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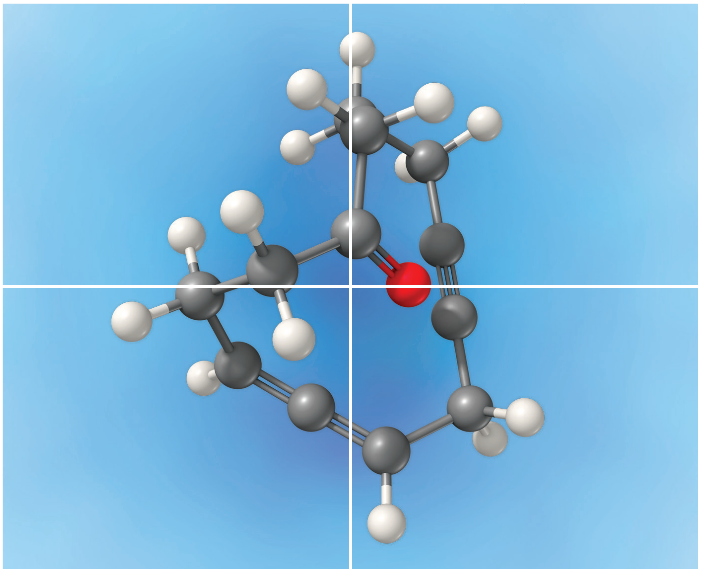

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ARTICLE TYPE

Palladium–Catalyzed, Copper–Mediated Construction of Benzene Rings from the Reactions of Indoles with *in–situ* Generated Enones

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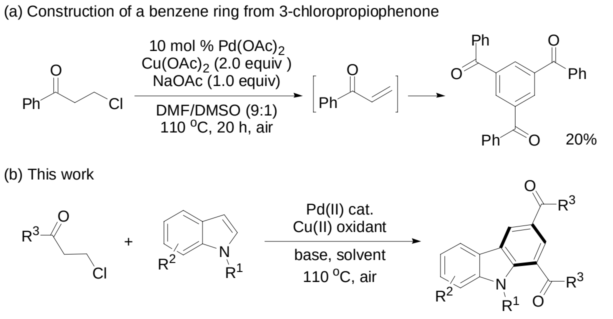
Construction of the benzene ring in carbazoles was efficiently realized through a domino dehydrochlorination/alkenylation/ cycloaddition-oxidation sequence by means of palladium(II)-catalyzed, copper(II)-mediated reactions of *N*-protected 2,3-unsubstituted indoles with 3-chloropropiophenones in the presence of a base. 3-Alkenylated indole was confirmed to be formed as the reaction intermediate which then underwent Diels-Alder cycloaddition to the initially *in-situ* generated enone from a 3-chloro-propiophenone substrate, and the subsequent dehydrogenative aromatization yielded the carbazole product. The strategy to employ *in-situ* generated enones as the reactive species avoided use of large excess of labile substrates and lessened the side reactions.

Construction of benzene rings is usually the key step to establish important aromatic systems.[1] Functionalized aromatics are traditionally prepared through aromatic electrophilic substitution reactions or by transition-metal catalyzed multistep transformations generally involving alkynes.[2] Polycyclic (hetero)-arenes have demonstrated valuable utilities in synthetic chemistry, and their concise synthesis is strongly desired from the reactions of readily available building blocks, among which formal oxidative cross-coupling of three alkenes seems to be the promising route to a benzene ring.[3]

Carbazoles are an important class of aromatic heterocyclic nuclei as structural motifs in many synthetic compounds and naturally occurring alkaloids.[4] The cross-coupling reactions of C-H/C-X bonds (X = halo, N, O, and C, etc.) have been employed for their synthesis.[5-9] Oxidative intramolecular C-H/C-H cross-coupling of prefunc-tionalized diarylamines was realized for the same purpose.[10] 2-Aryl and 2-heteroarylindoles were reported to react with alkynes to prepare carbazoles.[11,12] Using a trimetallic system i.e., $Pd(OAc)_2/Cu(OAc)_2/Ag(OCOCF_3)$, *N*-methylindoles reacted with 10 equiv of methyl or phenyl vinyl ketone to form diacetyl- and dibenzoylcarbazoles, respectively.[13] Although indoles can react with α,β-unsaturated carbonyls,[14] synthesis of carbazoles from their reactions with electron-deficient alkenes is still challenging because aryl vinyl ketones (enones) are usually not commercially available due to their susceptibility to heat, light and oxygen during preparation and storage. Palladium-catalyzed dehy-drogenation of alkyl ketones was thus documented to prepare enones, but the synthesis generally requires high catalyst loading and relatively harsh conditions.[15] As an alternative route, *in-situ* generation of enones has recently attracted attention by using saturated alkyl ketones and *β*-keto esters as the alkene sources.[15c,16]

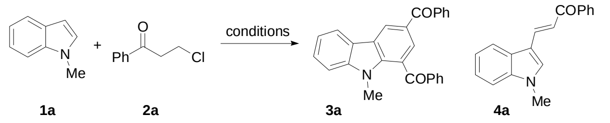
Recently, we found that *β*-chloroalkyl aryl ketones and their ester and amide derivatives can be utilized as precursors to *α,β*-unsaturated carbonyls in Rh(I)-catalyzed conjugate addition by arylboronic acids.[17] Under an oxygen atmosphere, $PdCl_2$-catalyzed trimerization of phenyl vinyl ketone afforded 1,3,5-tribenzoylbenzene in 25% yield.[3b] We thus envisioned that 3-chloropropiophenone might undergo the same reaction via the *in-situ* generated enone intermediate. To our delight, such a reaction occurred to give the target trimerization product in 20% yield (Scheme 1a). Retrosynthetic analysis suggests that construction of a benzene ring is plausible from the reaction of a 3-chloroalkyl carbonyl (as the enone precursor) with indole (as an alkene building block) because palladium-catalyzed indole alkenylation with electron-deficient acrylates and alkenes has been well-known.[18] Herein, we report synthesis of functionalized carbazoles by the reactions of 3-chloroalkyl ketones with indoles through a domino sequence[19] (Scheme 1b).



Scheme 1. Synthesis of carbazoles via *in-situ* generated enones

Initially, *N*-methylindole (**1a**) was reacted with 3-chloropropiophenone (**2a**) in dioxane at 100 °C under a nitrogen atmosphere by using 10 mol % $Pd(OAc)_2$ as the catalyst, $Cu(OAc)_2$ as the oxidant, and Na_2CO_3 as the base, giving the desired product **3a** in 10% yield (Table 1, entry 1). Changing the solvent to DMSO or DMF improved the reaction efficiency, and a 9:1 mixture of DMF and DMSO promoted the reaction to form **3a** in 74% yield (Table 1, entries 2-4). $Cu(OAc)_2$ acted as the most effective oxidant among those screened, i.e., $Cu(OAc)_2$, $Cu(OAc)_2{\cdot}H_2O$, AgOAc, $AgCO_3$, benzoquinone (BQ), and *t*BuOO*t*Bu, while the reaction hardly occurred without an added oxidant or by using CuOAc as the sole oxidant (Table 1, entries 5 and 6). Elevating the temperature to 110 °C improved the reaction (Table 1, entry 7). A catalyst was necessary for the reaction, and $Pd(OAc)_2$ was shown as the most efficient one among the screened Pd(II) and Pd(0) sources (see the Supporting Information). A base was required for the reaction, and NaOAc behaved better than Na_2CO_3. Air atmosphere slightly improved the yield of **3a** (82%), but oxygen as the sole oxidant did not facilitate the reaction (Table 1, entry 12). Using less $Cu(OAc)_2$ reduced the yield of **3a** (Table 1, entry 13). Although both CuOAc and oxygen can't be used as the sole oxidants, their combination worked well (Table 1, entry 14). A reduced loading of the catalyst (5 mol %) led to a lower yield of **3a** (70%) (Table 1, entry 15). It should be noted that only a trace amount of **4a** was detected during the reaction.

Table 1. Screening of conditions for reaction of *N*-methylindole (**1a**) with 3-chloropropiophenone (**2a**)[a]



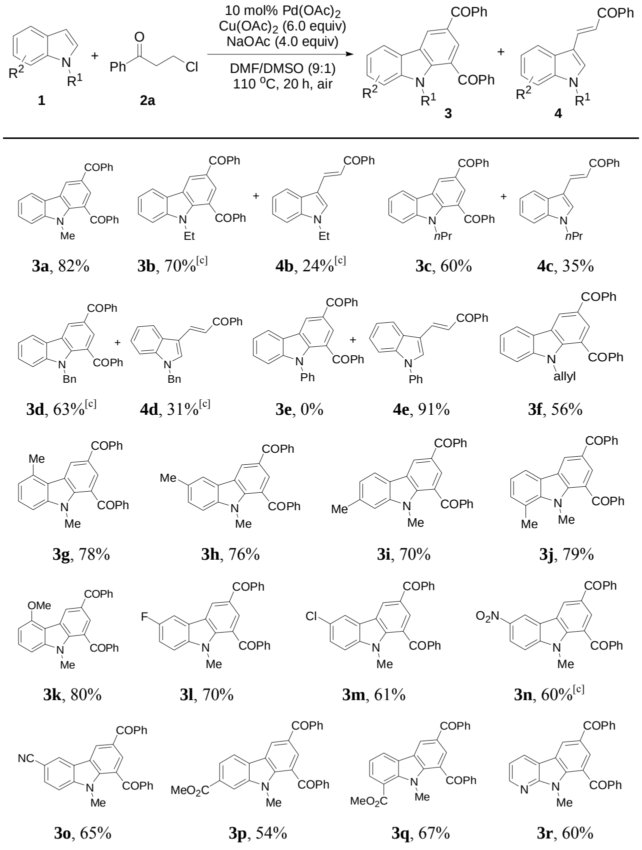
1a **2a** **3a** **4a**

Entry	Catalyst	Oxidant	Base	Temp (°C)	Yield[b] of **3a** (%)
1[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	100	10
2[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	100	43
3[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	100	51
4	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	100	74
5	$Pd(OAc)_2$		Na_2CO_3	100	<1
6	$Pd(OAc)_2$	CuOAc	Na_2CO_3	100	<1
7	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	110	77
8	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	120	73
9		$Cu(OAc)_2$	Na_2CO_3	110	0
10	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	110	81
11[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	110	82
12[f]	$Pd(OAc)_2$	air	NaOAc	110	<1
13[f,g]	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	110	63
14[f]	$Pd(OAc)_2$	CuOAc	NaOAc	110	51
15[f,h]	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	110	70

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), catalyst (0.02 mmol), base (0.8 mmol), oxidant (1.2 mmol), solvent (2.5 mL，DMF/DMSO, v/v = 9:1), 0.1 MPa N_2, 20 h. [b] Isolated yield. [c] in dioxane. [d] in DMSO. [e] in DMF. [f] In air. [g] $Cu(OAc)_2$ (1.0 mmol) was used. [h] Using 5 mol % catalyst.

Next, the indole scope was explored to probe the protocol generality (Table 2). As the steric hindrance of the *N*-R moiety in indoles was increased from methyl to ethyl, *n*-propyl, benzyl, and phenyl, yields of the desired products were gradually decreased from 82% (R = Me for **3a**) to 0% (R = Ph for **3e**). 3-alkenylated indoles **4b-4d** were formed as the minor products (24-35%), while in the case of *N*-phenylindole **4e** was formed as the only product (91%). The reaction of *N*-allylindole with **2a** afforded **3f** (56%) with its allyl functional group unchanged. The electron-donating substituents on the aryl rings of the indole substrates did not obviously affect the reaction efficiency as **3g-3k** were obtained in 70-80% yields, whereas the electron-withdrawing fluoro, chloro, nitro, cyano, and CO_2Me groups lessened formation of the desired products **3l-3q** (54-70%). *N*-Methyl-7-azaindole also underwent the reaction with **2a** to form **3r** (60%). The molecular structures of compounds **3** were further confirmed by the X-ray single crystal structural determination of **3i** (Figure 1).

Table 2. Reactions of **2a** with indoles **1**.[a,b]



3a, 82% **3b**, 70%[c] **4b**, 24%[c] **3c**, 60% **4c**, 35%

3d, 63%[c] **4d**, 31%[c] **3e**, 0% **4e**, 91% **3f**, 56%

3g, 78% **3h**, 76% **3i**, 70% **3j**, 79%

3k, 80% **3l**, 70% **3m**, 61% **3n**, 60%[c]

3o, 65% **3p**, 54% **3q**, 67% **3r**, 60%

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (6 equiv), NaOAc (4 equiv), DMF/DMSO (2.5 mL, v/v = 9/1), 20h. [b] Isolated yields. [c] 30 h.

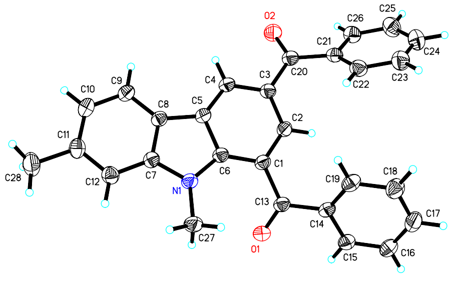
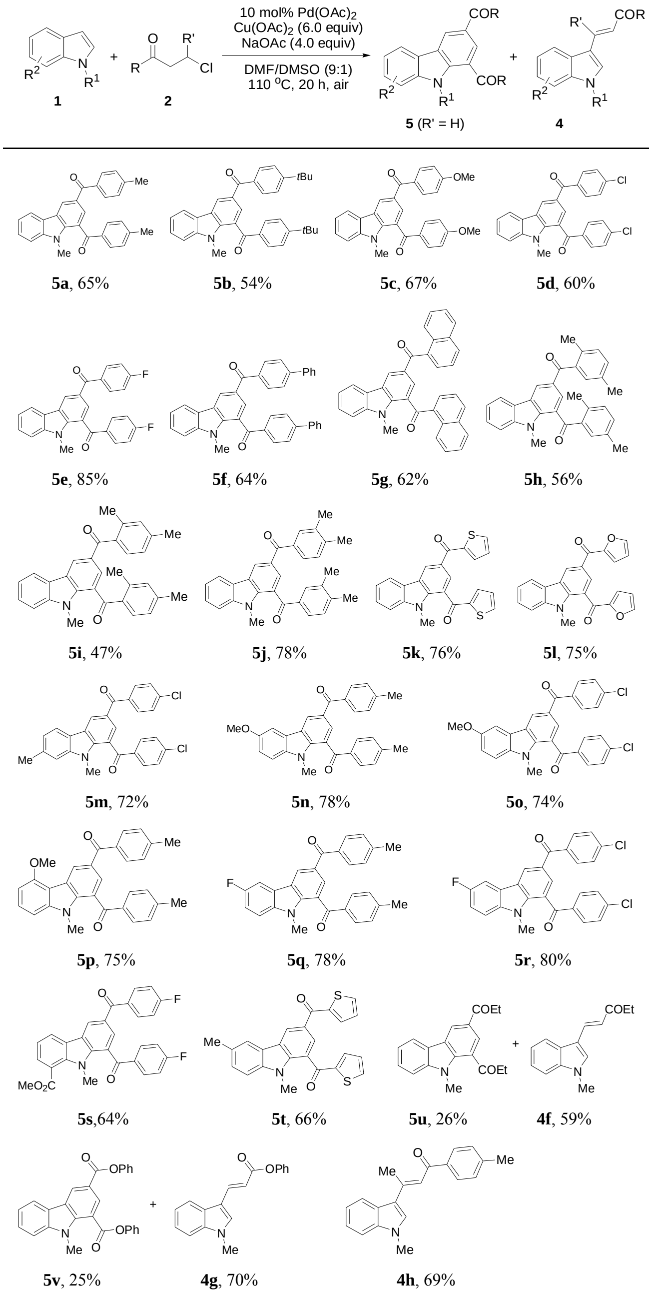


Figure 1. Molecular structure of **3i**

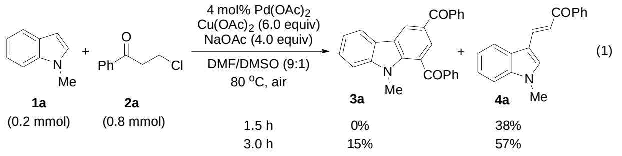
The protocol generality was then investigated by reacting indoles with various 3-chloroalkyl ketones (Table 3). Treatment of **1a** with substituted 3-chloroalkyl ketones (**2**) formed the desired products **5a**-**5e** in 74-85% yields. Increasing steric hindrance of the aryl moiety in **2** deteriorated the production of **5f**-**5i** (47-64%), and the reduced steric hindrance from 3,4-dimethyl groups only had slight influence on the yield of **5j** (78%). Heteroaryl 3-chloropropionones underwent the same reactions to generate 1,3-diheteroaroylindoles **5k** (76%) and **5l** (75%), respectively. Substituted *N*-methylindoles also efficiently reacted with 3-chloroalkyl aryl ketones to afford products **5m**-**5r** (72%-80%). A 7-CO_2Me in **1** or thienyl in **2** led to reduced yields for **5s** (64%) and **5t** (66%), respectively. However, the reaction of 5-chloropentan-3-one with **1a** only gave **5u** in 26% yield with 3-alkenylated indole **4f** (59%) as the major product. Similar results were obtained in the case of 3-chloropropionic acid phenyl ester, forming **5v** (25%) and **4g** (70%). The *β*-methyl group in **2** completely inhibited the target reaction, resulting in **4h** (69%) as the only product.

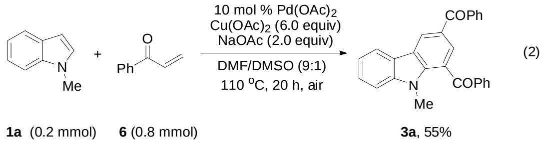
Table 3. Reactions of β-chloro ketones and their ester derivatives **2** with indoles **1**[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (6 equiv), NaOAc (4 equiv), DMF/DMSO (2.5 mL, v/v = 9/1). [b] Isolated yields.

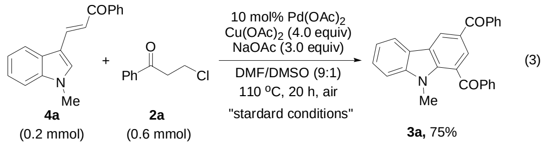
To determine whether the 3-alkenylated indole of type **4** was an intermediate, the reaction of **1a** with **2a** was conducted at 80 °C by using 4 mol % catalyst (eqn (1)). It was found that the reaction initially formed **4a**, which was then gradually converted to the desired product **3a**. Analysis of the reaction mixture at 3 h by GC revealed the presence of unreacted enone **6**.[17] Reacting **1a** with **6** under the typical conditions afforded **3a** in 55% yield (eqn (2)), which is comparable with the 53% yield of the same reaction with 10 equiv of **6** by means of the trimetallic system.[13] These results have revealed that the present bimetallic system employing *in-situ* generated enone **6** is efficient for carbazole synthesis.





To probe further into the reaction pathway of the 3-alkenylated indole intermediate with the *in-situ* generated enone species, the controlled reaction of **4a** with **2a** was investigated (Table 4). Deviation of the standard conditions by omitting one or two reaction parameters changed the formation of **3a**. Under the standard conditions as shown in eqn 3, **3a** was formed in 75% yield (Table 4, entry 1). Without $Pd(OAc)_2$ as the catalyst, the

Table 4. Controlled reactions of **4a** with **2a**

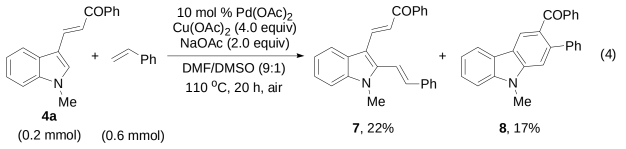


Entry	Conditions	Yield[a]
1	standard conditions	75%
2	without $Pd(OAc)_2$	78%
3	without $Pd(OAc)_2$ under 0.1 MPa N_2	83%
4	without $Cu(OAc)_2$	51%
5	without both $Pd(OAc)_2$ and $Cu(OAc)_2$	48%
6	without both $Pd(OAc)_2$ and $Cu(OAc)_2$ under 0.1 MPa N_2	complicated

[a] Isolated yield of **3a**.

reaction was not affected much to give **3a** (78% yield in air, 83% yield under atmospheric nitrogen) (Table 4, entries 2 and 3). Without $Cu(OAc)_2$, or in the absence of both $Pd(OAc)_2$ and $Cu(OAc)_2$, **3a** was still obtained in 48-51% yields, whereas the same reaction became complicated under a nitrogen atmosphere (Table 4, entries 4-6), suggesting that an added oxidant or air should be used as the oxidant for the reaction to occur properly. These results have revealed that a palladium catalyst is not necessary for the reaction as shown in eqn 3, and the reaction can occur without $Cu(OAc)_2$ in air, but an added oxidant such as $Cu(OAc)_2$ promotes the reaction better than air.

Reacting **4a** with styrene under the standard conditions (eqn (4)) afforded 2,3-dialkenylated indole **7** (22%) and carbazole **8** (17%) through multiple C-H activation of the indole substrate. The X-ray single crystal structure of **8** was also confirmed (Figure 2). No product of type **7** was obtained from the reaction of **4a** with **2a**, excluding a C-H activation pathway. These results led us to deduce that Diels-Alder cycloaddition and subsequent oxidation were involved to form the benzene ring in the overall reaction.



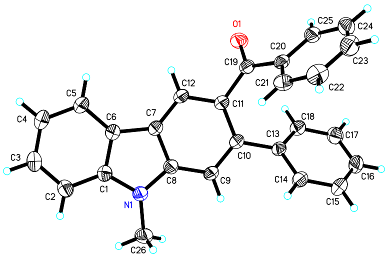
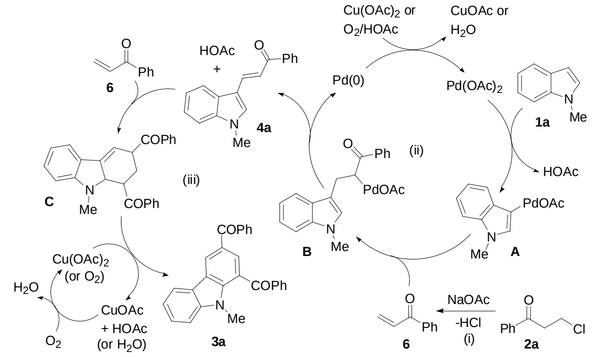


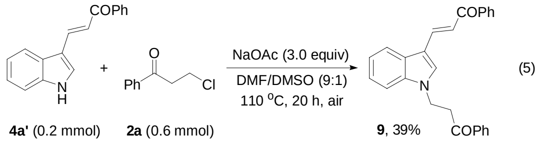
Figure 2. Molecular structure of **8**

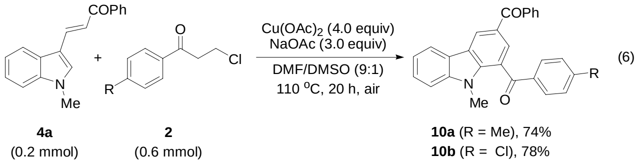
A proposed mechanism is depicted by the reaction of **1a** with **2a** (Scheme 2). The indole substrate initially undergoes palladation at its 3-position to form palladated species **A** and HOAc. **A** reacts with the *in-situ* generated enone **6** from **2a** to yield an alkene insertion species **B**, which undergoes reductive elimination to produce 3-alkenylated indole **4a** and a Pd(0) species. A Diels-Alder cycloaddition of **6** to **4a** forms tetrahydrocarbazole **C**, which is subsequently oxidized to form the desired product **3a**. Air facilitates regeneration of the Cu(II) oxidant and Pd(II) catalyst.

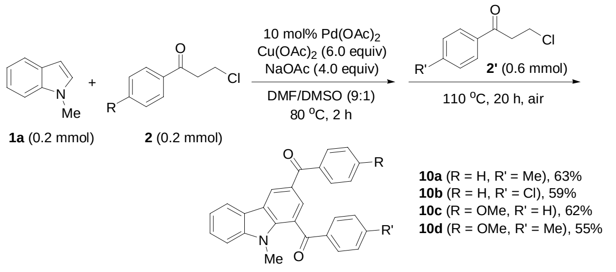
Finally, the protocol was extended to the reactions of *N*-unprotected indoles. It was found that the *N*-unprotected analogue of **4a** reacted with **2a** in the presence of NaOAc to form *N*-(3-oxo-3-phenylp-ropyl)-substituted product **9** (39%), affording no desired carbazole product (eqn (5)). For the versatile synthesis of carbazoles, the reactions of **4a** with 3-chloroalkyl aryl ketones were performed, producing carbazoles **10a** (74%) and **10b** (78%) bearing two different substituents (eqn (6)). A one-pot, two-step procedure was also established to synthesize the mixed aroyl-substituted carbazoles **10a-10d** (55-63%) (Scheme 3), providing a potentially applicable route to functionalized carbazoles.



Scheme 2. Proposed mechanism







Scheme 3. One-pot synthesis of functionalized carbazoles

In summary, the palladium(II)-catalyzed, copper(II)-mediated synthesis of carbazoles has been efficiently realized through a domino dehydrochlorination / alkenylation / cycloaddition-oxidation sequence by means of the reactions of *N*-protected indoles with 3-chloropropiophenones in the presence of a base. The strategy employed *in-situ* generated *α,β*-unsaturated carbonyls to avoid using large excess of labile substrates and lessen side reactions. The present method provides a concise route to functionalized carbazoles.

Experimental Section

A typical procedure for the synthesis of carbazoles: Synthesis of 3a

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A mixture of *N*-methylindole (**1a**) (26 mg, 0.2 mmol), 3-chloropropio-phenone (**2a**) (133 mg, 0.8 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), Cu(OAc)$_2$ (218 mg, 1.2 mmol), and NaOAc (66 mg, 0.8 mmol) in 2.5 mL DMF/DMSO (v/v = 9:1) was stirred at 110 ^{o}C under an air atmosphere for 20 h. After cooled to ambient temperature, 10 mL CH$_2$Cl$_2$ was added and the resultant mixture was filtered through a short pad of silica gel, followed by rinsing with 20 mL CH$_2$Cl$_2$. The combined filtrate was washed with brine (15 mL) and separated. The organic phase was dried over anhydrous Na$_2$SO$_4$, filtered, concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^{o}C) /EtOAc /CH$_2$Cl$_2$ = 30:1:2, v/v/v) to afford **3a** as a white solid (64 mg, 82%).

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, compound characterization and NMR spectra. CCDC 973030 and CCDC 973031. For ESI and crystallographic data in CIF or other electronic format, See DOI: 10.1039/b000000x

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