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SITE-SELECTIVE C–H FUNCTIONALIZATION OF CARBAZOLES

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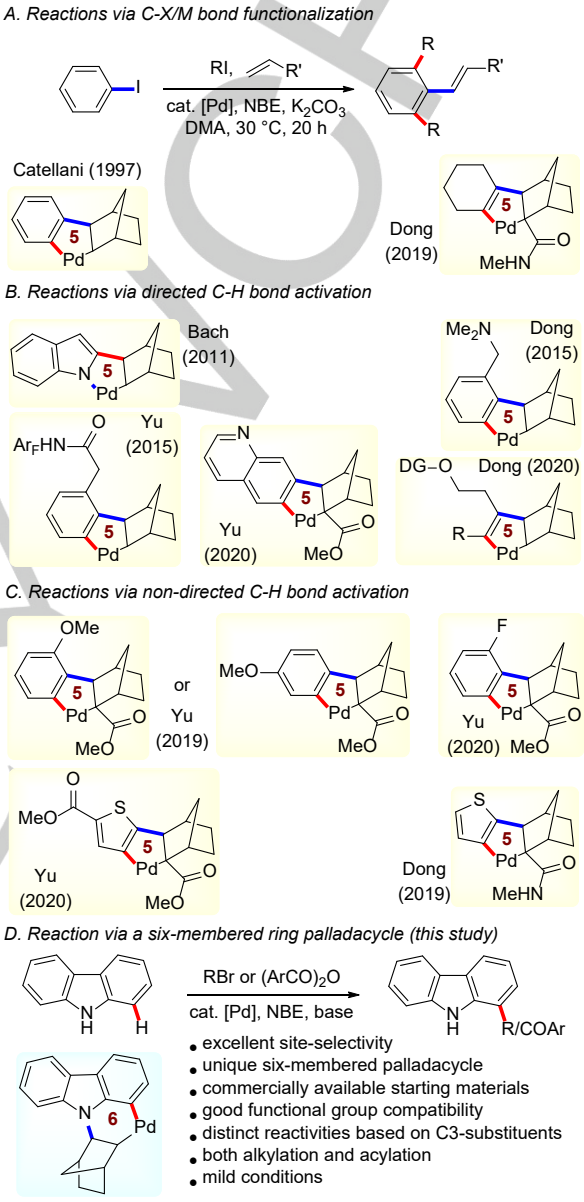
Site-Selective C–H Functionalization of Carbazoles

Mazen Elsaid,[a] ‡ Robbie Ge,[a] ‡ Chong Liu,[a] Debabrata Maiti[b]* and Haibo Ge[a]*

Abstract: *Carbazole alkaloids hold great potential in pharmaceutical and material sciences. However, the current approaches for C1 functionalization of carbazoles rely on the use of a pre-installed directing group, severely limiting their applicability and hindering their overall efficiency. Herein, we report for the first time the development of direct Pd-catalyzed C−H alkylation and acylation of carbazoles assisted by norbornene (NBE) as a transient directing mediator. Notably, the involvement of a six-membered palladacycle intermediate was suggested in this case, representing the first example of such intermediacy within the extensively studied Pd/norbornene reactions realm.*

Carbon-carbon bond construction is a central topic in organic chemistry. The Catellani reaction, a palladium-catalyzed process developed in 1997, represents a unique and powerful strategy for constructing a carbon-carbon bond (Scheme 1a).[1] By virtue of norbornene as an *ortho* directing transient mediator, this reaction, which involves C−H bond activation, allows for bi- and tri-functionalization of aryl iodides in a single step with excellent site-selectivity. As such, over the past two decades, extensive efforts have been devoted to broaden the applications of this reaction and its substrate scope, and many research groups have garnered considerable progress towards this field.[2] While aryl iodides were originally used in the reaction, it was later demonstrated that aryl bromides, triflates, and boronates could also act as effective substrates.[3] Recently, the substrate scope was successfully extended to alkenyl triflates and bromides, allowing for the di-functionalization of alkenes in a highly efficient manner.[4] Furthermore, a directing group-enabled C−H palladation pathway of (hetero)arenes was also achieved (Scheme 1b),[5] and was successfully expanded to non-directional patterns in later cases (Scheme 1c).[6] Notably, this process allows for double C−H bond functionalization as demonstrated by Dong.[7] Site-selective C−H functionalization of alkenes was also recently reported with the assistance of a directing group, significantly broadening the substrate scope.[8] Mechanistically, all of the above mentioned reactions rely on the formation of a five-membered palladacycle intermediate, which directs subsequent C−H functionalization on the *ortho* position. Theoretically, conceptualization of a larger ring intermediate would allow for distal functionalization of a C−H bond, opening the doors to previously challenging and unsought transformations.



Scheme 1. Progress on Catellani reactions.

Originating from the family of Rutaceae, carbazole alkaloids boast a wide range of biological activities including anti-bacterial, anti-cancer, anti-convulsant, anti-diabetic, anti-inflammatory, anti-oxidant, and anti-psychotic properties (Figure 1).[9] Additionally, due to the high thermal and chemical stability and excellent electron donating and charge transporting nature of carbazole structures, derivatives have been extensively studied in the field of photoluminescent and electronic materials.[10] As such, carbazole derivatives have attracted considerable attention from the synthetic organic, medicinal chemistry, and material science communities. Among various synthetic approaches towards

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carbazole derivatives,[11] direct C−H functionalization of free *NH*-carbazoles arguably represents the most efficient pathway since it dismisses the need to pre-installing any additional functional groups and dodges tedious protection/deprotection process. Utilizing the electron-rich nature of the C3 position, direct C−H functionalization of *NH*-carbazoles was well established on this site via electrophilic aromatic substitution (EAS)-type processes. Unfortunately, selective functionalization of *NH*-carbazoles on other positions is challenging, with no reports on the C1 position so far. As such, a method for direct access to C1 substituted carbazoles would be highly beneficial to synthetic and medicinal chemical societies in large. Herein, we report selective C1 alkylation and acylation of *NH*-carbazoles via a palladium/norbornene cascade process mediated via unique six-membered palladacycle intermediacy (Scheme 1d).

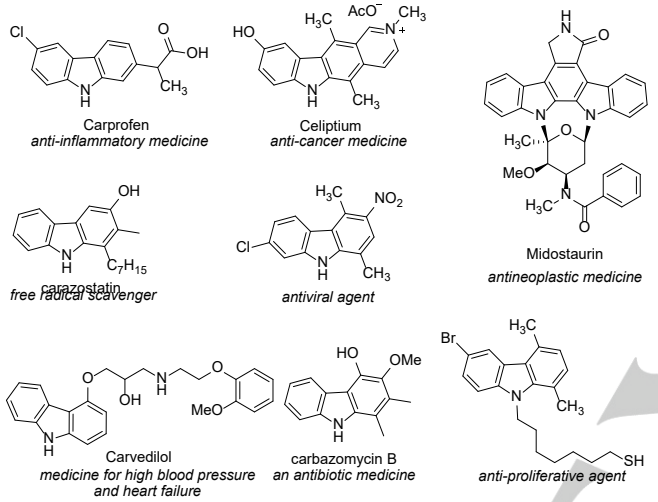
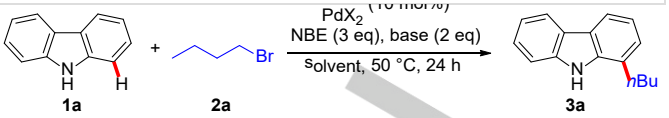


Figure 1. Examples of biologically active carbazole alkaloids.

Our investigation on the reaction parameters was carried out with carbazole (**1a**) as the substrate and 1-bromobutane (**2a**) as the coupling partner in the presence of catalytic $Pd(OAc)_2$ and stoichiometric amounts of norbornene and K_2CO_3 at 50 °C (Table 1). Taking into consideration that addition of water could potentially help to the dissolution of the base and the hydrolysis of the carbazole-palladium species to complete the catalytic cycle, stoichiometric amounts of water were added in the reaction system. Results from initial solvent screening showed that a moderate yield of the desired product **3a** could be obtained with DMF or DMA along with a decent amount of the *N*-alkylation side product. In comparison, smaller amounts of this side product were observed with acetonitrile as the solvent, albeit with a lower yield of the desired product (entries 1-4). Realizing that a weaker base might be able to inhibit the formation of side product, thus favoring the desired process, various organic and inorganic bases were screened (entries 5-8). Gratifyingly, a good yield of **3a** was obtained with KOPiv or CsOAc. Subsequent screening of Pd(II) sources was performed, but they failed to improve on the process (entries 9-13). To our delight, it was observed that a high yield of product **3a** could be obtained by increasing the amount of water to 4.17 equivalents (entry 17). Notably, the desired product was not observed in the absence of a palladium catalyst or norbornene (entries 20-21). It should also be mentioned that excellent site-selectivity was observed in the reaction, since the C2-, C3-, or C4-alkylated products were not obtained under any conditions.

Table 1. Optimization of reaction conditions[a,b].

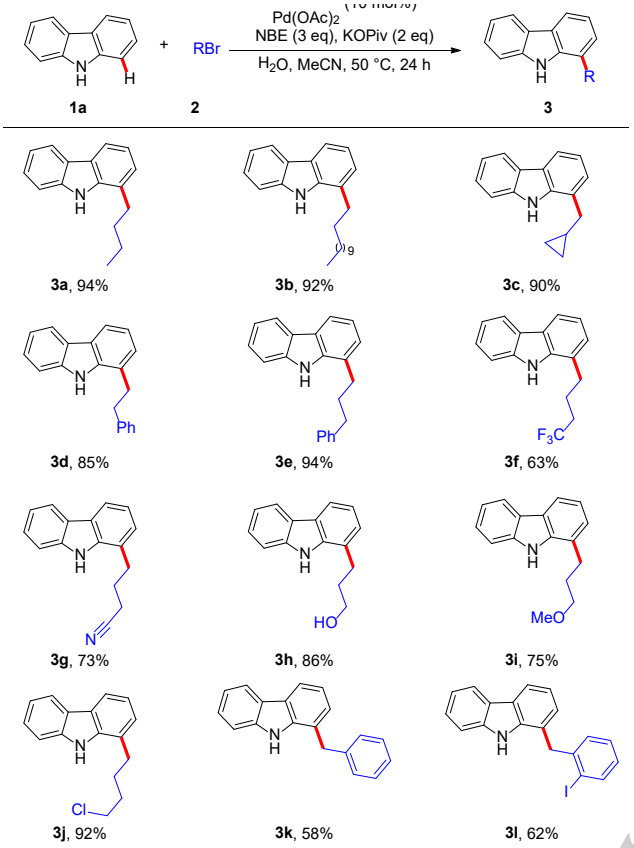


1a **2a** **3a**

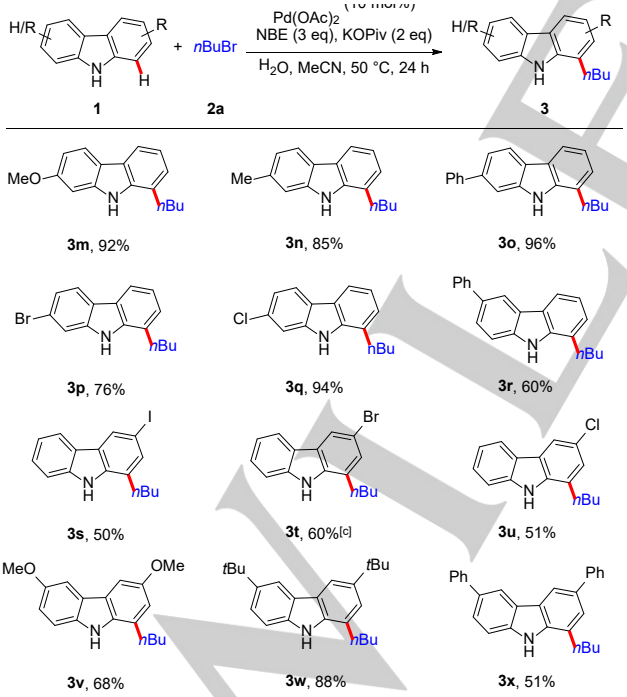
Entry	PdX_2	Base	H_2O (μL)	Solvent	Yield (%)
1	$Pd(OAc)_2$	K_2CO_3	9	MeCN	10
2	$Pd(OAc)_2$	K_2CO_3	9	Acetone	25
3	$Pd(OAc)_2$	K_2CO_3	9	DMF	35
4	$Pd(OAc)_2$	K_2CO_3	9	DMA	39
5	$Pd(OAc)_2$	Na_2CO_3	9	MeCN	0
6	$Pd(OAc)_2$	KOAc	9	MeCN	10
7	$Pd(OAc)_2$	KOPiv	9	MeCN	61
8	$Pd(OAc)_2$	CsOAc	9	MeCN	66
9	$Pd(acac)_2$	KOPiv	9	MeCN	10
10	Pd(dppf)Cl_2	KOPiv	9	MeCN	27
11	Pd(Ph-CN)$_2Cl_2$	KOPiv	9	MeCN	30
12	$Pd(TFA)_2$	KOPiv	9	MeCN	45
13	$PdCl_2$	KOPiv	9	MeCN	61
14	$Pd(OAc)_2$	KOPiv	3	MeCN	51
15	$Pd(OAc)_2$	KOPiv	6	MeCN	55
16	$Pd(OAc)_2$	KOPiv	12	MeCN	84
17	$Pd(OAc)_2$	KOPiv	15	MeCN	96(94)[c]
18[d]	$Pd(OAc)_2$	KOPiv	15	MeCN	72
19	$Pd(OAc)_2$	KOPiv	0	MeCN	51
20	-	KOPiv	5	MeCN	0
21[e]	$Pd(OAc)_2$	KOPiv	15	MeCN	0

[a] Reaction conditions: **1a** (0.2 mmol), PdX_2 (10 mol%), **2a** (0.6 mmol), NBE (0.6 mmol), base (0.4 mmol), solvent (1.0 mL), 50 °C, 24 h. [b] Yields are based on **1a**, determined by ^{1}H-NMR using dibromomethane as an internal standard. [c] Isolated yield. [d] 5 mol% $Pd(OAc)_2$. [e] No NBE.

With the optimized reaction conditions in hand, a substrate scope study for alkyl bromides was performed (Scheme 2). As expected, primary alkyl bromides exhibited good reactivity, independent of chain length. Notably, high functional group compatibility was observed for this reaction: a series of functional groups including cyclopropyl, cyano, ether, nitro, phenyl, and trifluoromethyl were well tolerated. Additionally, halogens and the hydroxyl group were also compatible, allowing for the further manipulation of the initial products (**3h** and **3j**). It should also be noted that benzyl bromides were typically poor substrates in Pd-catalyzed norbornene-enabled directed or non-directed C−H bond functionalization reactions, presumably due to the steric effects. To our delight, these substrates were well-tolerated under our standard reaction conditions (**3k** and **3l**).



Scheme 2.[a,b] Scope of carbazoles. [a] Reaction conditions: **1a** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), **2** (0.6 mmol), NBE (0.6 mmol), KOPiv (0.4 mmol), H_2O (15 µL), MeCN (1.0 mL), 50 °C, 24 h. [b] Isolated yields.



Scheme 3.[a,b] Scope of carbazoles. [a] Reaction conditions: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), **2a** (0.6 mmol), NBE (0.6 mmol), KOPiv (0.4 mmol), H_2O (15 µL), MeCN (1.0 mL), 50 °C, 24 h. [b] Isolated yields. [c] DMA instead of MeCN.

Next, the substrate scope study of carbazoles was carried out (Scheme 3). As expected, C2-substituted carbazoles provided desired products in good yields with excellent site-selectivity, resulting in the formation of the C8 products exclusively due to the steric effect (**3m-3q**), even at elevated temperatures and alkyl bromide loading. Interestingly, C3-substituted carbazoles showed different reactivities: while a C8 alkylated product was obtained using an electron-donating group-substituted carbazole substrate (**3s**), carbazoles bearing an electron-withdrawing group favored the formation of C1 products (**3s-3u**), suggesting that an electrophilic aromatic substitution mode may not apply to the C−H bond cleavage step in the catalytic cycle. Furthermore, disubstituted carbazoles also provided the desired products in good yields (**3v-3x**).

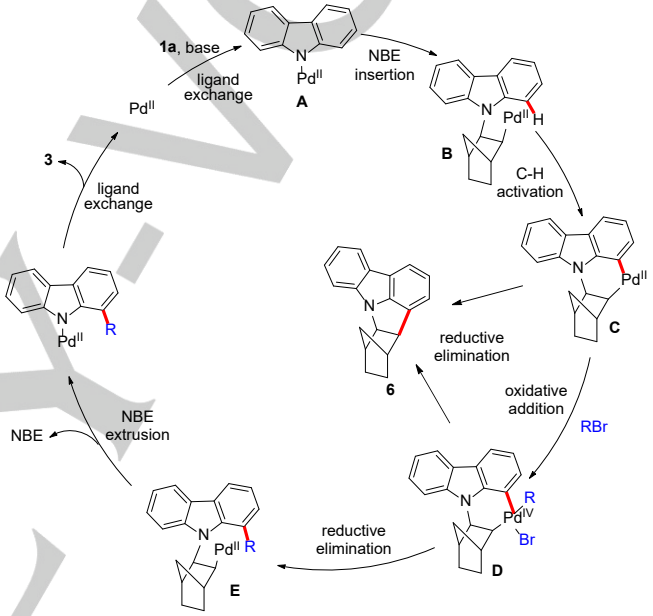
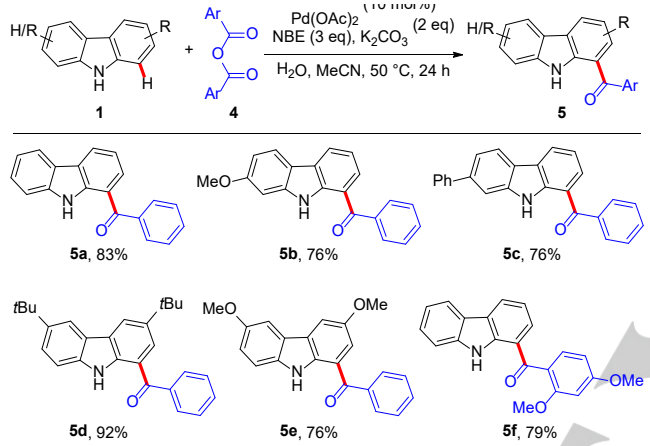


Figure 2. Proposed catalytic cycle.

On the basis of the above observations and previous reports,[1,12] a plausible catalytic cycle of this reaction was proposed (Figure 2). First, ligand exchange on the palladium catalyst with carbazole in the presence of a base generates the intermediate **A**, which undergoes norbornene insertion to provide the intermediate **B**. Following this, site-selective C−H palladation occurs to give rise to the six-membered ring intermediate **C**. Direct C−H activation during this step is the more likely process as opposed to incorporation of palladium through Electrophilic Aromatic Substitution (EAS) like pathway since it is more in line with the observed regioselectivity of C3-substituted carbazoles in Scheme 3. A Kinetic Isotope Effect (KIE) study was administered and a KIE value of 3.04 was observed, we have also observed the lack of H/D exchange at the C8 position of the product upon subjecting carbazole-d_8 to standard reaction conditions. These results indicate that the proposed direct C-H activation and the formation of the key 6-membered palladacycle intermediate **C** is the rate determining step. Oxidative addition of this intermediate with an alkyl bromide provides the palladium (IV) intermediate **D**, which then experiences reductive elimination to afford the palladium (II) intermediate **E**. Notably, the norbornene coupled side product **6** was isolated in the reaction due to the reductive elimination of **C** or **D**, supporting the existence of the cyclopalladium intermediate

C. Subsequently, the palladium (II) intermediate **E** undergoes a norbornene extrusion process followed by ligand exchange to yield the desired product **3**.

Furthermore, selective C1 acylation of carbazoles with aromatic anhydrides was also achieved under slightly modified reaction conditions via a six-membered ring palladacycle intermediate (Scheme 4). It is worth mentioning that this study represents the first reported example of acylation reactions occurring under Pd-catalyzed norbornene-enabled directed or non-directed C−H bond functionalization strategies. The analogy in reaction conditions hint towards a similar catalytic cycle to that described for alkylation. The scope is currently limited to some benzoic anhydrides, thus, further optimization and scope extension to aliphatic anhydrides and other acylating agents such as acids and acid halides is certainly an intriguing direction for future studies.



Scheme 4.[a,b] Site-selective acylation of carbazoles. [a] Reaction conditions: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), **4** (0.6 mmol), NBE (0.6 mmol), K_2CO_3 (0.4 mmol), H_2O (15 µL), MeCN (1.0 mL), 50 °C, 24 h. [b] Isolated yields.

In summary, we have developed palladium-catalyzed C−H alkylation and acylation reactions of carbazoles with norbornene as a transient directing mediator. This reaction avoids the use of an external directing group, allowing for direct C−H functionalization of *NH* carbazoles, and granting much needed access to carbazole derivatives with excellent site-selectivity and good functional group compatibility. Mechanistically, a six-membered palladacycle is suggested to be involved in the catalytic cycle, making it a unique process, and opening the door for future designs of distal C−H functionalization reactions. Considering the wide presence of carbazole alkaloids in biologically active molecules and organic materials, this newly established method could potentially find broad synthetic applications in both the chemical and material science communities. Further studies are currently being conducted in our laboratory to deepen our understanding of the detailed catalytic pathway and develop new transformations.

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Conflicts of Interest

The authors declare no conflict of interest.

Keywords: Palladium • C(sp^2)–H functionalization • Norbornene • Transient directing mediator • Carbazole

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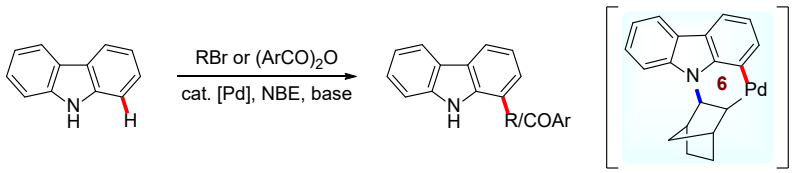

Carbazole alkaloids are of great interest to organic and medicinal chemists and material scientists. This unique direct C−H functionalization has enabled efficient derivatization of commercially available carbazoles in a highly site-selective manner via a unique six-membered palladacycle intermediate. This reaction boasts good functional group compatibility and displays distinct reactivities based on C3-substituents of unsymmetrical substrates.