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Site-Selective Aerobic C−H Monoacylation of Carbazoles Using Palladium Catalysis

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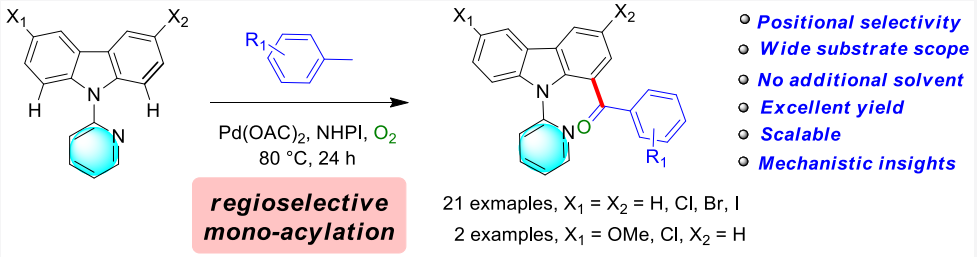

ABSTRACT: This manuscript describes the development of a remarkably general palladium-catalyzed monoacylation of carbazoles using toluene derivatives playing the dual role of acyl source and organic solvent. The method uses NHPI as the cocatalyst and oxygen as the sole oxidant. Interestingly, the acylation of monosubstituted *N*-pyridylcarbazoles takes place regioselectively at the C-8 position. The scope of the method is explored using aldehyde as the acyl source. This highly site-selective acylation proceeds through a radical process.

INTRODUCTION

C−H bond functionalization has emerged as one of the most powerful tools for generating new carbon−carbon and carbon−heteroatom bonds.[1] However, selective C−H functionalization at a particular position is challenging.[1a,2] Carbazoles are one of the most ubiquitous heteroaromatic motifs found in myriad of natural products, photorefractive materials, organic dyes,[3] and bioactive molecules.[4] Despite significant progress achieved in the synthesis and functionalization of carbazoles, only a few methods are known to afford C1/C8-substituted carbazoles.[5] Further, due to the nucleophilic character of the C3 and C6 positions of carbazole, electrophilic substitution occurs mostly at the C3 and C6 positions.[6] Therefore, regioselective functionalization at the less activated C1 and C8 positions of the carbazole without protecting the C3 and C6 positions[5,7] is challenging.

Recently, Pd(II)-catalyzed direct 1-arylation of pyridine-protected carbazoles,[8] 1,8-diolefination of carbazoles,[9] Ru- and Cu-cocatalyzed dehydrogenative C1−N carbazolation,[10] and Ru-catalyzed regioselective C1 and C8 diacetoxylation of *N*-pyridylcarbazoles[11] have been reported for the functionalization of carbazoles at the C1 and C8 positions. We have recently reported palladium(II)-catalyzed 1,8-diacylation of carbazoles using aldehydes as the acyl source and TBHP as the oxidant.[12] Most of the oxidative C−H activation processes proceed through a Pd(II)/Pd(IV)[13] manifold involving stoichiometric oxidant (TBHP, $K_2S_2O_8$, $Cu(OAc)_2$, DDQ, PIDA, etc.). Focusing on the growing demand for sustainable synthesis, we envisioned to carry out acylation of carbazoles using natural and inexpensive molecular O_2 as oxidant.[14]

Till now, few methods have been known for the synthesis of 1-acylated carbazoles. The synthesis of 1-aroylcarbazoles by photolysis of *N*-aroylcarbazoles in low yields (∼15−30%) was reported in 1987.[15] The Katritzky group reported the synthesis of 1-aroylcarbazoles by ortho-lithiation of *N*-pyrrolidinomethyl-carbazole and subsequent addition of electrophiles such as aromatic aldehydes to the reaction mixture.[16] The Friedel−Crafts acylation of carbazole with benzoyl chloride was reported to afford a mixture of mono- and dibenzoylcarbazole derivatives.[17] Bandgar and co-workers reported one example of 1-benzoylcarbazole by Pd-catalyzed cross-coupling of (9*H*-carbazol-1-yl)boronic acid with benzoyl chloride.[18] Wu and Yang et al. illustrated the synthesis of pyrimidine-protected 1-acylated carbazole derivatives by tandem Rh-catalyzed C−H activation of pyrimidine-protected indoles and subsequent Brønsted acid-catalyzed cyclization (Scheme 1).[19] Acylation of a pyrimidine-protected carbazole with 4-methylbenzaldehyde using both Pd(II) catalyst and Ru(II) photocatalyst in the presence of visible light and external oxidant TBHP was recently reported (Scheme 1).[20a] Kim et al. also reported synthesis of a

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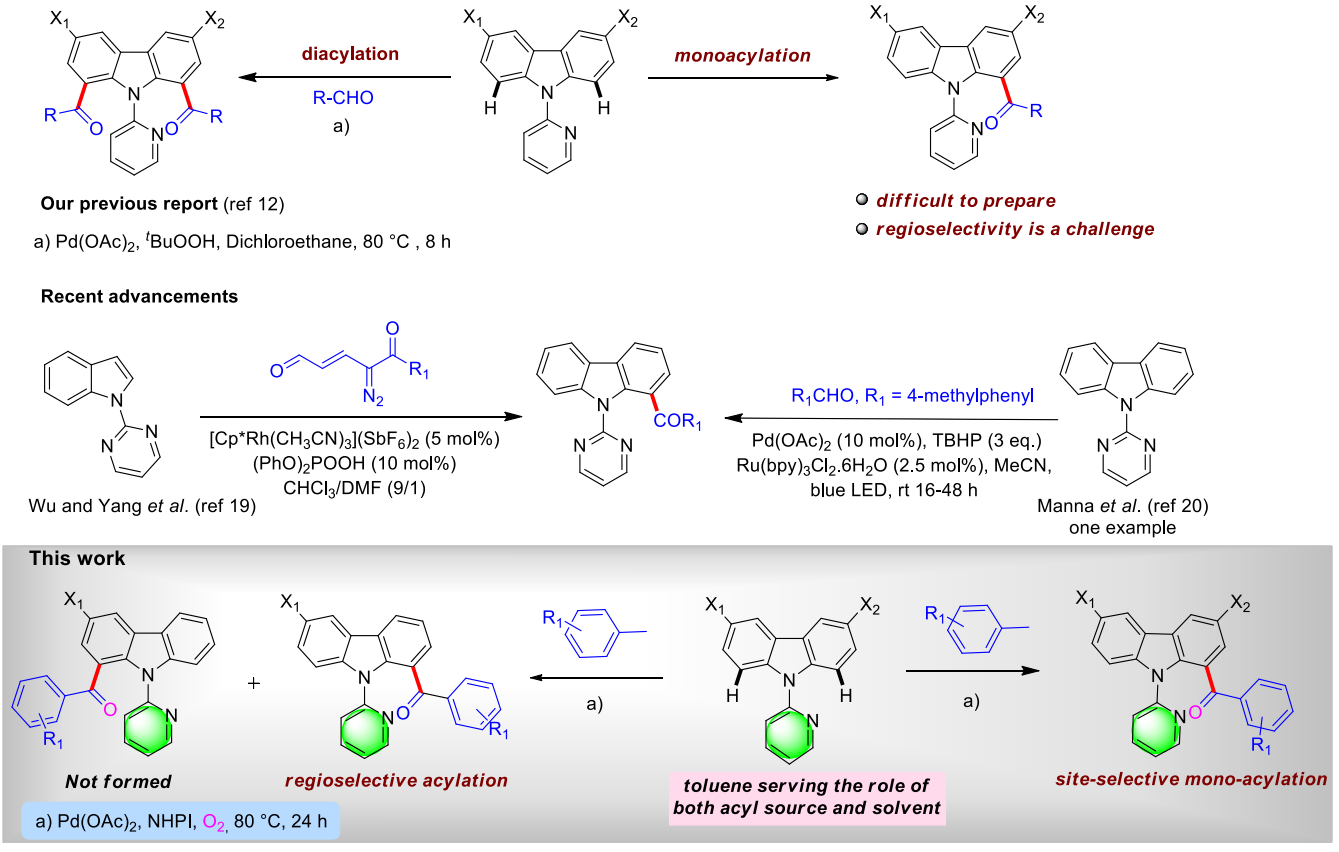
Scheme 1. Previous Reports and Our Approach for the Synthesis of 1-Acylcarbazoles



N-acyl-protected 1-acylcarbazole derivative using Pd-catalyzed decarboxylative acylation of phenylglyoxylic acid.[20b] Therefore, site-selective synthesis of 1-acylated carbazole derivatives using easily accessible starting materials and a metal catalyst without added oxidant is clearly worth exploring.

Pd(II)-catalyzed aerobic oxidative radical processes involving Pd(III) or -(IV) intermediates have been reported for C−H functionalization.[21] *N*-Hydroxyphthalimide (NHPI) is used as cocatalyst, which is oxidized by O_2 to generate PINO (phthalimido-*N*-oxyl) radical.[22] PINO initiates the radical oxidative reaction with the formation of benzoyl radical from toluene. Inspired by these transformations, we employed NHPI and O_2 for the Pd(II)-catalyzed 1-acylation of carbazole using toluene as the acyl source (Scheme 1).[22,23] Versatile C−H functionalization of toluene derivatives using metal catalysis has been previously reported.[24]

RESULTS AND DISCUSSION

As a model reaction, the acylation of 9-(pyridin-2-yl)-9*H*-carbazole **1** was performed in the presence of 10 mol % $PdCl_2$ and 30 mol % of NHPI as cocatalyst in 1 mL of toluene **2a** under 1 atm O_2 at 80 °C for 12 h (see Table S1; Supporting Information, SI). The reaction provided 10% yield of 1-acylated carbazole derivative **3a** (Table 1, entry 1). The yield of **3a** was only marginally increased even with prolonged reaction time (Table 1, entries 2, 3). The yield of the reaction did not improve on increasing or lowering the reaction temperature (Table 1, entries 4, 5). The reaction did not proceed at room temperature (entry 6). Other Pd sources such as $Pd(TFA)_2$ and $Pd_2(dba)_3$ provided product **3a** in 55% and 29% isolated yields, respectively (Table 1, entries 7, 8). We were delighted to observe that with 10 mol % $Pd(OAc)_2$, the reaction gave 76% yield of **3a** along with 5% yield of 1,8-diacylated carbazole **4a** at 80 °C for 24 h (Table 1, entry 9). When the reaction was carried out using 2 mol % of $Pd(OAc)_2$ and 10 mol % of NHPI at elevated temperature, a trace amount of product could be detected (entry 10). $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ failed to give any desired product (Table 1, entries 11, 12). Thus, $Pd(OAc)_2$ was used as the preferred catalyst for this transformation. Next, instead of NHPI, different one-electron oxidants such as BQ, TEMPO, or $Cu(OAc)_2$ were also investigated. No desired product was formed (Table 1, entries 13−15). The yield of the reaction was slightly decreased when molecular oxygen was replaced by air (Table 1, entry 16).

In the absence of either NHPI or $Pd(OAc)_2$, the reaction did not proceed (Table 1, entries 17, 20). Even at elevated temperature or in the presence of TBHP no reaction occurred in the absence of metal catalyst (entries 18, 19). Furthermore, the reaction did not occur under an argon atmosphere (Table 1, entry 21). It is worth noting that the reaction could be scaled (1.0 g of **1**) without a loss of yield under the optimized conditions (entry 22). Thus, the optimization study implied that $Pd(OAc)_2$, NHPI, and O_2 are respectively the most suitable catalyst, cocatalyst, and oxidant for the site-selective 1-acylation of 9-(pyridin-2-yl)-9*H*-carbazole **1**.

With the optimized reaction conditions, we then explored the 1-acylation of 9-(pyridin-2-yl)-9*H*-carbazole **1** with a variety of toluene derivatives **2**. 4-Chlorotoluene **2b** showed slightly higher reactivity than 3-chlorotoluene **2c**, producing the desired products **3b** (78%) and **3c** (71%) in high yields. 4-Bromotoluene **2d** and 3-bromotoluene **2e** displayed comparable reactivity, generating the desired products **3d** and **3e** in 73% and

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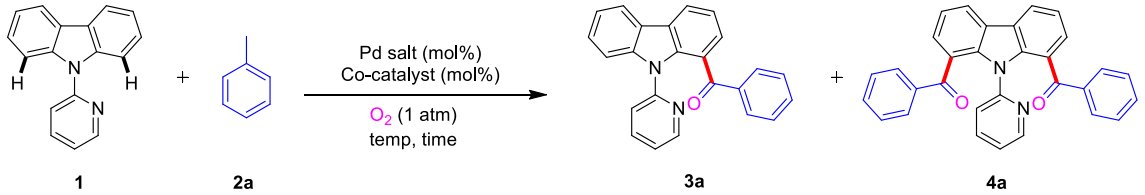
Table 1. Optimization of Reaction Conditions[a]



1 2a 3a 4a

entry	Pd catalyst (10 mol %)	co-cat. (30 mol %)	oxidant	time (h)	temperature (°C)	yield[b] of **3a** (%)	yield[b] of **4a** (%)
1	$PdCl_2$	NHPI	O_2	12	80	10	-
2	$PdCl_2$	NHPI	O_2	24	80	27	trace
3	$PdCl_2$	NHPI	O_2	36	80	29	trace
4	$PdCl_2$	NHPI	O_2	24	100	26	trace
5	$PdCl_2$	NHPI	O_2	36	60	10	trace
6	$PdCl_2$	NHPI	O_2	36	rt	NR[d]	-
7	$Pd(TFA)_2$	NHPI	O_2	24	80	55	trace
8	$Pd_2(dba)_3$	NHPI	O_2	24	80	29	trace
9	$Pd(OAc)_2$	NHPI	O_2	24	80	76	5
10[c]	$Pd(OAc)_2$	NHPI	O_2	24	120	trace	-
11	$Pd(PPh_3)_2Cl_2$	NHPI	O_2	24	80	NR[f]	-
12	$Pd(PPh_3)_4$	NHPI	O_2	24	80	NR[f]	-
13	$Pd(OAc)_2$	BQ	O_2	24	80	NR[f]	-
14	$Pd(OAc)_2$	TEMPO	O_2	24	80	NR[f]	-
15	$Pd(OAc)_2$	$Cu(OAc)_2$	O_2	24	80	NR[f]	-
16	$Pd(OAc)_2$	NHPI	Air	24	80	67	ND[g]
17	-	NHPI	O_2	24	80	NR[d]	-
18	-	NHPI	O_2	24	120	NR[f]	-
19[d]	-	NHPI	TBHP	24	80	NR[f]	
20	$Pd(OAc)_2$	-	O_2	24	80	NR[f]	-
21	$Pd(OAc)_2$	NHPI	Ar	24	80	NR[f]	-
22[e]	$Pd(OAc)_2$	NHPI	O_2	24	80	70	10

[a]9-(Pyridin-2-yl)-9*H*-carbazole **1** (0.25 mmol), toluene **2a** (1 mL). [b]Isolated yields. [c]Reaction was carried out using 2 mol % $Pd(OAc)_2$ and 10 mol % NHPI. [d]Reaction was performed using TBHP (2 equiv) instead of molecular O_2. [e]Preparative scale experiment. [f]No reaction occurred. [g]Not determined.

74% isolated yields, respectively. Similarly, 4-fluorotoluene **2f** and 3-fluorotoluene **2g** afforded the desired products **3f** and **3g** in high yields. However, the reactivity of 2-fluorotoluene **2h** decreased considerably, furnishing the desired product **3h** in 33% yield. Toluene derivatives bearing other electron-withdrawing groups, apart from halogens, also participated well in the 1- acylation reaction. For instance, 4-methylbenzonitrile **2i**, 3-methylbenzonitrile **2j**, and methyl 4-methylbenzoate **2k** reacted to provide the desired products **3i**, **3j**, and **3k** in 77%, 75%, and 79% yields, respectively.

The toluene derivative 4′-methylacetophenone **2l** reacted with **1** to furnish the desired product **3l** in excellent yield (94%). Toluene derivatives having an electron-donating group were also well tolerated. For example, 2-methylanisole **2m** afforded 1-acylated carbazole derivative **3m** in 67% isolated yield. Also, *m*-xylene **3n**, *o*-xylene **2o**, and mesitylene **2p** participated in the reaction effectively to provide the desired products in good to moderate yields (Table 2, products **3n**, **3o**, and **3p**). The structure of monoacylated products **3f** (CCDC 1989688) and **3i** (CCDC 1989676) were confirmed by single crystal X-ray analysis (Table 2; Figures S1 and S2, SI).[25] Gram-scale experiments using 1 g of **1** were successful to obtain monoacylated carbazoles **3a** and **3b** in good yields (Table 2; see experimental section for synthetic procedure).

Next, the 1-acylation was examined with various substituted *N*-pyridylcarbazoles. Symmetrical 3,6-dichloro-*N*-pyridylcarbazole **5** reacted with 4-chlorotoluene **2b** to afford 1-acylated product **10b** in 83% yield (Table 3). 3,6-Dibromo-*N*-pyridylcarbazole **6** reacted with electron-rich 1-methoxy-4-methylbenzene **2q** and electron-deficient 4-methylbenzoate **2k** to give **11q** and **11k** in 66% and 68% yields, respectively (Table 3), whereas 3,6-diiodo-*N*-pyridylcarbazole **7** reacted with toluenes to provide the desired products **12q** and **12k** in moderate yields (Table 3). It is intriguing to find that when unsymmetrical monosubstituted *N*-pyridylcarbazole was used, acylation occurred exclusively at the ortho position of the unsubstituted ring. Unsymmetrical *N*-pyridylcarbazole **10** having a 3-chloro substituent produced 1-acylated product **13a** in 69% yield. The structure of **13a** was confirmed by X-ray crystal analysis (Table 3, CCDC 1989702; Figure S3, SI).[25] *N*-Pyridylcarbazole **12** having a 3-methoxy group furnished the 1-acylated product **13b** in 60% yield.

To validate our hypothesis about the in situ generation of the aldehyde from toluene in the reaction media, we performed the reaction by using aldehydes **16** instead of toluenes **2** in chlorobenzene as solvent (Table 4). The desired products were obtained in good isolated yields. The reaction proceeded well with heptaldehyde **16e**, providing the desired product **3r** in 75% yield (Table 4). Inspired by the result, we carried out the acylation of carbazole **15** with heptaldehyde **16e** to synthesize the acyl precursor **18** of carbazole alkaloid carazostatin.[26] The acylation provided exclusively the regioisomeric acyl derivative **17e** in 70% yield (Table 4).

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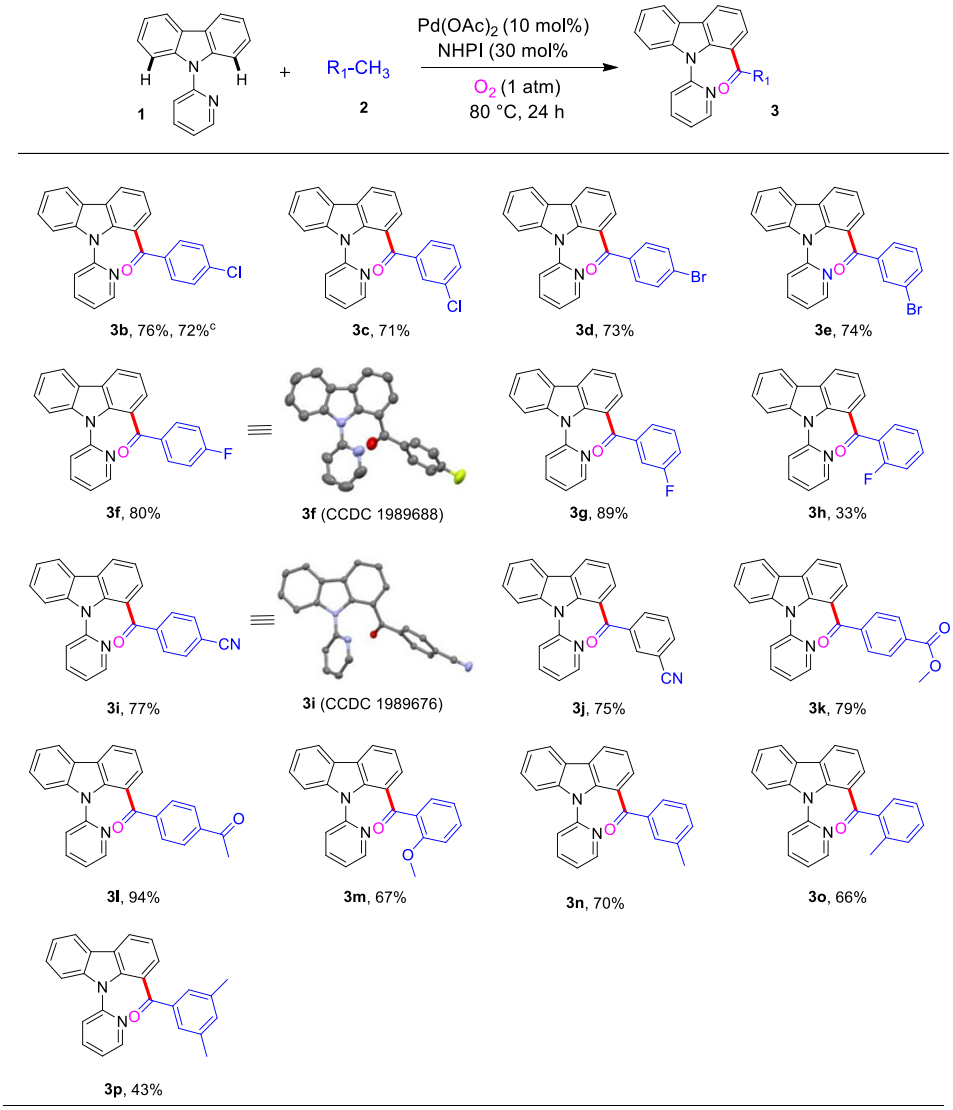
Table 2. Acylation of Unsubstituted *N*-Pyridylcarbazoles with Toluene Derivatives[a,b]



[a]*N*-Pyridylcarbazole **1** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (30 mol %), toluene **2** (1 mL), O_2 (1 atm), 80 °C. [b]Isolated yields. [c]Yield obtained when reaction was performed with 1 g of **1**.

To gain insight into the reaction mechanism, we carried out several control experiments. The reaction did not proceed in the presence of argon atmosphere (Table 1, entry 21), suggesting that molecular O_2 plays a key role in this transformation. The ^{18}O labeling experiment confirms that the oxygen atom of the keto-carbonyl group in the monoacylated product **3a′** originates from molecular oxygen (Scheme 2; Scheme S4, SI).

Further control experiments were performed using dimeric Pd(II) complex CP, prepared following the literature procedure.[8] When the acylation of **1** (1 equiv) was carried out using CP (5 mol %) instead of $Pd(OAc)_2$, the desired product **3b** was obtained in good yield (Scheme 3, a). However, when complex CP was used as both catalyst and substrate, no desired product was obtained (Scheme 3, b). Interestingly, the reaction of 3-methoxy-*N*-pyridylcarbazole **9** with **2b** in the presence of CP (25 mol %) provided **14b** in 50% yield and **3b** in 28% yield (Scheme 3, c). These experimental observations suggest that decomposition of the strong dimeric Pd(II) complex to the active monomeric Pd(II) intermediate might be essential for this transformation.

To know whether the reaction proceeds through a radical or ionic pathway, the reaction was performed in the presence of a radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl). The starting material **1** was fully recovered and the acyl adduct **19** was obtained in 70% yield (Scheme 4; Scheme S5, SI). This result indicated that acyl radical is trapped by the TEMPO free radical.

Based on experimental observations and previous reports,[21,22] a possible reaction mechanism is proposed (Scheme 5). The first step involves the generation of PINO radical from NHPI and dioxygen. The in situ-generated PINO radical abstracts hydrogen radical from toluene **2a** to form the benzylic radical which on reaction with molecular oxygen forms the reactive benzoyl radical via in situ formation of benzaldehyde. Pd(II)-catalyzed chelation-directed C−H activation followed by ligand-assisted proton abstraction in **A** leads to the cyclopalladated complex **B**. Complex **B** undergoes oxidative addition to bezoyl radical to generate the intermediate Pd(IV) species **C**. Reductive elimination of **C** provides the desired monoacylated product **3a** and regenerates Pd(II) catalyst.

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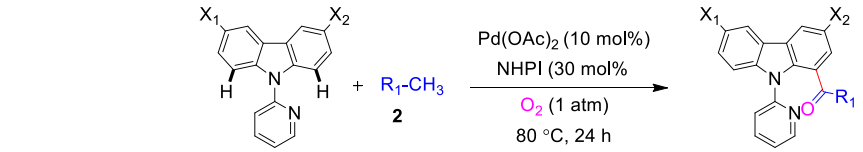
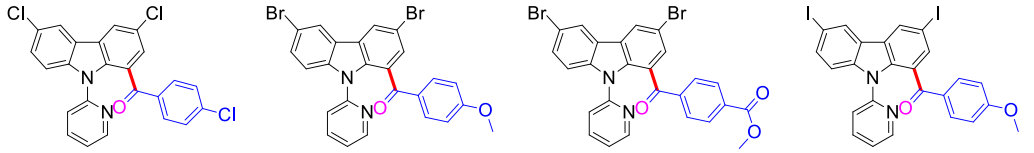
Table 3. Acylation of Substituted *N*-Pyridylcarbazoles with Toluene Derivatives[a,b]

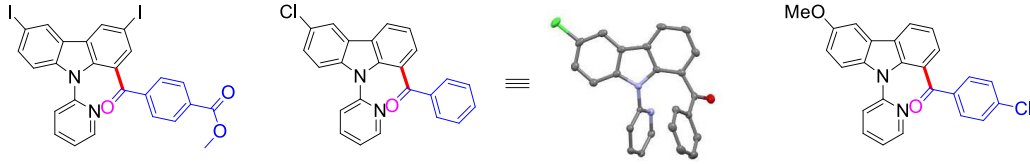


5: X_1, X_2 = Cl
6: X_1 = H, X_2 = Br
7: X_1 = I, X_2 = I
8: X_1 = H, X_2 = Cl
9: X_1 = OMe, X_2 = H

10: X_1, X_2 = Cl
11: X_1 = H, X_2 = Br
12: X_1 = I, X_2 = I
13: X_1 = H, X_2 = Cl
14: X_1 = OMe, X_2 = H



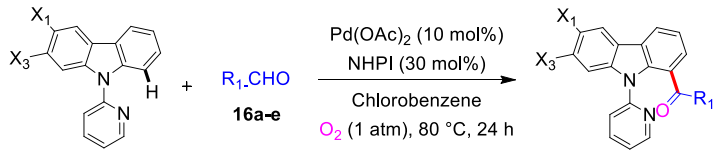
10b, 83% **11q**, 72% **11k**, 74% **12q**, 51%



12k, 58% **13a**, 69% **13a** (CCDC 1989702) **14b**, 60%

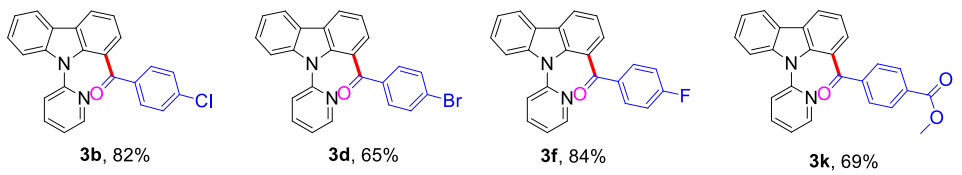
[a]*N*-Pyridylcarbazole **5**–**9** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (30 mol %), toluene **2** (1 mL), O_2 (1 atm), 80 °C. [b]Isolated yields.

Table 4. Acylation of *N*-Pyridylcarbazoles with Aldehydes[a,b]

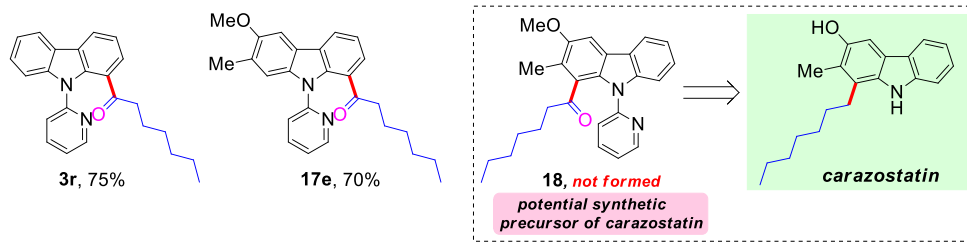


1: X_1, X_3 = H
15: X_1= OMe, X_3 = Me

3: X_1, X_3 = H
17: X_1= OMe, X_3 = Me



3b, 82% **3d**, 65% **3f**, 84% **3k**, 69%



3r, 75% **17e**, 70%

[a]*N*-Pyridylcarbazole **1** or **15** (0.25 mmol), aldehyde **16** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (30 mol %), chlorobenzene (1 mL), O_2 (1 atm), 80 °C. [b]Isolated yields.

CONCLUSION

In summary, we have developed a palladium-catalyzed highly site-selective method for the synthesis of monoacylated carbazole derivatives using toluene as the acyl source in the presence of molecular O_2 as oxidant. For monosubstituted *N*-pyridylcarbazoles, acylation takes place regioselectively in the unsubstituted benzene ring, providing C-1 acylated carbazoles in high yields. Notably, the method does not require any additional organic solvent. Thus, our approach provides a practical and general route for site-selective C–H acylation of carbazoles via an oxidative catalytic transformation. The operational simplicity, substrate compatibility, and use of molecular oxygen as sole

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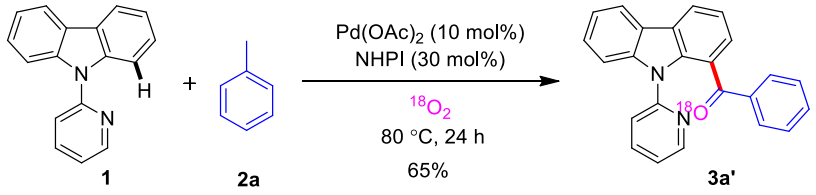
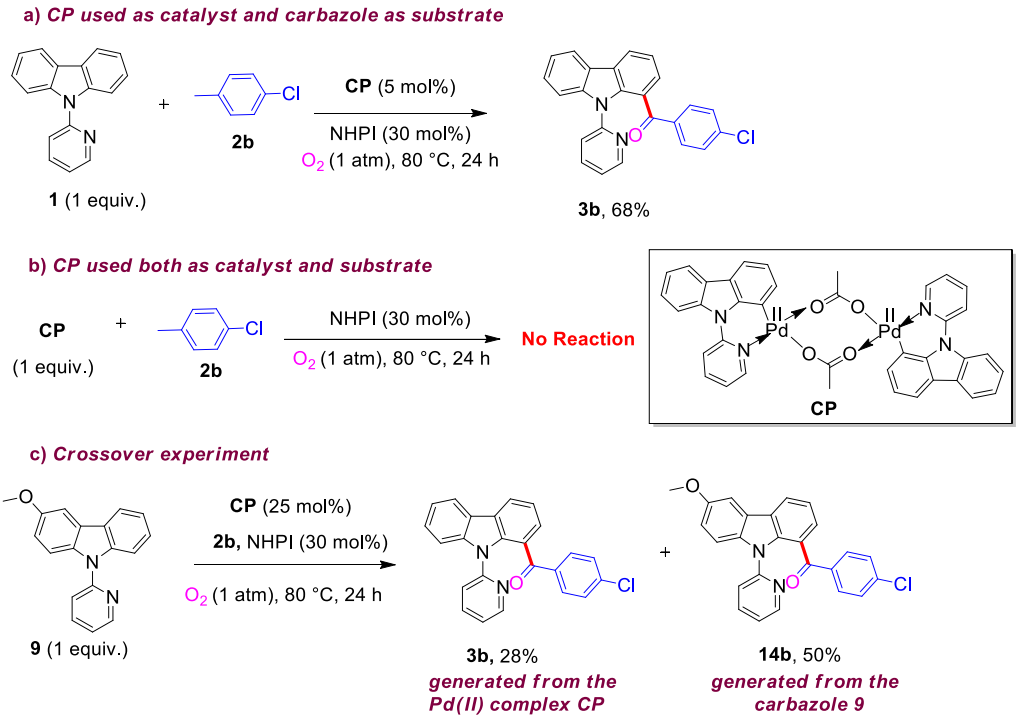
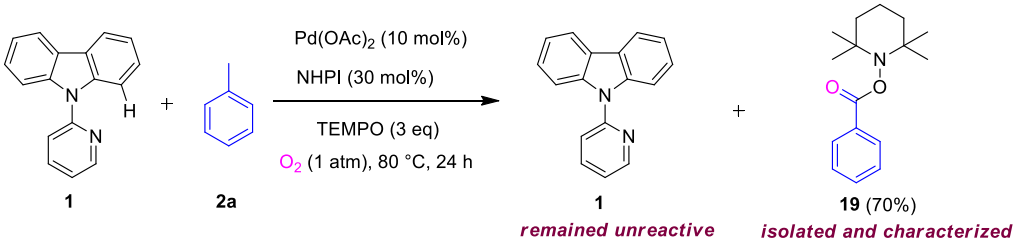
Scheme 2. ^{18}O Labeling Experiment



Scheme 3. Control Experiments



Scheme 4. Radical Quenching Experiment



oxidant make the present protocol synthetically useful and environmentally attractive.

EXPERIMENTAL SECTION

General Information. All experiments were carried out under an inert atmosphere of argon or under oxygen atmosphere in oven-dried flasks, sealed tubes, and Schlenk tubes. Solvents were dried according to standard procedures. All starting materials were obtained from commercial suppliers and used as received. Products were purified by column chromatography on silica gel (100−200 mesh, Merck). Unless otherwise stated, yields refer to analytically pure samples. NMR samples were dissolved in $CDCl_3$ and DMSO-d_6. The ^1H NMR spectroscopic data were recorded with 500 or 400 MHz instruments at 298 K. Signals are reported as δ values in ppm by using the residual signal of the protonated solvent as the internal standard (for $CHCl_3$, δ = 7.26 ppm). Data are reported in the order of chemical shift, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), br (broad), and m (multiplet)], coupling constant (J) in hertz, and integration values. The ^{13}C NMR spectroscopic data were recorded with complete proton decoupling with either a 100 or 125 MHz spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane with the solvent as the internal reference (for $CDCl_3$, δ = 77.16 ppm). HRMS analyses were performed with Q-TOF high resolution instruments by using positive ion mode electrospray ionization.

General Procedure for the Synthesis of Carbazole Derivatives 1, 5, and 8. Following the literature,[27] 9*H*-carbazole **S1** (167.2 mg, 1.0 mmol) or 3,6-dichloro-9*H*-carbazole **S2** (236.1 mg, 1.0 mmol) or 3-chloro-9*H*-carbazole **S3** (201.6 mg, 1.0 mmol) was placed in an oven-dried 5 mL vial with a magnetic stir bar. To this vial were added Cs_2CO_3 (325.8, 1.0 mmol), 2-bromopyridine (105 μL, 1.1 mmol), CuI (19 mg, 10 mol %), and 2 mL of dry DMF. Then the vial was sealed with a cap, irradiated for 45 min at 220 °C in a microwave reactor, and then cooled to room temperature. The reaction mixture was diluted with saturated aqueous ammonium chloride, and product was isolated by extraction with ethyl acetate. The organic layer was dried over sodium

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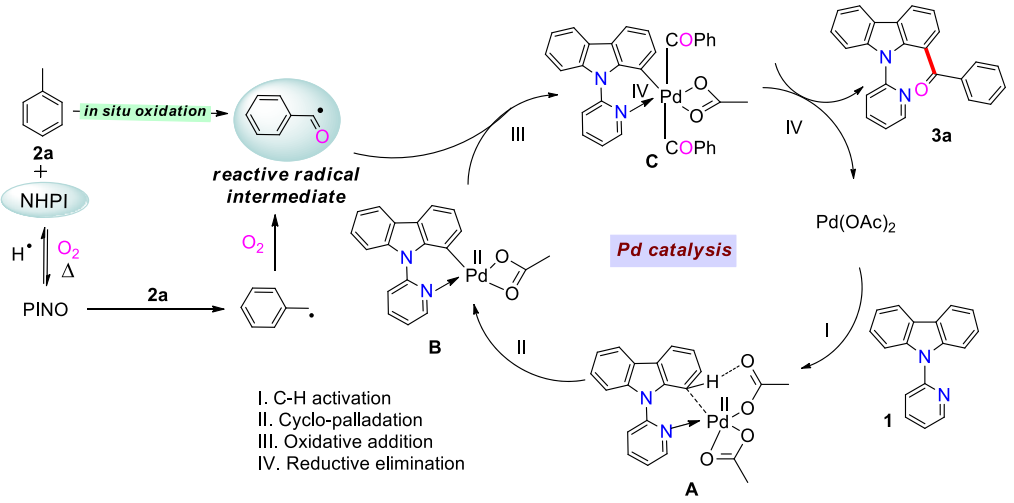
Scheme 5. Probable Catalytic Cycle of the Reaction



sulfate and concentrated under reduced pressure. The product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to give pyridine-protected carbazole derivatives **1**, **5**, and **8** as solids (Scheme S1, SI).

General Procedure for the Synthesis of 3,6-Dibromo-9-(pyridin-2-yl)-9*H*-carbazole 6. As reported in the literature,[12] to 9-(pyridin-2-yl)-9*H*-carbazole **1** (444.6 mg, 2 mmol) in dichlomethane (25 mL), containing silica (100−200 mesh, Merck, 8 g), was added a solution of NBS (712 mg, 4 mmol in 25 mL of dichloromethane) dropwise. The reaction mixture was stirred for 4.5 h in the absence of light at 18 °C until TLC indicated that the reaction was completed. The reaction mixture was filtered, and the silica was washed with dichloromethane. The combined extracts were washed with water (100 mL), and the organic layer was dried and evaporated. The residue was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to give 3,6-dibromo-9-(pyridin-2-yl)-9*H*-carbazole **6** (563 mg, 70%) as a white solid (Scheme S2, SI).

General Procedure for the Synthesis of 3,6-Diiodo-9-(pyridin-2-yl)-9*H*-carbazole 7. As reported in the literature,[12] 10 mL of glacial acetic acid was placed in a 50 mL round-bottom flask equipped with a magnetic stir bar and boiled. To this boiling acetic acid were added 9-(pyridin-2-yl)-9*H*-carbazole **1** (444.6 mg, 2 mmol) and KI (431.6 mg, 2.6 mmol). Then the mixture was cooled, potassium iodate (642.0 mg, 3 mmol) was added, and the reaction mixture was again boiled until a clear straw color was observed. The hot solution mixture was decanted from the undissolved potassium iodate and then diluted with saturated sodium thiosulfate solution, and the product was isolated by extraction into ethyl acetate. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to provide 3,6-diiodo-9-(pyridin-2-yl)-9*H*-carbazole **7** (397.0 mg, 40%) as a white solid (Scheme S3, SI).

General Procedure for the Mono C−H Acylation of Carbazole Derivatives Using Toluene as the Acyl Source (GP-1). Carbazole derivative **1**, **5**, **6**, **7**, **8**, or **9** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (30 mol %), and dry toluene **2** (1.0 mL) were added to a 10 mL Schlenk tube with a magnetic bar under O_2. The resulting mixture was evacuated and backfilled with O_2 two to three times. The reaction mixture was placed in a preheated oil bath at 80 °C for 24 h and monitored by TLC analysis. The solution was then cooled and diluted with dichloromethane (3 × 15 mL), washed with sodium bicarbonate (3 × 10 mL) and brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) to obtain products **3**, **10**, **11**, **12**, **13**, or **14**. The structure of the products was confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry analyses.

General Procedure for the Mono C−H Acylation of Carbazole Derivatives Using Aldehyde as the Acyl Source (GP-2). Carbazole derivative **1** or **15** (0.25 mmol), aldehyde **16** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (30 mol %), and dry chlorobenzene (1.0 mL) were added to a 10 mL Schlenk tube with a magnetic bar under O_2. The resulting mixture was evacuated and backfilled with O_2 two to three times. The reaction mixture was placed in a preheated oil bath at 80 °C for 24 h and monitored by TLC analysis. The solution was then cooled and diluted with dichloromethane (3 × 15 mL), washed with sodium bicarbonate (3 × 10 mL) and brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) to obtain products **3** or **17**. The structure of the products was confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry analyses.

Crystal Growth Procedure. Crystallizations of compounds **3f**, **3i**, and **13a** were carried out using a vapor diffusion method. A solution of the compound was prepared in chloroform in a small glass vial and then placed in a larger container containing hexane, and the outer vessel well was sealed. Over time, hexane evaporated and diffused over the gas phase into chloroform, leading to oversaturation and finally crystallization. The crystals were then analyzed.

Gram-Scale Experiment. *Preparation of Phenyl(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone (**3a**).* An oven-dried 50 mL round-bottom flask equipped with a stirring bar was charged with **1** (1 g, 4.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %, 92.0 mg), NHPI (30 mol %, 200.6 mg), and 15.0 mL of dry toluene **2a**. The resulting solution was purged with O_2 for 7 min, and the flask was then fitted with a reflux condenser having O_2 (balloon) on top of it and heated at 80 °C (preheated oil bath) for 24 h. After completion of the reaction, the solution was cooled to room temperature and diluted with dichloromethane (3 × 35 mL), washed with sodium bicarbonate (3 × 20 mL) and brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude reaction mixture was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20) to afford product **3a** (1.02 g, 70%) as a white solid.

*Preparation of (4-Chlorophenyl)[9-(2-pyridyl)-9H-carbazol-1-yl]-methanone (**3b**).* An oven-dried 50 mL round-bottom flask equipped with a stirring bar was charged with **1** (1 g, 4.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %, 92.0 mg), NHPI (30 mol %, 200.6 mg), and 15.0 mL of dry toluene **2b**. The resulting solution was purged with O_2 for 7 min, and the flask was then fitted with a reflux condenser having O_2 (balloon) on top of it and heated at 80 °C (preheated oil bath) for 24 h. After completion of the reaction, the solution was cooled to room temperature and diluted with dichloromethane (3 × 35 mL), washed with sodium bicarbonate (3 × 20 mL) and brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude reaction mixture was purified using column chromatography on

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silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15) to afford product **3b** (1.4 g, 72%) as a yellow solid.

^{18}O Labeling Experiment. To an oven-dried 5.0 mL Schlenk tube equipped with a magnetic stir bar was placed $Pd(OAc)_2$ (6.5 mg, 0.02 mmol). The tube was evacuated under vacuum and back-filled with argon (three times). To the tube were added 1 mL of freshly distilled toluene **2a**, NHPI (9.8 mg, 30 mol %), and **1** (50.0 mg, 0.2 mmol, 1.0 equiv). The mixture was degassed by the freeze−pump−thaw procedure three times. Finally, the tube was evacuated while placing it in a liquid nitrogen bath and filled with $^{18}O_2$ (provided from a 98% $^{18}O_2$ cylinder). The solution was heated at 80 °C for 24 h. The solution was allowed to cool to room temperature and diluted with dichloromethane (3 × 15 mL), washed with sodium bicarbonate (3 × 10 mL) and brine (2 × 10 mL), and concentrated under vacuum. The crude mixture was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20) to obtain the desired product **3a′** (48.0 mg, 70%). The incorporation of ^{18}O in the product was confirmed by HRMS of the sample (Scheme S4, SI).

Radical Quenching Experiment. The reaction was performed according to GP-1, combining **1** (50.0 mg, 0.2 mmol, 1.0 equiv), TEMPO (78.0 mg, 0.6 mmol, 3.0 equiv), Pd(II) catalyst (10 mol %, 6.5 mg), NHPI (9.8 mg, 30 mol %), and O_2 from a balloon in 1.0 mL of toluene **2a** at 80 °C (preheated oil bath) for 24 h. TLC analysis of the crude mixture revealed that the desired monoacylated product did not form. However, the acyl radical and TEMPO free radical adduct **19** was isolated (70%, 36 mg) using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 90:10) and characterized by NMR (Scheme S5, SI). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (dd, J = 8.3, 1.2 Hz, 2 H), 7.57−7.53 (m, 1 H), 7.45−7.42 (m, 2 H), 1.80−1.66 (m, 3 H), 1.59−1.55 (m, 2 H), 1.46−1.42 (m, 1 H), 1.26 (s, 6 H), 1.11 (s, 6 H) ppm; $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ = 166.4, 132.9, 130.0, 129.6, 128.6, 60.5, 39.3, 32.1, 21.0, 17.2 ppm.

Analytical Data of Compounds. *3,6-Dichloro-9-(pyridin-2-yl)-9H-carbazole* ***5***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 98:2 to 95:5); white solid (85%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, J = 3.6 Hz, 1 H), 8.02 (s, 2 H), 7.95 (t, J = 7.5 Hz, 1 H), 7.75 (d, J = 8.8 Hz, 2 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.41 (d, J = 8.6 Hz, 2 H), 7.36−7.33 (m, 1 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 151.3, 150.1, 138.9, 138.5, 127.1, 126.9, 124.6, 121.9, 120.2, 119.0, 112.6 ppm. HRMS (ESI): calcd for $C_{17}H_{11}Cl_2N_2$ $[M + H]^+$ 313.0294; found 313.0298.

3-Chloro-9-(pyridin-2-yl)-9H-carbazole ***8***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 98:2 to 95:5); white solid (82%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 4.0 Hz, 1 H), 8.08−8.07 (m, 2 H), 7.94 (t, J = 7.7 Hz, 1 H), 7.80 (t, J = 8.6 Hz, 2 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.47 (t, J = 7.8 Hz, 1 H), 7.39 (dd, J = 8.8, 1.9 Hz, 1 H), 7.33 (t, J = 7.3 Hz, 2 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 151.7, 149.9, 140.1, 138.7, 138.1, 127.1, 126.5, 126.4, 125.7, 123.5, 121.6, 121.4, 120.6, 120.1, 119.1, 112.5, 111.4 ppm. HRMS (ESI): calcd for $C_{17}H_{12}ClN_2$ $[M + H]^+$ 279.0683; found 279.0685.

3,6-Dibromo-9-(pyridin-2-yl)-9H-carbazole ***6***.[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 98:2 to 95:5); white solid (70%). ^1H NMR (400 MHz, $CDCl_3$): 8.72 (1H, d, J = 4.9 Hz), 8.18 (2H, d, J = 1.8 Hz), 7.96 (1H, dt, J = 7.9, 1.7 Hz), 7.71 (2H, d, J = 8.5 Hz), 7.59−7.53 (3H, m), 7.35 (1H, dd, J = 7.1, 5.1 Hz); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): 151.2, 150.0, 138.9, 138.7, 129.8, 125.1, 123.3, 122.0, 119.1, 114.2, 113.0; HRMS (ESI) calcd for $C_{17}H_{11}Br_2N_2$ $[M + H]^+$: 400.9289; found: 400.9282.

3,6-Diiodo-9-(pyridin-2-yl)-9H-carbazole ***7***.[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 99:1 to 97:3); white solid (40%). ^1H NMR (500 MHz, $CDCl_3$): 8.72 (1H, d, J = 4.0 Hz), 8.37 (2H, d, J = 1.1 Hz), 7.97−7.93 (1H, m), 7.71−7.69 (2H, m), 7.60−7.55 (3H, m), 7.34 (1H, dd, J = 7.1, 5.1 Hz); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): 151.3, 150.1, 139.1, 139.0, 135.4, 129.5, 125.6, 122.1, 119.2, 113.5, 84.3; HRMS (ESI) calcd for $C_{17}H_{11}I_2N_2$ $[M + H]^+$: 496.9012; found: 496.9009.

Phenyl(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone ***(3a)***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20); white solid (76% using GP-1), mp 200−202 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (dd, J = 7.8, 1.0 Hz, 1 H), 8.20 (d, J = 7.7 Hz, 1 H), 8.15 (dd, J = 4.9, 1.3 Hz, 1 H), 7.73 (dt, J = 7.8, 1.9 Hz, 1 H), 7.60−7.29 (m, 11 H), 7.10 (dd, J = 7.7, 4.6 Hz, 1 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 195.9, 152.4, 149.3, 140.9, 138.6, 137.9, 137.8, 137.6, 132.2, 129.8, 128.2, 127.8, 126.8, 125.9, 124.4, 123.9, 123.1, 122.0, 121.4, 120.5, 120.4, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{17}N_2O$ $[M + H]^+$ 349.1335; found 349.1337.

(4-Chlorophenyl)[9-(2-pyridyl)-9H-carbazol-1-yl]methanone ***(3b)***.[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); yellow solid (76% using GP-1 and 82% using GP-2), mp 214−218 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, J = 7.6 Hz, 1 H), 8.07 (d, J = 7.7 Hz, 1 H), 8.03−8.02 (m, 1 H), 7.68−7.65 (m, 1 H), 7.44−7.41 (m, 4 H), 7.34−7.24 (m, 4 H), 7.20−7.16 (m, 2 H), 7.01 (dd, J = 5.1, 7.4 Hz, 1 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.7, 152.4, 149.3, 140.9, 139.1, 138.7, 137.7, 136.0, 134.7, 131.3, 128.9, 128.5, 127.7, 127.0, 126.0, 123.9, 123.7, 122.2, 121.5, 120.5, 120.4, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{16}ClN_2O$ $[M + H]^+$ 383.0951; found 383.0954.

(3-Chlorophenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone ***(3c)***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (71% using GP-1), mp 218−222 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (dd, J = 1.3, 1.0 Hz, 1 H), 8.18−8.15 (m, 2 H), 7.76 (dt, J = 7.7, 1.8 Hz, 1 H), 7.55−7.49 (m, 3 H), 7.45−7.30 (m, 5 H), 7.24 (t, J = 7.8 Hz, 2 H), 7.15 (dd, J = 7.3, 4.9 Hz, 1 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.6, 152.3, 149.4, 140.9, 139.3, 138.8, 137.7, 134.6, 132.5, 129.5, 129.3, 128.2, 127.9, 127.0, 126.0, 123.9, 123.8, 123.6, 122.2, 121.6, 120.6, 120.5, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{16}ClN_2O$ $[M + H]^+$ 383.0946; found 383.0944.

(4-Bromophenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone ***(3d)***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); yellow solid (73% using GP-1 and 65% using GP-2), mp 182−184 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 7.6 Hz, 1 H), 8.17 (d, J = 7.7 Hz, 1 H), 8.12 (d, J = 3.9 Hz, 1 H), 7.77 (dt, J = 7.8, 1.5 Hz, 1 H), 7.46−7.34 (m, 10 H), 7.10 (dd, J = 7.1, 5.1 Hz, 1 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.9, 152.4, 149.3, 140.9, 138.7, 137.7, 136.4, 131.6, 131.4, 127.8, 127.7, 127.0, 126.0, 124.0, 123.9, 123.4, 122.2, 121.6, 120.5, 120.4, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{16}BrN_2O$ $[M + H]^+$ 427.0440; found 427.0442.

(3-Bromophenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone ***(3e)***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); yellow solid (74% using GP-1), mp 192−194 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, J = 7.4 Hz, 1 H), 8.10 (d, J = 7.1 Hz, 2 H), 7.68 (dt, J = 7.7, 1.8 Hz, 1 H), 7.59 (s, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.47 (d, J = 7.2 Hz, 1 H), 7.42 (d, J = 8.2 Hz, 1 H), 7.39−7.27 (m, 4 H), 7.23−7.18 (m, 2 H), 7.22 (d, J = 8.0 Hz, 1 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.9, 152.4, 149.3, 140.9, 138.7, 137.7, 136.4, 131.6, 131.4, 127.8, 127.7, 127.0, 126.0, 124.0, 123.9, 123.4, 122.2, 121.6, 120.5, 120.4, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{16}BrN_2O$ $[M + H]^+$ 427.0440; found 427.0445.

(4-Fluorophenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone ***(3f)***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); yellow solid (80% using GP-1 and 84% using GP-2), mp 204−206 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dd, J = 7.7, 1.0 Hz, 1 H), 8.17 (d, J = 7.6 Hz, 1 H), 8.12 (dd, J = 4.8, 1.1 Hz, 1 H), 7.75 (dt, J = 7.8, 1.9 Hz, 1 H), 7.60 (dd, J = 8.8, 5.5 Hz, 2 H), 7.53−7.50 (m, 2 H), 7.44−7.32 (m, 4 H), 7.09 (dd, J = 7.1, 4.6 Hz, 1 H), 6.97 (t, J = 8.6 Hz, 2 H) ppm. $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.5, 166.8, 164.2, 152.4, 149.3, 140.9, 138.7, 137.7, 134.6, 134.0, 133.9, 132.5, 132.4, 127.7, 127.0, 126.0, 123.2, 122.2, 121.5, 120.5, 120.4, 115.5, 115.3, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{15}FN_2OK$ $[M + K]^+$ 405.0800; found 405.0804.

(3-Fluorophenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone ***(3g)***. Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); yellow solid (89% using GP-1), mp 198−202 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 7.6 Hz, 1 H), 8.17 (d, J = 7.7 Hz, 1 H), 8.14 (d, J = 3.6 Hz, 1 H), 7.76

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(dt, J = 7.6, 1.5 Hz, 1 H), 7.54−7.50 (m, 2 H), 7.44−7.32 (m, 5 H), 7.30−7.27 (m, 2 H), 7.17 (dt, J = 8.2, 2.2 Hz, 1 H), 7.13−7.11 (m, 1 H) ppm. ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ = 194.6, 163.6, 161.6, 152.4, 149.4, 140.9, 139.8, 139.7, 138.7, 137.7, 129.9, 129.8, 127.8, 127.0, 126.0, 125.9, 124.0, 123.9, 123.5, 122.2, 121.6, 120.5, 120.5, 120.4, 119.7, 119.6, 116.1, 116.0, 110.3 ppm. HRMS (ESI): calcd for $C_{24}H_{16}FN_2O$ $[M + H]^+$ 367.1241; found 367.1243.

(2-Fluorophenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone (**3h**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); yellow solid (33% using GP-1), mp 210−212 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 7.0 Hz, 2 H), 8.15 (d, J = 7.7 Hz, 1 H), 7.79 (dt, J = 7.9, 1.9 Hz, 1 H), 7.57−7.54 (m, 2 H), 7.44−7.33 (m, 6 H), 7.16−7.14 (m, 1 H), 7.09 (t, J = 7.6 Hz, 1 H), 7.03−6.99 (m, 1 H) ppm. ^{13}C NMR{1H} (125 MHz, $CDCl_3$): δ = 192.2, 162.0, 152.8, 149.5, 141.3, 138.8, 137.6, 133.9, 133.8, 132.0, 128.4, 126.9, 126.3, 125.3, 124.0, 123.9, 122.2, 121.6, 120.5, 120.4, 120.1, 116.8, 116.6, 110.7 ppm. HRMS (ESI): calcd for $C_{24}H_{16}FN_2O$ $[M + H]^+$ 367.1241; found 367.1243.

4-(9-(Pyridin-2-yl)-9H-carbazole-1-carbonyl)benzonitrile (**3i**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20); white solid (77% using GP-1), mp 242−244 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, J = 7.5, Hz, 1 H), 8.17 (d, J = 7.7 Hz, 1 H), 8.09 (d, J = 4.9 Hz, 1 H), 7.87 (dd, J = 5.3, 3.1 Hz, 1 H), 7.79−7.75 (m, 2 H), 7.67 (d, J = 8.3 Hz, 2 H), 7.61 (d, J = 8.3 Hz, 2 H), 7.51 (t, J = 8.1 Hz, 2 H), 7.45−7.33 (m, 2 H), 7.11 (dd, J = 7.3, 5.0 Hz, 1 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 194.2, 168.0, 152.3, 149.3, 140.8, 140.7, 138.9, 137.6, 134.4, 132.8, 132.1, 130.1, 127.8, 127.2, 126.2, 123.9, 123.7, 123.2, 122.2, 121.8, 120.6, 120.3, 118.2, 115.7, 110.3 ppm. HRMS (ESI): calcd for $C_{25}H_{15}N_3ONa$ $[M + Na]^+$ 396.1107; found 396.1115.

3-(9-(Pyridin-2-yl)-9H-carbazole-1-carbonyl)benzonitrile (**3j**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20); white solid (75% using GP-1), mp 228−232 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (dd, J = 7.7, 0.9 Hz, 1 H), 8.18 (d, J = 7.7 Hz, 1 H), 8.10 (dd, J = 4.8, 1.2 Hz, 1 H), 7.86 (s, 1 H), 7.79−7.73 (m, 3 H), 7.51 (d, J = 7.6 Hz, 2 H), 7.45−7.32 (m, 5 H), 7.16−7.13 (m, 1 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 193.7, 152.4, 149.3, 140.8, 138.9, 138.6, 137.6, 135.4, 134.4, 133.8, 133.1, 129.2, 127.7, 127.2, 126.2, 123.9, 123.7, 123.1, 122.3, 121.8, 120.6, 120.4, 118.0, 112.8, 110.3 ppm. HRMS (ESI): calcd for $C_{25}H_{16}N_3O$ $[M + H]^+$ 374.1288; found 374.1287.

Methyl 4-(9-(pyridin-2-yl)-9H-carbazole-1-carbonyl)benzoate (**3k**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 75:25); white solid (79% using GP-1 and 69% using GP-2), mp 160−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 7.6 Hz, 1 H), 8.17 (d, J = 7.7 Hz, 1 H), 8.09 (d, J = 3.6 Hz, 1 H), 7.97 (d, J = 8.3 Hz, 2 H), 7.87−7.86 (m, 1 H), 7.76−7.73 (m, 2 H), 7.64 (d, J = 8.2 Hz, 2 H), 7.53−7.49 (m, 2 H), 7.43−7.31 (m, 2 H), 7.09−7.07 (m, 1 H), 3.94 (s, 3 H) ppm. ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ = 195.2, 168.0, 166.5, 152.4, 149.3, 141.0, 140.9, 138.8, 137.8, 134.4, 133.4, 132.8, 129.7, 129.4, 127.9, 127.0, 126.1, 124.0, 123.7, 123.6, 122.2, 121.6, 120.5, 120.4, 110.3, 52.5 ppm. HRMS (ESI): calcd for $C_{26}H_{18}N_2O_3Na$ $[M + Na]^+$ 429.1210; found 429.1213.

1-(4-(9-(Pyridin-2-yl)-9H-carbazole-1-carbonyl)phenyl)ethanone (**3l**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 75:25); white solid (94% using GP-1), mp 168−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 7.6 Hz, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 8.07 (d, J = 3.7 Hz, 1 H), 7.88 (d, J = 8.2 Hz, 2 H), 7.74 (dt, J = 7.7, 1.6 Hz, 1 H), 7.68 (d, J = 8.2 Hz, 2 H), 7.51 (d, J = 7.8 Hz, 2 H), 7.44−7.34 (m, 4 H), 7.08 (dd, J = 7.1, 5.1 Hz, 1 H), 2.61 (s, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 197.7, 195.1, 152.3, 149.3, 141.0, 140.9, 139.7, 138.8, 137.7, 130.0, 128.1, 127.8, 127.0, 126.1, 123.9, 123.6, 122.2, 121.6, 120.5, 120.4, 120.3, 110.3, 27.0 ppm. HRMS (ESI): calcd for $C_{26}H_{19}N_2O_2$ $[M + H]^+$ 391.1441; found 391.1442.

(2-Methoxyphenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone (**3m**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20); white solid (67% using GP-1), mp 216−220 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (dd, J = 4.9, 1.9 Hz, 1 H), 8.27 (d, J = 7.6 Hz, 1 H), 8.14 (d, J = 7.7 Hz, 1 H), 7.77−7.74 (m, 1 H), 7.58 (d, J = 8.3 Hz, 1 H), 7.53 (d, J = 7.3 Hz, 1 H), 7.42−7.37 (m, 3 H), 7.35−7.31 (m, 3 H), 7.14−7.12 (m, 1 H), 6.89−6.84 (m, 2 H), 3.61 (s, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 194.4, 158.4, 153.0, 149.4, 141.5, 138.5, 137.7, 134.5, 134.4, 133.0, 131.7, 129.0, 128.2, 126.8, 126.3, 126.1, 123.9, 123.6, 121.8, 121.4, 120.3, 120.2, 111.8, 110.8, 55.7 ppm. HRMS (ESI): calcd for $C_{25}H_{19}N_2O_2$ $[M + H]^+$ 379.1441; found 379.1445.

(9-(Pyridin-2-yl)-9H-carbazol-1-yl)(m-tolyl)methanone (**3n**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (70% using GP-1), mp 200−204 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dd, J = 7.7, 1.1 Hz, 1 H), 8.17 (d, J = 7.6 Hz, 1 H), 8.13 (dd, J = 4.9, 1.2 Hz, 1 H), 7.73 (dt, J = 7.8, 1.9 Hz, 1 H), 7.54 (dd, J = 7.4, 1.1 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 1 H), 7.43−7.27 (m, 7 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.10 (ddd, J = 7.4, 4.9, 0.8 Hz, 1 H), 2.31 (s, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 196.2, 152.4, 149.4, 141.0, 138.6, 138.0, 137.9, 137.7, 133.4, 130.1, 128.1, 128.0, 127.4, 126.8, 125.9, 124.6, 124.0, 123.1, 121.9, 121.2, 120.6, 120.5, 120.3, 110.3, 21.4 ppm. HRMS (ESI): calcd for $C_{25}H_{19}N_2O$ $[M + H]^+$ 363.1492; found 363.1497.

(9-(Pyridin-2-yl)-9H-carbazol-1-yl)(o-tolyl)methanone (**3o**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (66% using GP-1), mp 190−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30−8.27 (m, 2 H), 8.16 (d, J = 7.7 Hz, 1 H), 7.84 (dt, J = 7.8, 1.7 Hz, 1 H), 7.52−7.40 (m, 4 H), 7.39−7.31 (m, 4 H), 7.20−7.12 (m, 3 H), 2.34 (s, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 197.2, 152.8, 149.3, 141.4, 138.7, 138.6, 138.0, 137.7, 131.4, 131.2, 129.1, 127.9, 127.6, 126.8, 126.2, 125.9, 125.4, 123.8, 123.7, 122.1, 121.4, 120.4, 120.3, 110.4, 21.0 ppm. HRMS (ESI): calcd for $C_{25}H_{19}N_2O$ $[M + H]^+$ 363.1492; found 363.1495.

(3,5-Dimethylphenyl)(9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone (**3p**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (43% using GP-1), mp 206−208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dd, J = 6.7, 1.2 Hz, 1 H), 8.18−8.14 (m, 2 H), 7.75 (dt, J = 7.7, 1.8 Hz, 1 H), 7.53−7.48 (m, 2 H), 7.43−7.33 (m, 4 H), 7.21 (s, 2 H), 7.11−7.09 (m, 2 H), 2.23 (s, 6 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 196.5, 152.4, 149.4, 141.0, 138.6, 137.9, 137.8, 137.7, 134.3, 128.1, 127.6, 126.8, 125.9, 124.7, 124.0, 123.1, 121.9, 121.3, 120.6, 120.4, 120.2, 110.2, 21.2 ppm. HRMS (ESI): calcd for $C_{26}H_{21}N_2O$ $[M + H]^+$ 377.1648; found 377.1649.

(4-Chlorophenyl)(3,6-dichloro-9-(pyridin-2-yl)-9H-carbazol-1-yl)methanone (**10b**). Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (83% using GP-1), mp 222−224 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, J = 1.7 Hz, 1 H), 8.07−8.06 (m, 2 H), 7.80−7.77 (m, 1 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.40−7.39 (m, 2 H), 7.33 (d, J = 8.6 Hz, 3 H), 7.13−7.11 (m, 1 H) ppm. ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ = 193.3, 151.5, 149.4, 139.6, 139.0, 136.5, 135.2, 131.3, 129.5, 128.8, 127.8, 127.7, 127.4, 126.3, 126.2, 125.3, 124.2, 122.8, 122.7, 120.4, 120.3, 111.6 ppm. HRMS (ESI): calcd for $C_{24}H_{14}Cl_3N_2O$ $[M + H]^+$ 451.0166; found 451.0162.

(3,6-Dibromo-9-(pyridin-2-yl)-9H-carbazol-1-yl)(4-methoxyphenyl)methanone (**11q**).[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 90:10); white solid (72% using GP-1), mp 176−178 °C; ^{1}H NMR (500 MHz): δ = 8.32 (1H, d, J = 1.6 Hz), 8.23 (1H, d, J = 1.6 Hz), 8.08−8.07 (1H, m), 7.77 (1H, dt, J = 1.5 Hz, 7.6 Hz), 7.61−7.58 (3H, m), 7.51 (1H, dd, J = 1.7 Hz, 8.6 Hz), 7.33 (2H, dd, J = 1.7 Hz, 8.6 Hz), 7.11 (1H, dd, J = 4.9 Hz, 7.3 Hz), 6.82 (2H, d, J = 8.7 Hz), 3.86 (3H, s); ^{13}C{1H} NMR (100 MHz): δ = 192.9, 163.8, 151.4, 149.5, 139.9, 138.8, 136.8, 132.4, 130.3, 129.9, 126.5, 126.4, 125.4, 124.6, 123.4, 120.7, 120.5, 114.5, 113.7, 113.3, 112.1, 55.7; HRMS (ESI) calcd for $C_{25}H_{17}Br_2N_2O_2[M + H]^+$: 534.9657; found: 534.9653.

Methyl 4-(3,6-Dibromo-9-(pyridin-2-yl)-9H-carbazole-1-carbonyl)benzoate (**11k**).[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (74% using GP-1), mp 204−206 °C; ^{1}H NMR (500 MHz): δ = 8.35 (1H, d, J = 2.5 Hz), 8.22 (1H, d, J = 1.6 Hz,), 8.03−7.98 (3H, m), 7.76 (1H, dt, J = 1.7 Hz, 7.9 Hz), 7.65 (2H, d, J = 8.3 Hz), 7.60

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(1H, d, J = 2.5 Hz), 7.52 (1H, dd, J = 1.5 Hz, 9.1 Hz), 7.36 (1H, d, J = 8.35 Hz), 7.30 (1H, d, J = 7.55 Hz), 7.11 (1H, dd, J = 5.0 Hz, 7.3 Hz) 3.95 (3H, s); ^{13}C{1H} NMR (100 MHz): δ = 193.5, 188.3, 151.4, 149.4, 140.2, 139.8, 139.1, 136.7, 133.9, 130.5, 130.4, 129.7, 129.6, 126.7, 126.1, 125.5, 124.6, 123.5, 122.8, 120.2, 114.8, 113.4, 111.9, 52.6; HRMS (ESI) calcd for $C_{26}H_{17}Br_2N_2O_3$ [M + H]$^+$: 562.9606; found: 562.9611.

*(3,6-Diiodo-9-(pyridin-2-yl)-9H-carbazol-1-yl)(4-methoxyphenyl)methanone (**12q**).*[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 90:10); white solid (51% using GP-1), mp 184−186 °C; ^{1}H NMR (500 MHz): δ = 8.50 (1H,d, J = 1.5 Hz), 8.41 (1H, d, J = 1.4 Hz), 8.07 (1H, dd, J = 1.1 Hz, 4.7 Hz), 7.77−7.74 (2H, m), 7.67 (1H, dd, J = 1.5 Hz, 8.6 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.30 (1H, d, J = 7.9 Hz), 7.24 (1H, d, J = 8.7 Hz), 7.11 (1H, dd, J = 5.0 Hz, 7.0 Hz), 6.82 (2H, d, J = 8.8 Hz), 3.85 (3H, s); ^{13}C{1H} NMR (125 MHz): δ = 192.8, 163.7, 151.3, 149.4, 140.2, 138.8, 136.9, 135.8, 135.6, 132.3, 131.4, 129.9, 129.5, 126.7, 124.9, 122.7, 120.5, 113.7, 112.4, 84.4, 82.9, 55.6; HRMS (ESI) calcd for $C_{25}H_{17}I_2N_2O_2$ [M + H]$^+$: 630.9379; found: 630.9376.

*Methyl 4-(3,6-Diiodo-9-(pyridin-2-yl)-9H-carbazole-1-carbonyl)-benzoate (**12k**).*[12] Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 85:15); white solid (58% using GP-1), mp 194−196 °C; ^{1}H NMR (500 MHz): δ = 8.46 (1H, d, J = 5.3 Hz), 8.34 (1H, d, J = 5.2 Hz), 7.95−7.91 (3H, m), 7.69−7.66 (2H, m), 7.61−7.54 (3H, m), 7.22−7.15 (2H, m), 7.04−7.01 (1H, m), 3.86 (3H, d, J = 5.3 Hz); ^{13}C{1H} NMR (125 MHz): δ = 193.4, 166.3, 151.4, 149.4, 140.2, 140.1, 139.0, 136.9, 135.9, 135.8, 133.4, 132.2, 129.7, 129.6, 126.9, 125.9, 124.9, 122.7, 120.2, 112.4, 84.7, 82.9, 52.6; HRMS (ESI) calcd for $C_{26}H_{17}I_2N_2O_3$ [M + H]$^+$: 658.9329; found: 658.9325.

*(6-Chloro-9-(pyridin-2-yl)-9H-carbazol-1-yl)(phenyl)methanone (**13a**).* Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20); white solid (69% using GP-1), mp 198−200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (dd, J = 6.8, 1.0 Hz, 1 H), 8.12−8.09 (m, 2 H), 7.74 (dt, J = 7.7, 1.6 Hz, 1 H), 7.60−7.55 (m, 3 H), 7.50−7.30 (m, 7 H), 7.10 (dd, J = 7.1, 5.1 Hz, 1 H) ppm. ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ = 195.7, 152.0, 149.4, 139.3, 138.8, 138.3, 137.4, 132.8, 129.9, 128.6, 128.4, 128.3, 126.9, 125.2, 124.9, 124.6, 123.3, 122.4, 120.7, 120.4, 120.2, 111.5 ppm. HRMS (ESI): calcd for $C_{24}H_{16}ClN_2O$ [M + H]$^+$ 383.0946; found 383.0944.

*(4-Chlorophenyl)(6-methoxy-9-(pyridin-2-yl)-9H-carbazol-1-yl)-methanone (**14b**).* Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 80:20); white solid (60% using GP-1), mp 224−226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 7.2 Hz, 1 H), 8.24−8.10 (m, 1 H), 7.74 (dt, J = 6.0, 1.6 Hz, 1 H), 7.62 (d, J = 2.4 Hz, 1 H), 7.54−7.49 (m, 3 H), 7.43 (d, J = 8.8 Hz, 1 H), 7.38−7.27 (m, 4 H), 7.09−7.03 (m, 2 H), 3.95 (s, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 194.7, 155.4, 152.5, 149.2, 139.0, 138.7, 138.1, 136.0, 135.7, 131.3, 128.6, 127.8, 126.0, 124.6, 124.1, 123.3, 122.0, 120.2, 115.8, 111.2, 103.3, 56.2 ppm. HRMS (ESI): calcd for $C_{25}H_{18}ClN_2O_2$ [M + H]$^+$ 413.1051; found 413.1055.

*1-(9-(Pyridin-2-yl)-9H-carbazol-1-yl)heptan-1-one (**3r**).* Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 90:10); Colorless oil (75% using GP-2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (d, J = 3.6 Hz, 1 H), 8.25 (d, J = 7.9 Hz, 1 H), 8.13 (d, J = 7.7 Hz, 1 H), 7.96 (dt, J = 7.6, 1.5 Hz, 1 H), 7.66 (d, J = 7.5 Hz, 1 H), 7.59−7.55 (m, 2 H), 7.43 (t, J = 7.8 Hz, 1 H), 7.36−7.32 (m, 2 H), 7.29 (dd, J = 7.1, 5.0 Hz, 1 H), 2.82 (t, J = 7.6 Hz, 2 H), 1.49−1.45 (m, 2 H), 1.33−1.27 (m, 6 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 203.1, 153.1, 149.3, 141.5, 138.8, 136.8, 126.8, 126.5, 126.3, 126.1, 123.8, 123.4, 122.2, 121.4, 120.7, 120.3, 120.2, 110.5, 41.4, 31.7, 29.1, 24.2, 22.6, 14.1 ppm. HRMS (ESI): calcd for $C_{24}H_{25}N_2O$ [M + H]$^+$ 357.1961; found 357.1964.

*1-(6-Methoxy-7-methyl-9-(pyridin-2-yl)-9H-carbazol-1-yl)-heptan-1-one (**17e**).* Product was purified using column chromatography on silica gel (eluent: hexane/ethyl acetate 95:5 to 90:10); Colorless oil (75% using GP-2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, J = 4.4 Hz, 1 H), 8.16 (d, J = 7.8 Hz, 1 H), 7.95 (ddd, J = 5.8, 1.9, 1.5 Hz, 1 H), 7.59 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.48 (s, 1 H), 7.34 (s, 1 H), 7.32−7.27 (m, 2 H), 3.97 (s, 3H), 2.79 (t, J = 7.4 Hz, 2 H), 2.34 (s, 3 H), 1.46−1.41 (m, 2 H), 1.29−1.25 (m, 6 H), 0.88 (t, J = 3.9 Hz, 3 H) ppm. ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 203.4, 153.9, 153.4, 149.3, 138.9, 136.8, 136.0, 127.4, 126.8, 126.3, 125.6, 122.9, 122.0, 121.9, 120.5, 120.0, 112.3, 100.8, 56.0, 41.5, 31.8, 29.1, 24.3, 22.6, 17.6, 14.2 ppm. HRMS (ESI): calcd for $C_{26}H_{29}N_2O_2$ [M + H]$^+$ 401.2229; found 401.2222.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01746.

Synthesis of pyridine-protected carbazole derivatives, reaction optimization, labeling experiment, radical quenching experiment, X-ray crystallographic data, and NMR (^{1}H NMR and ^{13}C NMR) spectra of all the compounds (PDF)

Accession Codes

CCDC 1989676, 1989688, and 1989702 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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