H NMR and GCMS.

Scheme 3. Competitive Experiments.

A series of experiments were performed to delineate the mechanism of the reaction (Scheme 3). Intra- and inter-molecular competitive experiments of substrates containing different phenyl moieties were performed (Schemes 3a and 3b), and revealed that C–H bonds in the methoxyl substituted phenyl moiety are slightly preferred in the reaction. An intermolecular competitive experiment of the substrates with different azidophenyl moieties was performed. Interestingly, the reaction rate of the substrate was largely influenced by the substituted groups in the azidophenyl moiety (Scheme 3c). These results show that the electric properties of the azidophenyl moiety greatly influence the rate-determining step. Monodeuterated 2-azidobiphenyl (**1a-D**) was used as the substrate to perform the reaction under standard conditions (Scheme 3d). A kinetic isotope effect of 1.1/1 was observed with no H/D scrambling,[10h,11c] indicating that C–H bond cleavage may occur after the product-determining step of this Pd-catalyzed reaction.[11]

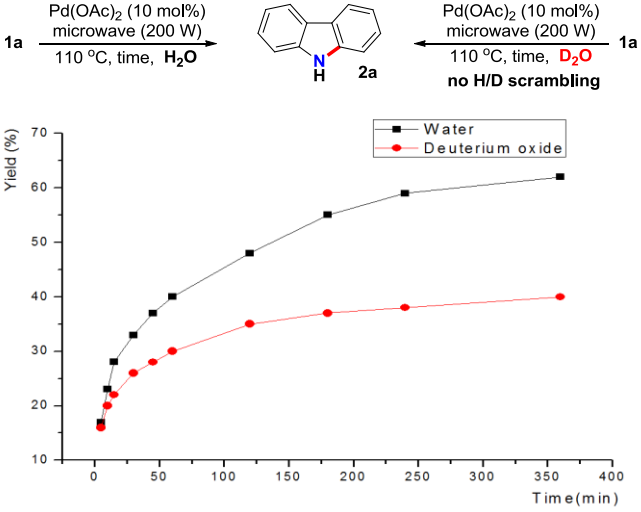


Figure 1. Performed in Water or Deuterium Oxide.

Finally, we conducted the experiments in water or in deuterium oxide separately (Figure 1). The rate of the reaction in water was faster than that in deuterium oxide, suggesting that water probably is involved in the catalytic cycle. In addition, no H/D scrambling was observed when the reaction was performed in deuterium oxide.

In conclusion, we have developed a new way to access Pd(II) nitrenes in water from azides. This methodology allows rapid access to carbazoles with water as both reagent and solvent and N_2 as the sole by-product. Good functional group tolerance is a characteristic of this catalytic procedure, which can be used to produce natural carbazole alkaloids, such as glycoborine, and clausine **C**, **L** and **H** efficiently. Although the role of water remains unclear, the catalytic process is promoted by water and the reaction is inefficient in all common organic solvents investigated. Efforts are underway to further expand the applications of metallonitrene chemistry in water.

Experimental Section

A 10 mL microwave tube with a magnetic stir bar was charged with $Pd(OAc)_2$ (9.0 mg, 20 mol%), distilled water (1.0 mL) and corresponding azide (0.20 mmol). The reaction mixture was stirred for 6 or 12 hours at 110 °C under microwave conditions (200 W). After cooling, the biphasic solution was diluted with 5 mL of water and 10 mL of CH_2Cl_2 and separated. The aqueous phase was extracted with an additional 3 × 10 mL of CH_2Cl_2. The organic phase was dried over Na_2SO_4 and filtered. The crude reaction mixture was purified by silica gel column chromatography with n-Hexane/EtOAc as an eluent to give the desired product.

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Keywords: C–H amination •arylazide•palladium catalysis •water•carbazole

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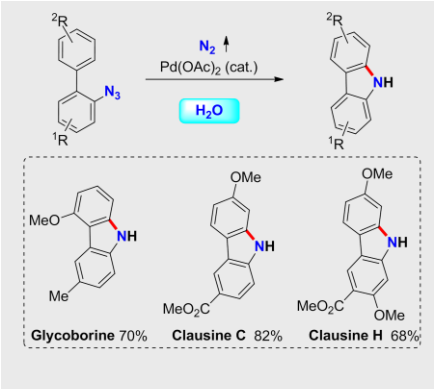
COMMUNICATION

Palladium-catalyzed intramolecular C–H amination reaction of 2-azidobiphenyls using water as solvent is described. This reaction shows a high functional group tolerance and is applicable to the synthesis of several natural carbazole alkaloids.



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Palladium-Catalyzed Intramolecular C–H Amination in Water