RECENT DEVELOPMENTS IN C−H FUNCTIONALIZATION OF CARBAZOLES

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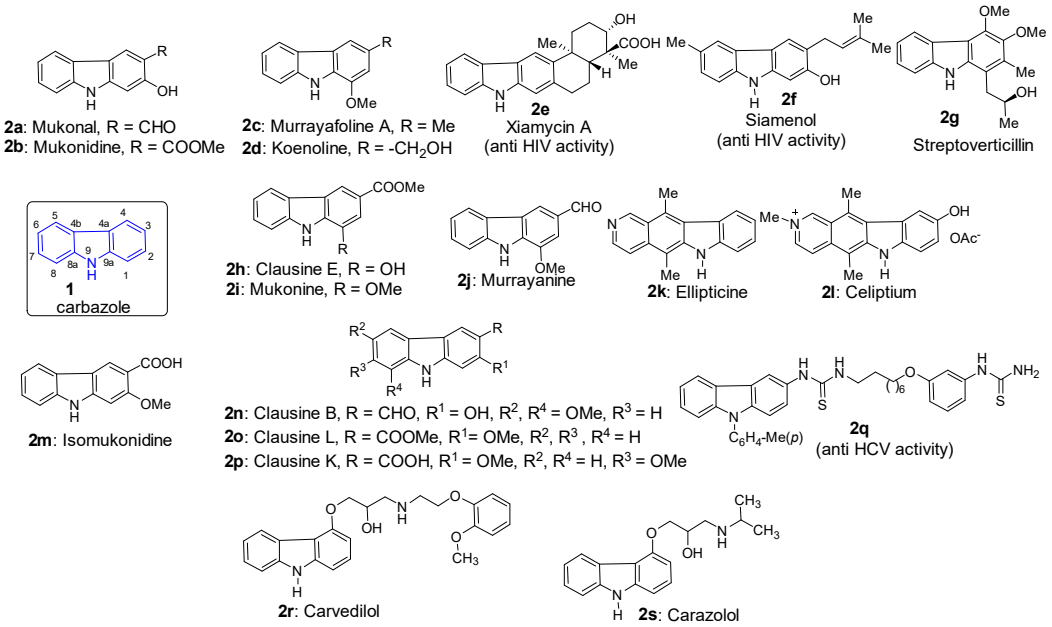
Abstract. *In recent years, the transition metal-catalyzed C−H activation and functionalization have emerged as valuable synthetic transformations for modifying small organic molecules and introducing functional groups in these molecules. Carbazole is a privileged class of nitrogen-containing heterocycles. Carbazole derivatives are used as key units in materials and medicinal chemistry research. Owing to their importance, several protocols including the C−H functionalization have been developed for synthesizing functionalized carbazole derivatives. This review delineates developments in the area pertaining to the modification of carbazole skeleton involving the transition metal-catalyzed C−H activation/functionalization of C−H bonds present in carbazole motif affording functionalized carbazoles.*

Contents

1. Introduction

Carbazole **1** is one of the privileged tricyclic nitrogen-containing motifs in the family of heterocycles.[1-4] The carbazole motif constitutes various naturally occurring alkaloids, such as clausine (clausine B, E, H, I, L and K), murrayanine, murrayafoline A, koenoline and mukonine derivatives. Carbazole motifs are prevalent in drug molecules (ellipticine, celiptium, carvedilol, carazolol, streptoverticillin, xiamycin A and siamenol), and biologically active compounds exhibiting anticancer antibiotic, anti-HIV, antidiabetic, antioxidant, anti-Alzhemeir's, and anti-HCV activities and used for the treatment of hypertension and other cardiovascular diseases (Scheme 1).[2,3] Selected examples of naturally occurring carbazole alkaloids and bioactive compounds **2a-s** are shown in Scheme 1. Apart from the utility of carbazoles as bioactive compounds, carbazole-based scaffolds are used as building blocks in material science due to their inherent physicochemical properties.[1-4] Carbazole motif functions as a key unit in various advanced functional materials including organic dyes, photovoltaics, conducting polymers, OLEDs,

optoelectronic photorefractive materials, *etc.* Structural modifications of all the available positions in carbazoles especially in C2, C3, C6, C7 and C9 positions afforded a wide range of carbazoles with tuned molecular and optical properties.[4]



Scheme 1. Representative examples of naturally occurring and bioactive carbazoles.

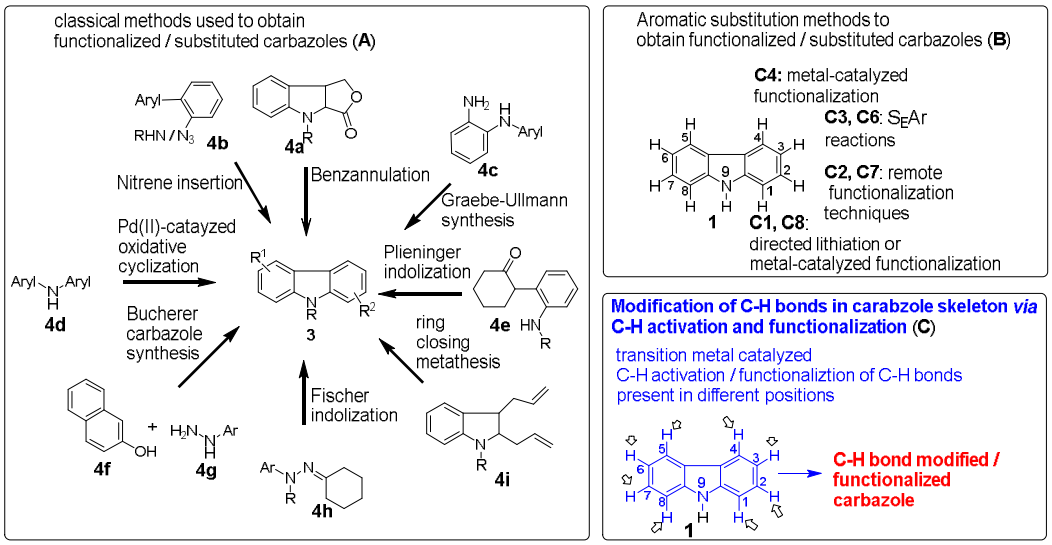
Owing to the applications of carbazoles in various fields of chemical sciences, many synthetic methods have been reported for synthesizing functionalized carbazole scaffolds **3** (Scheme 2). Borche-Drechsel cyclization, Bucherer synthesis, and Graebe-Ullmann reaction are some of the classical approaches to synthesizing carbazole moiety. The synthesis of carbazoles was accomplished using nitrene insertion, Fischer indolization, Pummerer cyclization, Diels-Alder reaction, and dehydrogenative cyclization of diarylamines, *etc.* Transition metal-mediated C−C and C−N bond formation, Suzuki-Miyaura coupling, cyclotrimerization, benzannulation, and ring-closing metathesis are some of the commonly employed methods for the synthesis of carbazole moiety.[5] Representative classical methods affording carbazole compounds **3** from corresponding building blocks **4a-i** are shown in Scheme 2. Furthermore, the newly emerged transition metal-mediated C−H functionalization route, in particular, 2-aminobiphenyls undergoing intramolecular C−H amination is a well-known method to generate carbazole derivatives (Scheme 2).[6]

The transition metal-catalyzed C−H functionalization route has emerged as a reliable synthetic protocol for the incorporation of functional groups at the C−H bonds of aromatic and aliphatic molecules. The C−H functionalization route is considered an alternative approach to the traditional cross-coupling reactions, which involves the use of organometallics reagents.[7-13] The regioselective C−H functionalization and differentiation of chemically or electronically identical C−H bonds in arenes or aliphatic chains is an inherent challenge associated with the transition metal-catalyzed C−H functionalization approach. To tackle the issue of regioselective C−H functionalization, a directing group is introduced to enable effective site-selective C−H activation followed by the introduction of a functional group at a given C−H bond. This process involves a regioselective cyclometallation *via* chelation assistance by the directing group at a given C−H bond followed by the subsequent coordination/oxidative addition of a coupling partner to the metal center and reductive elimination pathways affords the desired C−H-functionalized products. Along this line, in particular, the Pd(II)-catalyzed C−H functionalization assisted by a bidentate directing group has emerged as a dependable route to introduce functional groups at the C−H bonds in small organic molecules. Various

bidentate directing groups such as 8-aminoquinoline, 2-(methylthio)aniline, and picolinamide (2-picolinic acid) were developed as reliable directing groups to accomplish the site-selective C−H functionalization transformation.[11,12] Various classes of small organic molecules including aromatic, aliphatic, alicyclic, heterocyclic compounds and amino acid derivatives have been subjected to the site-selective C−H functionalization including arylation, alkylation, alkenylation, alkoxylation, halogenation, amination, *etc*. Along this line, the carbazole skeleton has also been subjected to transition metal-mediated C−H activation and functionalization approach to furnish substituted carbazoles.

Aromatic C−H functionalization is a direct approach for the formation of substituted carbazoles, but it is highly positional dependent. Functionalization at the C3, C6-positions is easily carried out *via* electrophilic aromatic substitution reaction,[14] while the C1, C8-positions are functionalized through directed lithiation or metal-catalyzed C−H activation strategy.[15] The C2, C7-functionalisation is less explored and C2, C7-positions are relatively difficult to access. However, remote functionalization approaches have been developed to access these positions by Baran and co-workers.[16] Recently, the C−H functionalization of the C4 position has been disclosed by the Frost group,[17a] involving Ru catalysis and the coupling of *N*-pyrimidinyl carbazoles with *α*-bromo esters (Scheme 2). Moreover, Grainger and co-workers unveiled the direct functionalization of sterically hindered C4, C5 positions of carbazoles *via* regioselective dilithiation.[17b]

Various reviews describe the available classical methods including aromatic substitution reactions affording modified carbazoles.[1-6] This review is focused on delineating the developments in the area pertaining to the modification of the carbazole skeleton involving the transition metal-catalyzed C−H activation/functionalization of C−H bonds present at different positions in the carbazole skeleton affording functionalized carbazoles (Scheme 2).



Scheme 2. Methods for the synthesis of functionalized carbazoles.

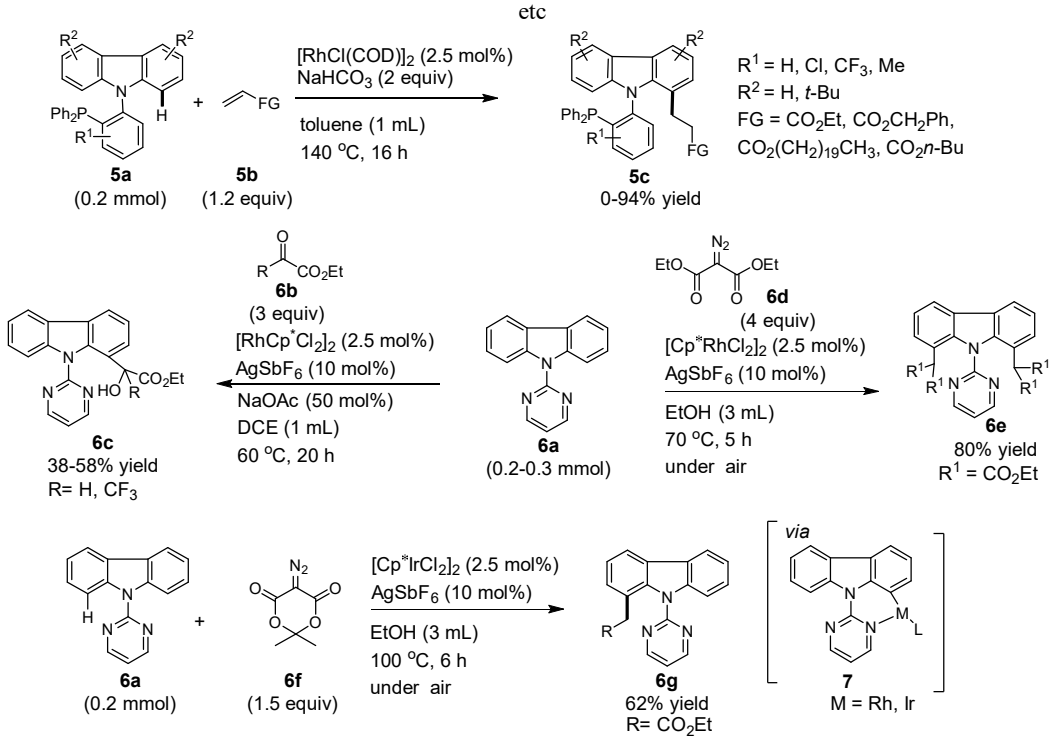
2. Synthesis of alkylated carbazoles *via* C−H alkylation

2.1. C1 Alkylation

In this section, we present the recent developments pertaining to the C−H alkylation of carbazole motifs *via* the directing group-aided C−H activation/functionalization. The Soulé group[18a] reported the synthesis of C1 alkyl substituted PhenCarPhos **5c** by C−H bond alkenylation of PhenCarPhos [*N*-(2-(diphenylphosphanyl)phenyl)carbazole] with alkenes **5b** catalyzed by a Rh(I) catalyst (Scheme 3). The trivalent phosphine unit present in the carbazole motif **5a** acted as a directing group and C−H bond functionalization occurred exclusively on the C1 position of the carbazole moiety **5a**. Further, C1 alkyl

substituted PhenCarPhos was tested as a ligand in Pd-catalyzed carbon dioxide-fixation reactions with propargylic amines. It was found to promote the Pd-catalyzed carbon dioxide-fixation reactions with propargylic amines with higher efficiency than other commercial or unfunctionalized phosphines.

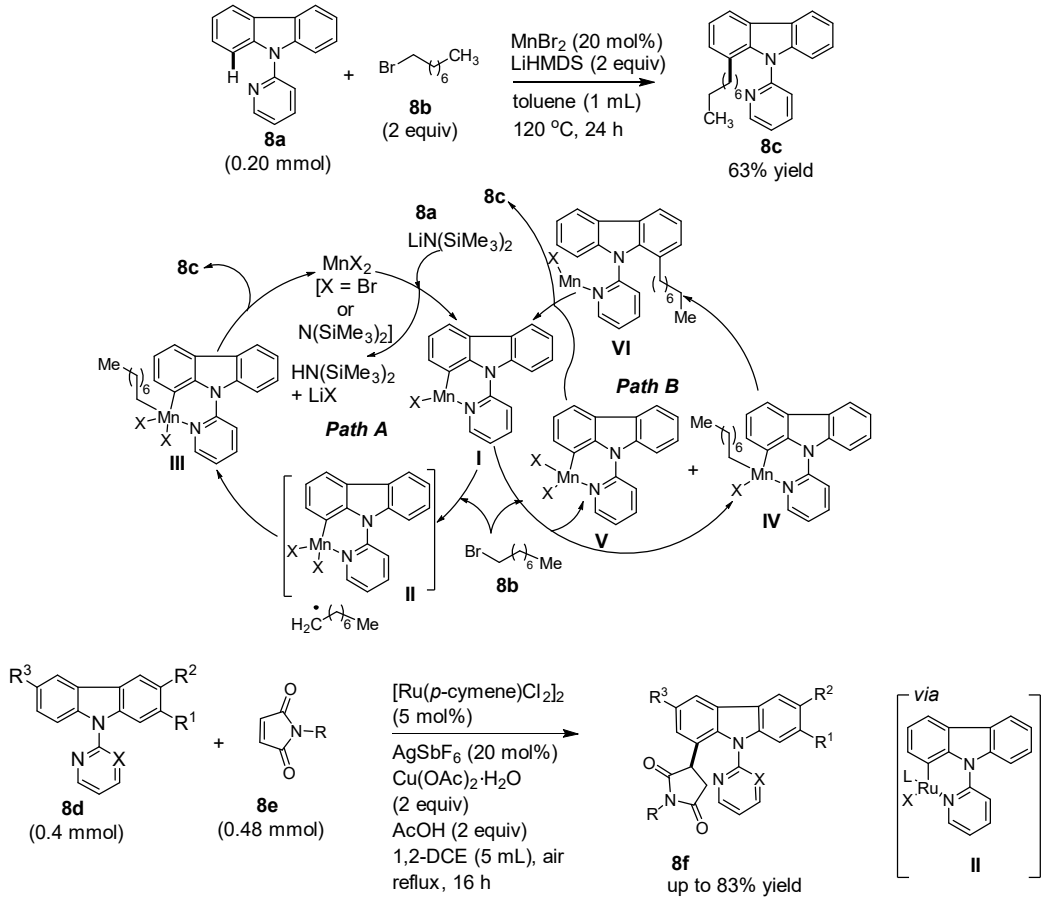
Kim and co-workers reported[18b] single examples of site-selective Rh(III)-catalyzed Grignard-type additions of carbazoles to activated carbonyl compounds *via* the C−H bond activation method (Scheme 3). The cationic Rh complex helps in the generation of C1-alkylated carbazoles. The carbazole derivative **6c** was synthesized by heating a mixture of **6a** (0.3 mmol), **6b** (5 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), NaOAc (50 mol%), DCE (1 mL) at 60 °C for 20 h. Zhou and co-workers[18c] reported a Rh-catalyzed reaction involving the mono-alkylation and bis-alkylation at the C1 and C8 positions of carbazoles **6a** possessing a pyrimidine unit as the directing group installed at the N9 position of carbazole **6a** *via* Rh catalysis by using diethyl diazomalonate **6d** as a coupling partner affording **6e**. The reaction exhibits high functional group tolerance and regioselectivity and nitrogen is released as the sole byproduct thus it is an environmentally benign method. Interestingly, the authors have successfully reported the Ir(III)-catalyzed pyrimidine directing group-assisted intermolecular insertion of arene C1−H bonds of carbazole with diazo compounds **6f** to afford the C1 functionalized carbazole **6g**. Based on the literature precedent on the Ru(II)-catalyzed C−H functionalization, the Ir(III)-catalyzed pyrimidine directing group-assisted intermolecular insertion of arene C1−H bonds of carbazole **6a** with diazo compounds proceeded through the plausible intermediate **7**.



Scheme 3. C1 and C8 Alkylated carbazoles *via* C−H alkylation.

In 2022, Punji *et al.* demonstrated[19a] manganese-catalyzed selective Csp^2−H alkylation of indolines, carbazoles and (2-pyridinyl)arenes with alkyl bromides without any assistance of a phosphine ligand or Grignard reagent. A single example of 2-pyridinyl carbazole **8a** with 1-octyl bromide **8b** (2 equiv) in the presence of $MnBr_2$ (20 mol%) catalyst, LiHMDS (2 equiv) base in toluene at 120 °C for 24 h was

demonstrated to furnish selective C1 mono-alkylated product **8c** in 63% yield, even though two Csp^2–H bonds (C1 and C8) were available for the alkylation (Scheme 4).



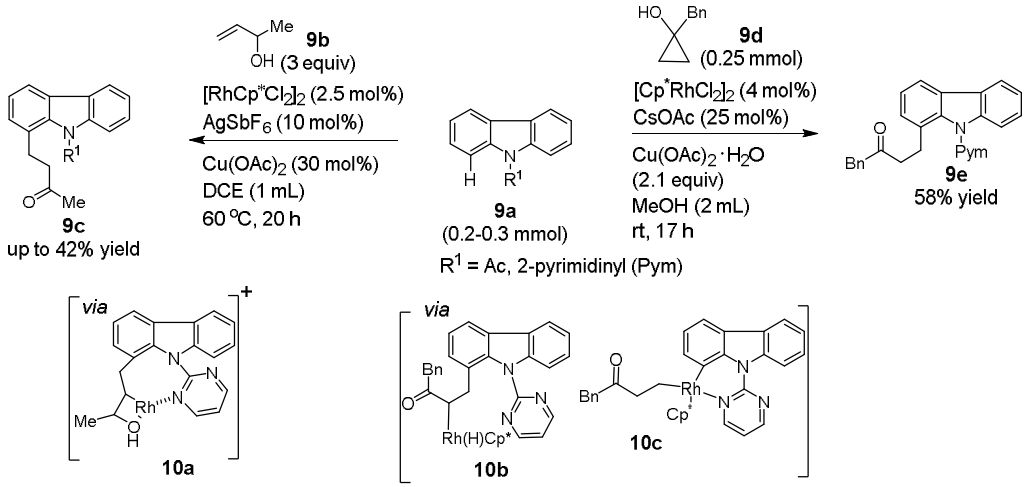
R^1 = H, Br; X = CH, N; R^2, R^3 = H, Br, Ph, OMe, Cl
R = Ph, Me, Bn, Et, cyclohexyl

Scheme 4. C1–H Alkylation of carbazole.

Preliminary mechanical studies revealed[19a] that alkylation proceeded through a single electron transfer (SET) pathway involving one electron oxidative addition of an alkyl bromide and a rate-limiting C–H metalation of 2- pyridinyl carbazole. Based on the study and precedents, two tentative catalytic cycles were proposed (Path A or Path B). It was claimed[19a] that the reaction commences with $MnBr_2$ or Mn(II)-amido species that reacts with C1–H of **8a** in the rate-limiting step to form intermediate **I** which triggers the halide atom transfer (HAT) of **8b**, leading to species **II** and alkyl radical (Path A). Controlled and radical clock studies have proved the involvement of alkyl radicals. Radical recombination followed by the reductive elimination from species **III** would result in the formation of **8c**. Alternately, two molecules of intermediate **I** can participate in homolytic cleavage of the C–Br bond in **8b** to afford the Mn(III) intermediates **IV** and **V** (Path B). Considering the positive fractional rate order of alkylation on catalyst concentrations, this pathway seems more feasible. The reductive elimination of **8c** would generate the product (or substrate) coordinated Mn(I) complex **VI**. Upon releasing **8c**, the Mn(I) with **V** may form active species **I** and MnX_2, which may re-enter the catalytic cycle. Lee and co-workers reported[19b] the Ru-catalyzed pyridyl or pyrimidyl directing

group-assisted regioselective C1−H activation and alkylation of carbazoles using maleimides. Synthesis of carbazole **8f** was carried out using **8d** (0.4 mmol), **8e** (0.48 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), AcOH (2equiv), 1,2-DCE (2 mL) under air for 16 h. This reaction provided a rapid approach to install the succinimide group at the C1 position of the carbazole moiety through a plausible intermediate **II** generated *via* chelation-assisted C−H activation. The reaction of **8d** with 2-methyl-*N*-phenylmaleimide failed to give the desired product. Carbazoles and maleimides tolerated various electron-donating and electron-withdrawing groups giving the desired products in good to excellent yields (Scheme 4).

Kim and co-workers reported[19c] the Rh(III)-catalyzed site-selective C−H alkylation of carbazoles with readily available allylic alcohols to afford *β*-aryl carbonyl heterocycles. The alkylated carbazole derivative **9c** was synthesized by heating **9a** (0.3 mmol) and **9b** (0.9 mmol) in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (30 mol%) and DCE (1 mL) at 60 °C for 20 h. It was observed that *N*-acetyl carbazole was not able to generate the desired product. The mechanistic pathway suggested that a cationic Rh(III) catalyst coordinates to a pyrimidine moiety of **9a**, affording a rhodacyclic intermediate which undergoes coordination with **9b** and subsequent 1,2-migratory insertion to generate intermediate **10a**. Finally, *β*-H elimination affords the corresponding enol product, which subsequently undergoes keto-enol tautomerization to give *β*-aryl ketone **9c** (Scheme 5). Along this line, Li and co-workers have reported[19d] the regioselective Rh(III)-catalyzed pyrimidine-directed C1 alkylation of carbazoles **9a** using cyclopropanols as the coupling partner. Cyclopropanols being highly reactive due to the strained 3-membered ring allowed the coupling to occur at room temperature *via* C−H activation of carbazoles and C−C cleavage of cyclopropanols. The product **9e** was synthesized by treating **9a** (0.2 mmol) and **9d** (0.25 mmol) in the presence of $[Cp^*RhCl_2]_2$ (4 mol%), CsOAc (25 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), MeOH (2 mL) at room temperature for 17 h. Based on the preliminarily mechanistic studies and previous work, the authors suggested that the C1 alkylated carbazole was obtained through the possible intermediate **10b**. It was stated[19d] that the reductive elimination of intermediate **10c** to **9e** and Rh(I) cannot be completely ruled out, although previous studies indicated that this was unlikely in the ring-opening coupling between *N*-pyrimidylindole and cyclopropanol.

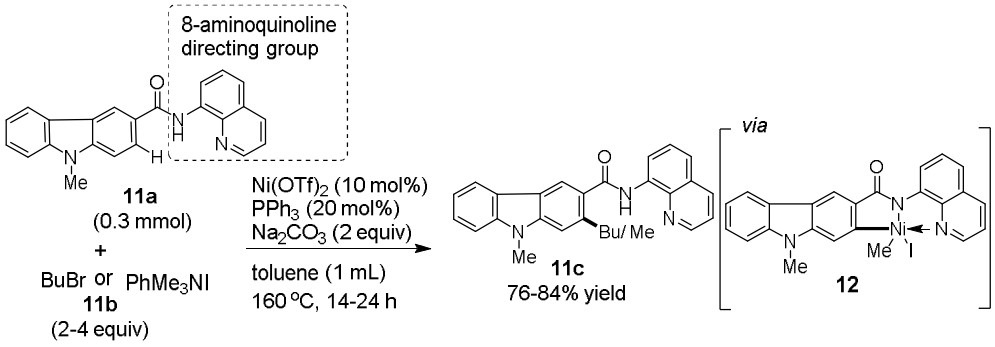


Scheme 5. Rh-Catalyzed selective Csp^2−H alkylation of carbazole with alcohols.

2.2. C2 Alkylation

Chatani and co-workers described a Ni-catalyzed, bidentate-directing group-assisted regioselective *ortho* C-H alkylation of aromatic amides linked with 8-aminoquinoline as the directing group using alkyl halides (including benzyl, allyl, alkyl, and methyl halides) as coupling partner.[20a,b] A single example of C2 butylation of carbazole amide linked with 8-aminoquinoline **11a** was described using butyl bromide **11b** (1.2

equiv) as an electrophilic coupling partner. Treatment of **11a** with **11b** in the presence of $Ni(OTf)_2$ (10 mol%) catalyst, PPh_3 (20 mol%) ligand, Na_2CO_3 (2 equiv) base at 160 °C for 24 h afforded the C-2 alkylated carbazole in 76% yield (Scheme 6). Furthermore, the direct methylation of the C-H bond of carbazole using phenyltrimethylammonium bromide or iodide as the methylating reagent was accomplished under Ni(II) catalysis, and the C2 methylated carbazole was obtained in 84% yield from **11a**. In general, the bidentate directing group 8-aminoquinoline assisted C–H activation and functionalization of carboxamides is proposed to undergo *via* a well-documented Pd(II)/Pd(IV) redox cycle mechanism involving the chelation assistance by the directing group. The C2 methylation/butylation is believed to undergo *via* the intermediate **12** which is generated from **11a** and Ni catalyst involving chelation-assisted *ortho* C−H activation followed by oxidative addition of $PhMe_3NI$. Reductive elimination and protonation results in the formation of the methylation product **11c** with the regeneration of the Ni(II) species.

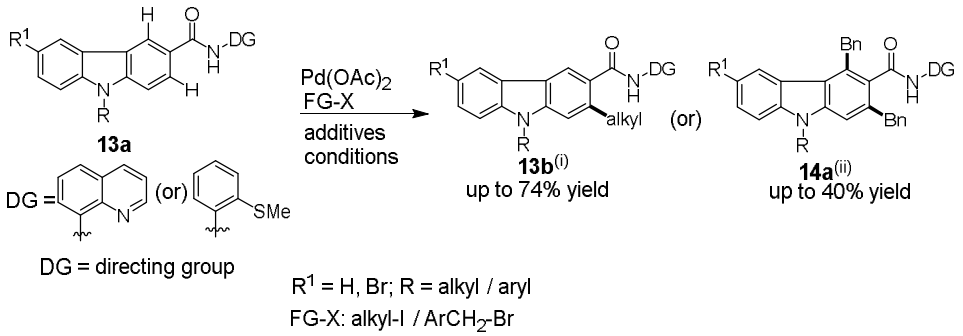


Scheme 6. Ni-Catalyzed Csp^2−H alkylation of carbazole *via* the bidentate directing group-aided C−H functionalization strategy.

Recently, we described the assembling of a library of C2, C3, C4 functionalized carbazole motifs and the application of the Pd(II)-catalyzed, bidentate directing group-aided *ortho* C−H functionalization strategy for the functionalization of the C2−H bonds of carbazole-3-carboxamide.[20c] We showed the Pd(II)-catalyzed, bidentate directing group-aided C2−H arylation, alkylation, benzylation and alkoxylation of carbazole-3-carboxamide substrates. Through screening of reaction conditions, we found that 8-aminoquinoline and 2-(methylthio)aniline are suitable directing groups. Especially, 2-(methylthio)aniline was found to be an efficient bidentate directing group in the Pd(II)-catalyzed C2−H arylation and alkylation, methoxylation of carbazole-3-carboxamides.[20c] While the Pd(II)-catalyzed, bidentate directing group-aided *ortho* C−H alkylation of carbazole-3-carboxamide **13a** selectively afforded the corresponding C2 alkylated carbazole-3-carboxamides **13b** (Scheme 7). Notably, the Pd(II)-catalyzed, bidentate-directing group-aided C−H benzylation of carbazole-3-carboxamide **13a** afforded the C2 and C4 dibenzylated carbazole-3-carboxamide **14a**.

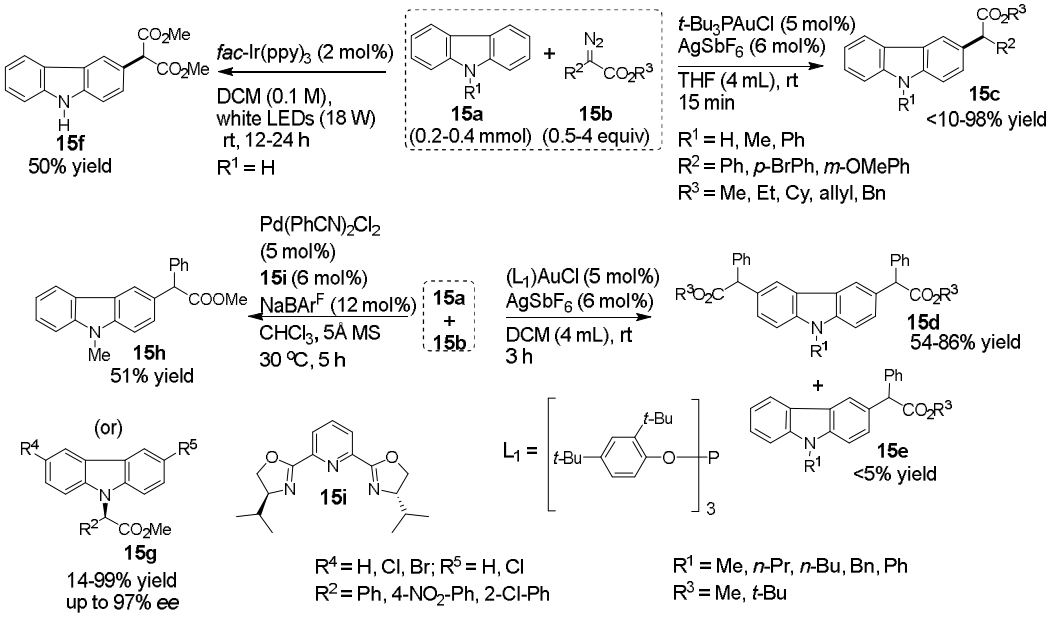
2.3. C3 Alkylation

The Koenigs group reported[21] a gold-catalyzed carbene transfer reaction for the selective C3−H functionalization of carbazole motif **15a** using diazo compound **15b** and synthesis of C3-alkylated carbazole **15c** (Scheme 8). Using monodentate carbene, Au(I) catalyst with tri-*t*-butylphosphine (ligand) and $AgSbF_6$ (additive), selective functionalization of C−H bonds of carbazoles was observed while leaving N−H untouched. N−H functionalization product was isolated only in the case of bidentate dppf (1,1'-bis(diphenylphosphino)ferrocene) ligand. Mechanistic studies indicated that a trace amount of water is crucial for the observed selectivity of the reaction. Further, Koenigs's group reported a bis C−H functionalization at the C3 and C6 positions of carbazoles *via* gold-catalyzed carbene transfer protocol affording **15d**/**15e**. Au(I)-catalyst with phosphite-derived ligand $\mathbf{L_1}$ gave the best results while Pd-, Rh- and Cu-based catalysts were found less efficient for this reaction. One pot stepwise C−H functionalization was also shown to selectively introduce two new functional groups onto the carbazole scaffolds.



(i) Alkyl-I (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), NaOTf (3 equiv), *t*-amylOH (1 mL), 130 °C, 36-48 h.
(ii) Ar-CH_2-Br (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), NaOTf (3 equiv), toluene (1 mL), 130 °C, 36 h.

Scheme 7. Pd-Catalyzed Csp^2–H alkylation of carbazole *via* the bidentate directing group-aided C–H functionalization strategy.

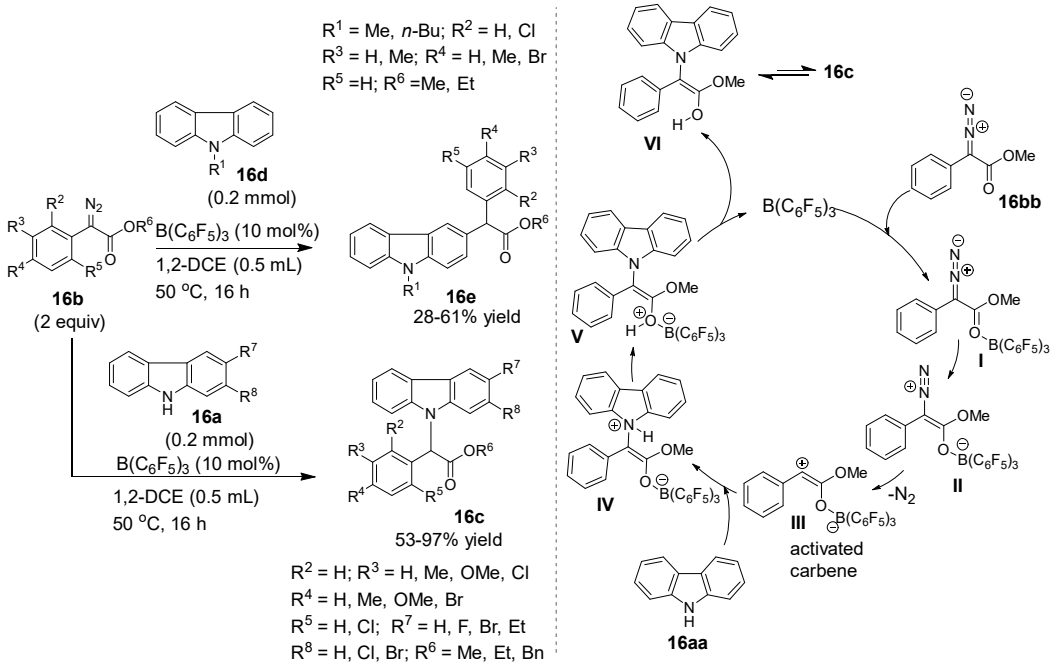


Scheme 8. C3–H Alkylation of carbazoles using diazo compounds.

The Cho group reported[22a] Ir(III) photocatalyst-catalyzed visible-light-induced selective radical-radical cross-coupling (C-H functionalization) of carbazole with diazomalonates and synthesis of a single example of C3–H alkylation of carbazole **15f** (Scheme 8). Several diazo compounds containing $-SO_2Ph$, –CN, $-P(O)(OEt)_2$, and $-CF_3$ substituents were found to be ineffective for either C–H or N–H functionalization, which proved that the reaction depends on the chemical structure of the diazo compound. The reaction mechanism was further validated by electrochemical, photophysical experiments, and computational studies. Vranken and co-workers reported[22b] the enantioselective Pd-catalyzed carbene insertion into the N–H bonds of aromatic heterocycles including carbazoles using (*S*,*S*)-*i*Pr-PyBOX and Pd(II) precatalyst. The substrate scope was shown by using a variety of diazo compounds and an efficient synthesis of *N*-alkylated carbazoles

15g was accomplished. On the other hand, 9-methylcarbazole was subjected to the C−H insertion reaction, which indeed afforded the C3−H alkylated product **15h** in 51% yield.

Koenigs *et al.* reported[23] the tris(pentafluorophenyl)-borane-catalyzed reaction of carbazoles with aryldiazoacetates. This method led to the synthesis of C3 alkylated carbazole **16e** by treating **16b** (0.2 mmol), *N*-substituted carbazole **16d** (0.4 mmol) in the presence of $B(C_6F_5)_3$ (10 mol%) in 1,2-DCE (0.5 mL) at 50 °C for 16 h. On the other hand, the N−H functionalization of *N*-unprotected carbazole **16a** occurred to give **16c** (Scheme 9). Different ester, alkyl, and halogen groups at the aromatic ring of the aryldiazoacetates were well tolerated. Diphenyl diazomethane and ethyl diazoacetate were found to be incompatible with the reaction conditions. From a mechanistic perspective, it was assumed that coordination of tris(pentafluorophenyl)borane to **16bb** would lead to the generation of a borane-stabilized vinyl cation or the activated carbene intermediate **III** (in accordance with previous reports on the Lewis acid-catalyzed activation of diazoacetates).[23] Intermediate **III** preferentially reacts with the N−H moiety of carbazole **16a** according to the principle of hard-soft Lewis acid and base. The C−H functionalization of carbazole is preferred less due to the soft nature of the nucleophilic carbon center. Following the addition of carbazole, a subsequent proton migration to the neighbouring carbonyl group gives an intermediate **V**, which upon tautomerization, provides the product **16c** and the catalyst is released. Zhao and Zhai have described[24] the C3 alkylation of carbazoles by treating unprotected carbazoles with donor-acceptor cyclopropanes. By employing $Sc(OTf)_3$ as the Lewis acid catalyst, the N−H functionalization of carbazoles was observed through a highly selective nitrogen-initiated nucleophilic ring opening of cyclopropanes. On the other hand, by using TfOH as the Brønsted acid catalyst, C3−H functionalization of carbazole proceeded *via* a Friedel-Crafts-type addition.

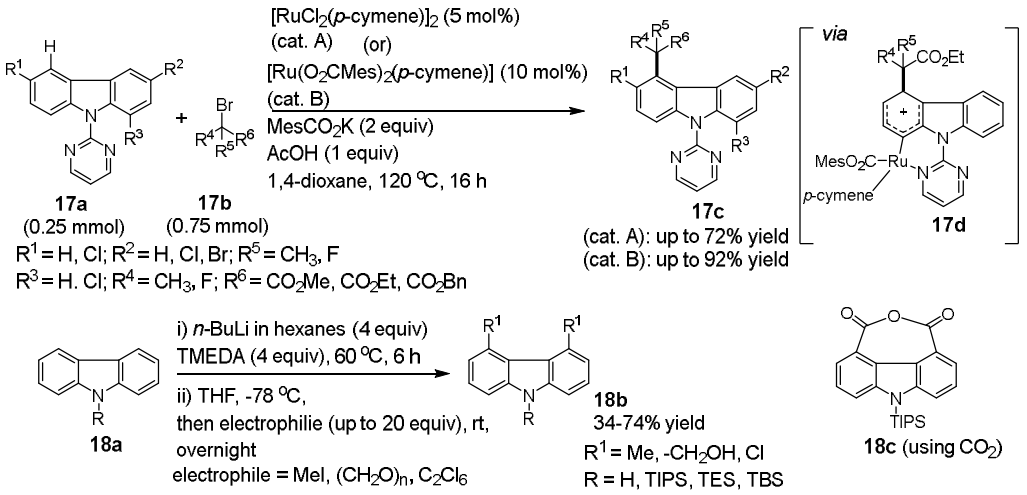


Scheme 9. C3−H Alkylation of carbazoles using diazo compounds.

2.4. C4 Alkylation

Frost and co-workers disclosed[17a] a remote C−H alkylation of carbazole derivatives selectively at the C4 position with the assistance of a pyrimidine directing group installed at the *N*9 position, The *N*-pyrimidinyl-carbazole **17a** was treated with substituted *α*-bromoisobutyrate **17b** as a coupling partner in

the presence of commercially available dimer $[RuCl_2(p\text{-cymene})]_2$, or the pre-synthesized monomer to furnish the C4 alkylated carbazole **17c** (Scheme 10). It was stated[17a] that carbazole bearing pyrimidine directing group enables σ-activation catalyzed *via* Ru metal center along with the formation of a stable and planar ruthenacycle intermediate **17d** at C1 directs the interaction of the C4 in *para* position with a tertiary alkyl radical. A single electron transfer process with an inner sphere or outer sphere Ru-complex can then generate the tertiary *α*-halocarbonyl radical. This radical then interacts with the sterically encumbered ruthenacycle at the *para* position to the metal center *via* a σ-activation process (likely due to a shift in electron density to the C4 position). Redox electron shuttling and proton abstraction enable re-aromatization of the arene, and protodemetalation gives the C4-alkylated carbazole **17c**. Grainger and co-workers revealed[17b] a novel methodology for the direct functionalization of sterically hindered bay position of carbazoles *viz.* C4 and C5 positions by using a simple combination of bulky TIPS group on carbazole nitrogen and *n*-BuLi-TMEDA for deprotonation and directed lithiation. The reaction was initiated by treating silyl-substituted carbazole **18a** with *n*-BuLi in hexane (4 equiv), TMEDA (4 equiv) at 60 °C for 6 h, followed by the subsequent addition of THF at -78 °C and an electrophile (up to 20 equiv) for overnight afforded the C4 and C5 substituted carbazole **18b**. Along this line, the synthesis of C4 and C5 substituted carbazole **18c** was accomplished by using CO_2 as an electrophile.

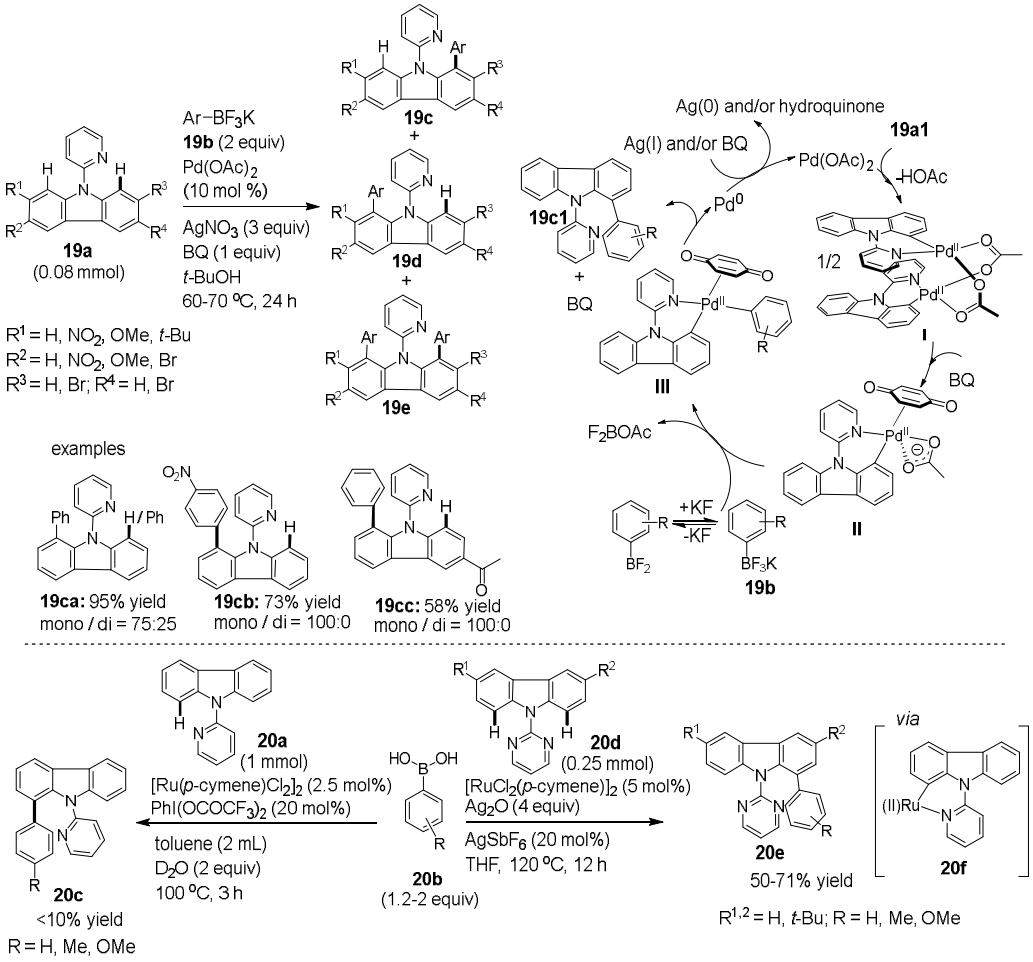


Scheme 10. C4−H/C5−H Alkylation of carbazoles.

3. Synthesis of C−H arylated carbazoles *via* C−H arylation

In this section, we present the recent developments pertaining to the C−H arylation of carbazole motifs **19a** *via* the directing group-aided C−H activation/functionalization. In 2012, Wu's group reported[25] the synthesis of C1 arylated 9-(pyridine-2-yl)-9*H*-carbazoles in moderate to excellent yields *via* Pd(II)-catalyzed C−H bond activation (Scheme 11). Depending on the substituent in the carbazole as well as in the potassium aryltrifluoroborate, the reaction yielded the corresponding mono or bis C−H arylated carbazole derivatives **19c-e**. Various oxidants like $AgNO_3$, Ag_2O, AgOAc, Ag_2CO_3 etc were screened, out of which $AgNO_3$ was found to be the most effective. The transmetalation and reductive elimination steps of the catalytic process utilized *p*-benzoquinone as a crucial ligand. The structure of 9-(pyridine-2-yl)-9*H*-carbazole palladacycle, a key intermediate of the reaction, was confirmed by X-ray crystallography. According to the results obtained from mechanistic investigations, a plausible catalytic mechanism was propoed by the authros[25] for the direct C1 arylation of **19a** with aryl potassium aryltrifluoroborate **19b**, as shown in Scheme 11. Initially, Pd(II) is coordinated with the nitrogen atom of the pyridine ring of 9-(pyridin-2-yl)-9*H*-carbazole **19a1** and, subsequently, the C1−H bond of the carbazole ring is cleaved by Pd(II) to form the intermediate **I**. Then, BQ (benzoquinone) coordinates with the Pd(II) center of intermediate **I** through a ligand-exchange process to form intermediate **II**. After that, aryldifluoroborane (generated from **19b**) and intermediate **II** participate in

the transmetalation step to generate another intermediate **III** by releasing F_2BOAc. Finally, intermediate **III** is converted into the desired product **19c1** by releasing Pd(0) and BQ through a reductive elimination step. Pd(II) is regenerated by the reoxidation of Pd(0) by Ag(I) and/or BQ with the release of Ag(0) and/or hydroquinone, and the regenerated Pd(II) restarts the catalytic cycle.

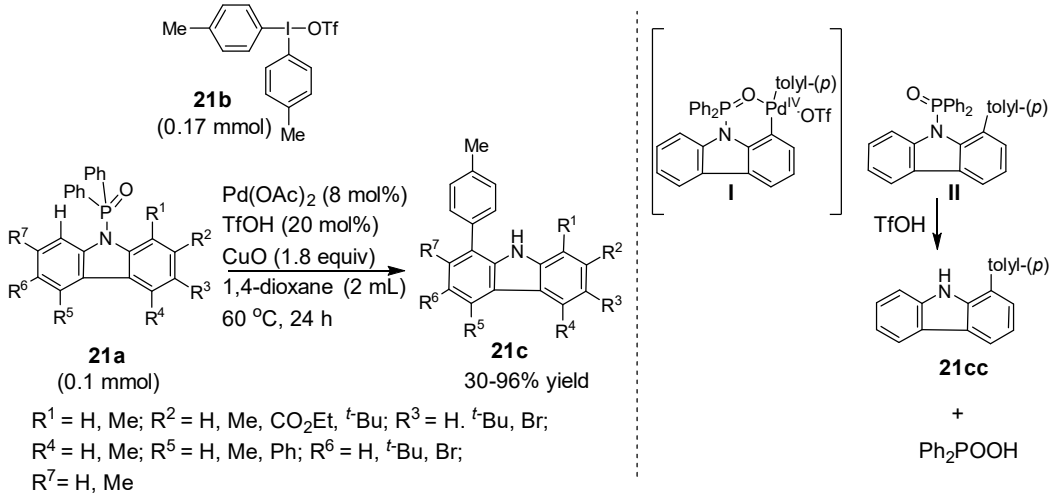


Scheme 11. C1-Arylated carbazoles *via* Pd- or Ru-catalyzed C−H bond functionalization of carbazole with the assistance of pyrimidine/pyridine.

Nageswar and co-workers reported[26a] an efficient regioselective Ru-catalyzed *ortho* or C1−H bond arylation of 9-(pyrimidin-2-yl)-9*H* carbazole **20d**. The 9-(pyrimidin-2-yl)-9*H* carbazole **20d** was subjected to *ortho* arylation using substituted boronic acids **20b** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) catalyst, Ag_2O (4 equiv) oxidant, $AgSbF_6$ (20 mol%) as an additive in THF at 120 °C for 12 h. Both electron-rich and electron-deficient groups on boronic acids were well tolerated to afford the product **20e** in good yields (Scheme 11). Maheswaran and co-workers reported[26b] the highly site-selective Ru-catalyzed direct *ortho* monoarylation of 9-(pyridin-2-yl)-9*H*-carbazole **20a** by using arylboronic acids and this reaction was mediated by $PhI(OCOCF_3)_2$ and this reaction yielded the product **20c**. However, the reaction did not proceed well because the yield obtained was less than 10% in all the cases, which is not very significant. The

authors suggested that the reaction proceeded through the active intermediate **20f** to furnish the desired product.

Yang and co-workers reported[27] the Pd-catalyzed P=O directing group-assisted C1−H bond arylation of carbazoles **21a** with diaryliodonium triflates **21b** using TfOH and CuO as additives affording the product **21c** (Scheme 12). The directing group released spontaneously in the reaction and the TfOH played a pivotal role in the release of the directing group. Mechanistic studies revealed that acid is mandatory for N−P bond cleavage. No diarylation product was observed in any of the cases. The *N*-free or *N*-unprotected carbazole failed to give any product, indicating the vital role of $P(O)Ph_2$ as the directing group. Additionally, $Cu(OTf)_2$ alone was not able to do the N−P bond cleavage. Based on the literature reports, a possible mechanism was shown. The P=O directing group enables the *ortho* (or) C1–H bond activation to form the six-membered Pd(II) intermediate. Subsequent oxidative addition of the Pd(II) complex with **21b** produces intermediate **I**, and reductive elimination of **I** results the intermediate **II**, which immediately reacts with TfOH to form the unstable ionic intermediate, which with the assistance of the H_2O in the system, generates the product **21cc** as well as $HOP(O)Ph_2$.

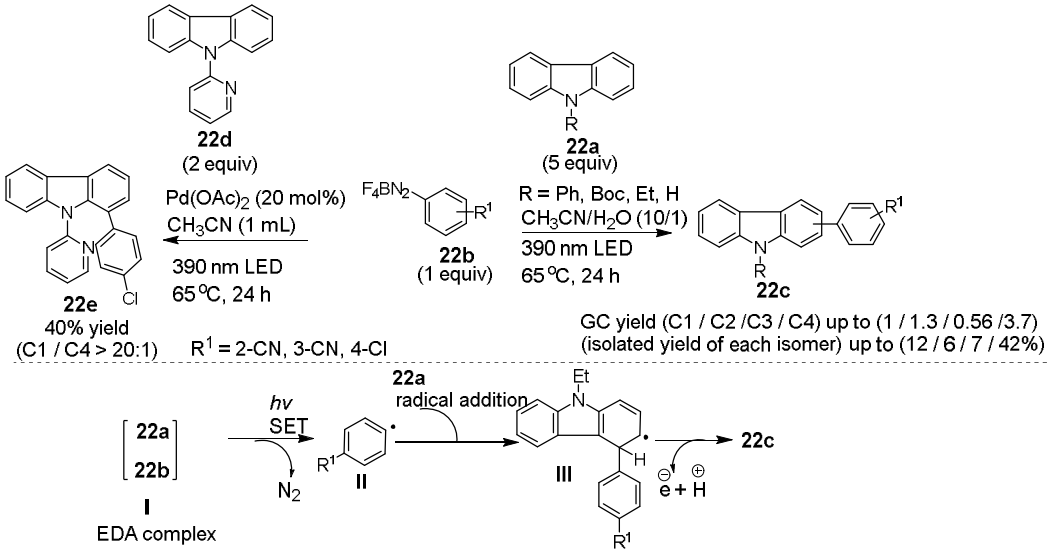


Scheme 12. C1 Arylated carbazoles *via* Pd(II)-catalyzed, P=O directing group-assisted C−H bond functionalization.

The Itami group described[28] photo-induced direct arylation of carbazoles with aryldiazonium salts to afford the arylated carbazole. However, the reaction was not regioselective. The C−H arylated *viz.* C1 and C4 arylated carbazoles were obtained as major isomers. A mixture of *N*-ethylcarbazole **22a** and benzenediazonium tetrafluoroborate **22b** were irradiated with 390 nm LED light in CH_3CN/H_2O (10/1) solvent mixture at 65 °C for 24 h to furnish the regioisomers at C1/C2/C3/C4 arylated carbazoles with up to 65% yield. The *N*-pyridyl carbazole **22d** successfully generated C1 arylated product **22e** in 40% yield with good regioselectivity using $Pd(OAc)_2$ (20 mol%) catalyst under similar reaction conditions (Scheme 13). A plausible reaction pathway for the transformation was proposed[28] by the authors. The substrates **22a**/**22b** form an electron donor-acceptor (EDA) complex **I**, which then absorbs the near-ultraviolet light. Photo-induced single electron transfer (SET) between carbazole **22a** and aryldiazonium salt **22b** occurs to generate aryl radical **II**. The resulting aryl radical **II** reacts with carbazole **22a** to form radical intermediate **III**. Consequently, intermediate **III** aromatizes to give the product **22c**.

We shown the Pd(II)-catalyzed, bidentate directing group-aided C2−H arylation of carbazole-3-carboxamide substrates.[20c] The selective C2−H arylation of carbazole-3-carboxamide **23a** was performed using 8-aminoquinoline and 2-(methylthio)aniline as the directing groups. In particular, 2-(methylthio)aniline was found to be an efficient bidentate directing group in the Pd(II)-catalyzed C2−H

arylation of carbazole-3-carboxamides **23a** affording **23b** (Scheme 14).[20c] Subsequently, examples involving the removal of the bidentate directing group after performing the C2−H functionalization of carbazole-3-carboxamides were also shown. In general, the bidentate directing group 8-aminoquinoline or 2-(methylthio) aniline-assisted C–H activation and functionalization of carboxamides is believed to undergo *via* the Pd(II)/Pd(IV) redox cycle mechanism.[29] In concurrence with the proposed mechanism in the literature,[9-12] a plausible mechanism for the 2-(methylthio)aniline bidentate directing group-directed Pd(II)-catalyzed arylation of the *ortho* Csp^2–H bond of carbazole-3-carboxamide **23ab** was proposed.[20c] The coordination of the 2-(methylthio)aniline directing group in carbazole-3-carboxamide **23ab** to the Pd(II) metal center is followed by concerted metalation deprotonation (CMD), forming the five-membered Pd(II) species **24b** *via* **24a**. Oxidative addition of the Pd(II) species **24b** with an aryl iodide then forms the Pd(IV) species **24c**. The Pd(IV) species **24c** then undergoes reductive elimination to form the new C–C bond in species **24d**. Halide abstraction by a halide ion scavenger (*e.g.* AgOAc) followed by the protonolysis of the intermediate **24d** generates the C2−H arylated carbazole derivative **24e** and the active Pd(II) species is regenerated in the catalytic cycle.



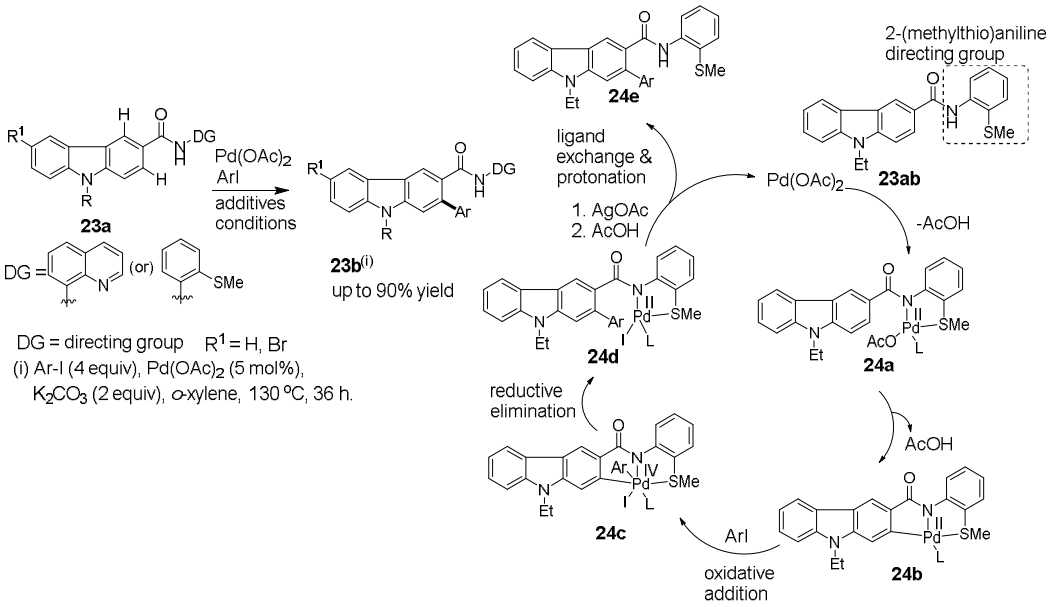
Scheme 13. Photo-induced direct arylation of carbazoles with aryldiazonium salts to afford the arylated carbazole.

4. Synthesis of C−H alkenylated, alkynylated, and allylated carbazoles

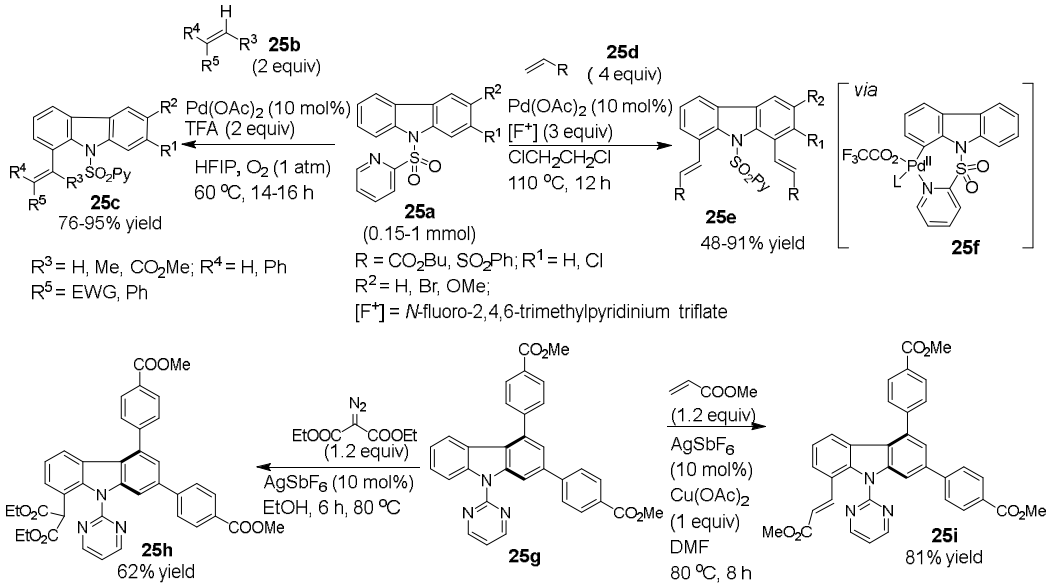
4.1. C1 Alkenylation/alkynylation/allylation

In this section, we present the recent developments related to C−H alkenylation/olefination, alkynylation, and allylation of carbazole motifs *via* the directing group-aided C−H activation/functionalization. The Carretero group reported[29a] the Pd-catalyzed C1−H/C8−H olefination of carbazoles **25a** directed by readily removable *N*-(2-pyridyl)sulfonyl group with **25d**, which also acts as a protecting group. This transformation led to the assembling of a range of bis alkenylated carbazoles **25e** and the directing group enabled the site-selective C1−H/C8−H olefination of **25a**. Various *N*-directing/protecting groups like Boc, acetyl, tosyl and SO_2(2-pyridyl) were examined for this transformation, and SO_2(2-pyridyl) was found to be the best directing group. Along this line, the Zhao group[29b] reported an efficient synthetic method comprising Pd(II)-catalyzed direct mono C1−H alkenylation of 9*H*-carbazole **25a** possessing *N*-(2-pyridyl)sulfanyl directing group with **25b**. This protocol was also used for the synthesis of bis C-H alkenylated carbazoles. A seven-membered palladacyclic intermediate **25f** was expected to be the plausible intermediate for generating the C1 alkenylated carbazole **25c** (Scheme 15). In 2015, Yi and co-workers disclosed[30] a highly efficient, one-pot cascade synthesis of carbazole scaffold using intermolecular

annulation of indoles with terminal alkynes assisted *via* Rh(III)-catalyzed system affording **25g**, which were then subjected to the Rh(III)-catalyzed direct C−H alkylation and alkenylation at C8 position to afford **25h** or **25i**.



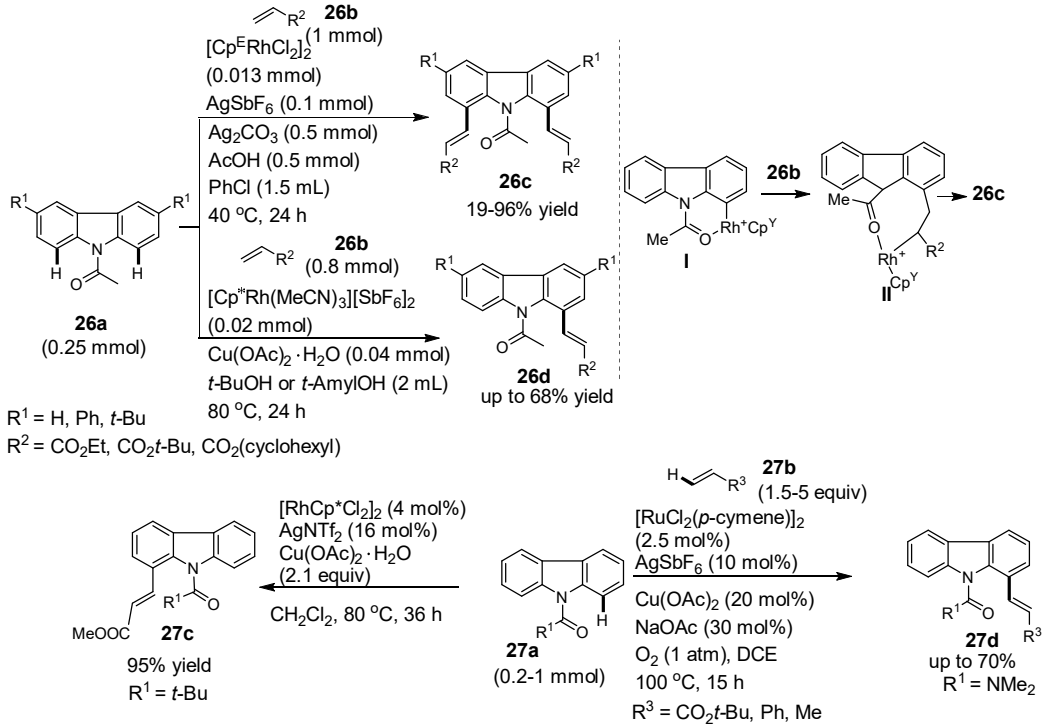
Scheme 14. Pd(II)-Catalyzed 2-(methylthio)aniline bidentate directing group-aided C2−H functionalization (arylation) of carbazole-3-carboxamide.



Scheme 15. Pd(II)-Catalyzed directing group-aided C1−H/C8−H alkenylation of carbazole **25a**.

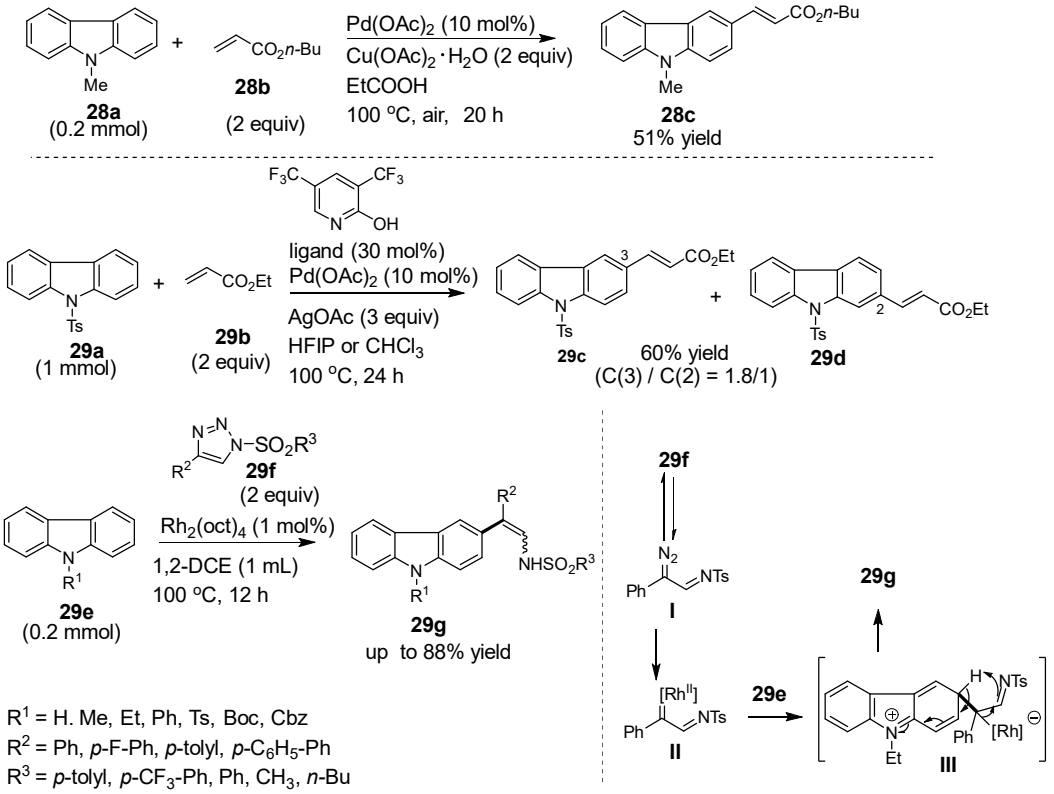
Satoh and co-workers reported[31] the Rh(III)-catalyzed ligand-dependent selective synthesis of mono and bis-alkenylated carbazoles **26c** and **26d** using **26a** and **26b** (Scheme 16). The C−H alkenylation of *N*-acetylcarbazoles proceeded smoothly at the C1-position in the presence of a cationic $Cp^*Rh(III)$ catalyst to produce 1-alkenylcarbazoles **26d** (Scheme 16). Interestingly, the usage of $Cp^ERh(III)$ catalyst being an electron-deficient system promoted a second alkenylation of affording bis C−H alkenylated (C1−H/C8−H alkenylated) carbazoles **26c**. A plausible reaction pathway was proposed by the authors for the coupling of **26a** with alkene **26b**. The first alkenylation of **26a** at the C1-position proceeded smoothly in both cases using Cp^*Rh^+ and Cp^ERh^+ catalysts. Coordination of the carbonyl oxygen of **26a** to a cationic Cp^YRh^+X species triggers cyclorhodation at the C1-position of **26a** to generate a six-membered rhodacycle intermediate **I**. Then, alkene insertion into the resulting Rh−C bond gives an intermediate **II**. Subsequently, a *β*-hydrogen elimination liberates monoalkenylated **26c** and reductive elimination seems to occur to generate a $Cp^YRh(I)$ species, which is oxidized by a Cu or Ag salt to regenerate an active Cp^YRh^+X species. In cases using a Cp^ERh^+ catalyst (Cp^Y=Cp^E), **26c** undergoes the second alkenylation at the C8 position in the catalytic cycle.

The Ma group demonstrated[32a] a Rh-catalyzed, selective C1 functionalization of *N*-pivaloyl protected carbazole **27a** with methyl acrylate in the presence of $[RhCp^*Cl_2]_2$ (4 mol%) catalyst, $AgNTf_2$ (16 mol%) additive, $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv) in CH_2Cl_2 at 80 °C for 36 h to furnish product **27c** in 95% yield. Song and co-workers described[32b] a highly selective Ru-catalyzed direct mono olefination of carbazole at the C1 position, which was assisted by a removable *N*-dimethylcarbamoyl group using O_2 as the terminal oxidant. *N*-dimethylcarbamoyl protected carbazole **27a** was treated with butyl acrylate **27b** (1.5 equiv) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) catalyst, $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (20 mol%) oxidant, NaOAc (30 mol%) additive in DCE at 100 °C for 15 h, to afford the mono alkenylated product **27d** selectively. It was observed that both acrylates and non-activated styrenes were well tolerated, although styrene exhibited lower yields compared to acrylates (Scheme 16).



Scheme 16. Rh-Catalyzed acetyl directing group-aided C1−H/C8−H alkenylation of carbazole.

A single example of regioselective Pd-catalyzed direct C3−H alkenylation of 9-methyl-9*H*-carbazole **28a** has been revealed by Miura's group.[33a] Compound **28a** was treated with *n*-butyl acrylate (2 equiv) **28b** in the presence of $AgOCOCF_3$ as an oxidant in $EtCO_2H$ at 100 °C under air for 20 h to furnish 3-alkenylated 9-methylcarbazole **28c** as a major product in 44% yield (Scheme 17). It was observed that by using $Cu(OAc)_2{\cdot}H_2O$ in place of $AgOCOCF_3$ as an oxidant increased the yield up to 51% yield. Yu *et al.* revealed[33b] an example of 2-pyridone ligand-enabled non-directed C3−H and C2−H alkenylation of carbazole **29a**. The reaction was carried out using carbazole **29a** in the presence of $Pd(OAc)_2$ (10 mol%) catalyst, AgOAc (3 equiv) additive, a pyridone ligand (30 mol%) in HFIP or $CHCl_3$ at 100 °C for 24 h to afford a mixture of C2 and C3 olefinated product **29c** and **29d**.

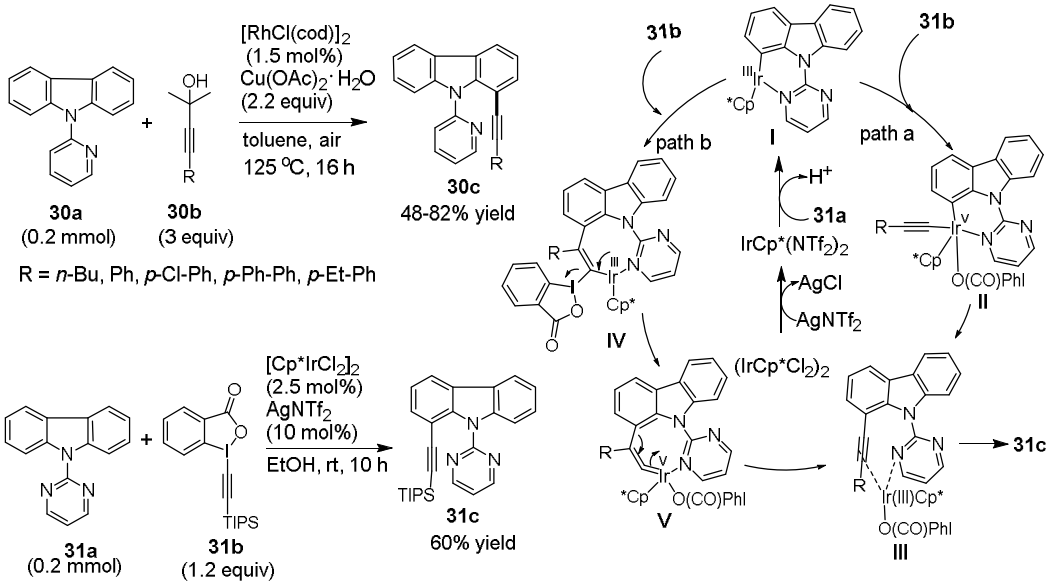


Scheme 17. C3−H/C2−H Alkenylation of carbazole.

Yoo and co-workers reported[33c] the regioselective functionalization of C3 position of 9*H*-carbazoles **29e** through Csp^2−H insertion of Rh(II) carbenoids generated *in situ* from 1-sulfonyl-1,2,3-triazoles **29f**. 9-Alkyl and 9-aryl substituted 9*H*-carbazoles underwent the alkenylation and introduction of an enamido group at the C3 position affording **29g**. In the case of unsubstituted 9*H*-carbazoles, instead of the functionalization at the C3 position, N−H insertion products were obtained. The reaction of 9*H*-carbazoles substituted with electron-withdrawing groups did not give the products. In contrast, alkyl and aryl substituents promoted the C3−H functionalization. Based on previous reports of Rh(II)-catalyzed Csp^2−H insertions of 1-sulfonyl-1,2,3-triazoles, a plausible reaction pathway was proposed[33c] by the authors. Initially, ring-chain tautomerization of the 1-sulfonyl-1,2,3-triazole generates an alpha-diazo imine intermediate **I**, which reacts with Rh(II) catalyst to generate an electrophilic alpha-imino Rh(II) carbenoid **II**. The nucleophilic addition of the C3 carbon atom of carbazole **29e** to the electrophilic intermediate **II** gives zwitterionic intermediate **III**. This nucleophilic attack requires the assistance of the nitrogen lone pair of the

9*H*-carbazole, which explains why only 9-alkyl- or 9-aryl-substituted 9*H*-carbazoles participated in the reaction. Next, the re-aromatization of intermediate **III** by deprotonation generates **29g** with regeneration of the Rh(II) catalyst in the catalytic cycle (Scheme 17).

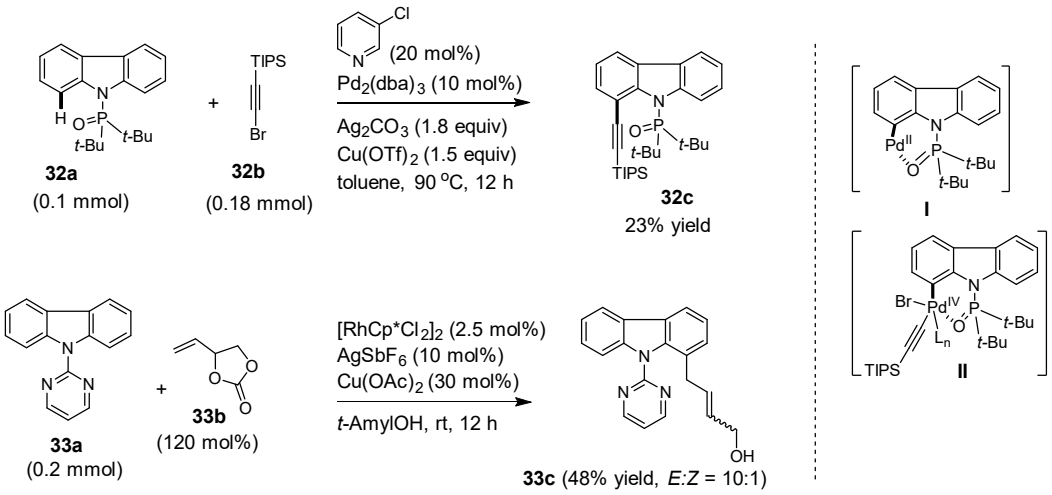
The Wen group developed[34a] a method for selective C1 alkynylation of *N*-pyridyl-carbazoles **30a** affording **30c** by Rh-catalyzed and Cu-mediated C−H alkynylation using *γ*-substituted *t*-propargyl alcohols **30b** as the alkynylating agent and pyridin-2-yl moiety as the directing group (Scheme 18). The control experiments revealed that the reaction did not work in the absence of either $[RhCl(cod)]_2$ or $Cu(OAc)_2{\cdot}H_2O$. Li *et al.* revealed[34b] examples of Ir(III)-catalyzed direct C−H alkynylation of carbazoles at the C1 position using *N*-pyrimidyl moiety as the directing group. A *N*-pyrimidyl protected carbazole **31a** and a hypervalent iodine reagent (TIPS-EBX) **31b** were treated with $[Cp^*IrCl_2]_2$ (2.5 mol%) and $AgNTf_2$ (10 mol%) in EtOH for 10 h under room temperature to afford the corresponding C1 alkynylated product **31c** in 60% yield. A plausible mechanistic pathway was proposed for the Ir(III)-catalyzed direct C−H alkynylation of carbazoles at the C1 position using *N*-pyrimidyl moiety as the directing group.[34b] Treatment of a dimeric Ir species with $AgNTf_2$ affords monomeric $IrCp^*(NTf_2)_2$. Then a six-membered cyclometalated Ir(III) complex **I** is generated *via* an Ir(III)-catalyzed C1−H bond cleavage. An oxidative addition to the hypervalent iodine compound occurs to generate the Ir(V) alkynyl species **II**, which undergoes reductive elimination to afford the Ir(III) alkyne intermediate **III** (path a). Alternatively, the species **I** may undergo a regioselective migratory insertion into the alkyne to generate the intermediate **IV**. Then, an *α*-elimination of 2-iodobenzoic acid from the intermediate **IV** occurs to afford the Ir vinylidene species **V**, which undergoes a concerted or stepwise aryl-migration and elimination to afford the intermediate **III**. Finally, alkyne dissociation from species **III** releases the C1−alkynylated carbazole **31c** and an active Ir(III) benzoate catalyst, which may undergo a C−H activation with **31a** to regenerate **I**.



Scheme 18. C1−H Alkynylation of carbazole.

Pd-Catalyzed regioselective C−H alkynylation between carbazole and haloalkyne was described by Wu's group[35] and selective C1 alkynylation of carbazole was carried out using di *t*-butylphosphinoyl as directing group. The C1 alkynylation of carbazoles was performed using $Pd_2(dba)_3$ (10 mol%) catalyst, 3-chloropyridine (20 mol%) ligand, Ag_2CO_3 (1.8 equiv) and $Cu(OTf)_2$ (1.5 equiv) as an additive in toluene at 90 °C for 12 h to give the product **32c** in only 23% yield (Scheme 19). A plausible catalytic cycle was stated for this C1-selective alkynylation. First, the Pd(II) species is formed by the oxidation of $Pd_2(dba)_3$ in

the presence of Ag_2CO_3 and $Cu(OTf)_2$. Then complexation between the Pd(II) species and **32a** and subsequently the palladacycle intermediate **I** is obtained by the intramolecular selective C1–H activation. The compound **32b** is activated by Ag(I) and Cu(II), and the intermediate **I** undergoes oxidative addition to form the Pd(IV) complex **II**. The reductive elimination of intermediate **II** leads to the formation of the alkynylation product **32c**. A single example of Rh(III)-catalyzed selective C−H allylation of carbazole **33a** with 4-vinyl-1,3-dioxolan-2-one **33b** was described by Kim and co-workers.[36] An efficient 2-pyrimidinyl moiety was used as the directing group to carry out selective mono allylation at C1 position to provide the product **33c** in moderate yield with the *E/Z* ratio=10:1.



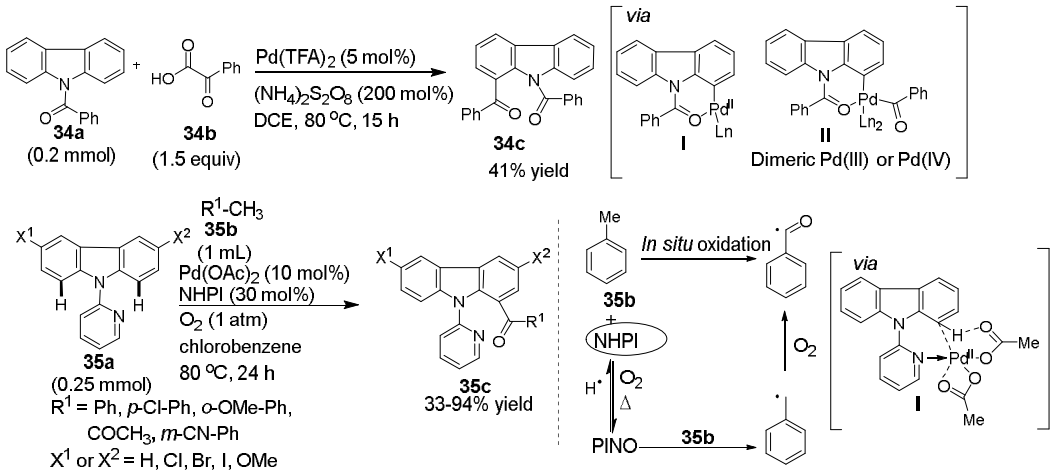
Scheme 19. C1−H Alkynylation and allylation of carbazole.

5. C-H Acylation, acetoxylation, cyanation, borylation, halogenation, perfluoroalkylation, chalcogenation, amidation/amination, and *N*-carbazolation of carbazole

5.1. C1 Acylation, acetoxylation, cyanation, and amidation reactions

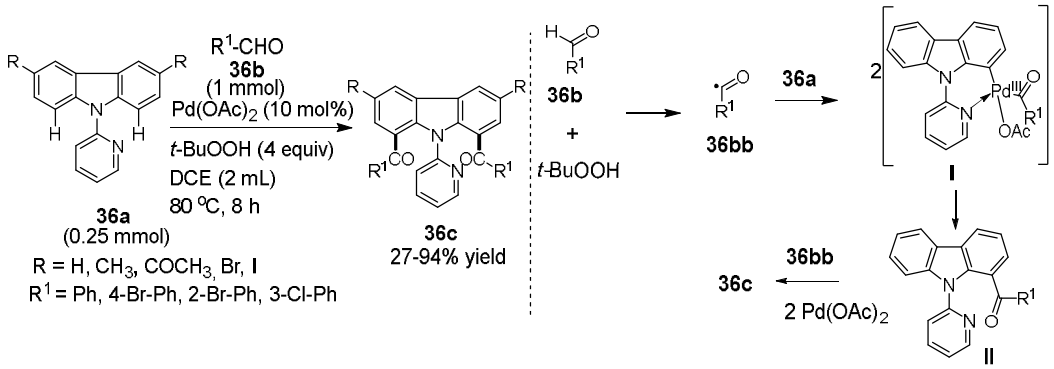
In this section, we present the recent developments pertaining to C−H acylation and acetoxylation of carbazole motifs *via* the directing group-aided C−H activation/functionalization. The Kim group reported[37a] a single example of Pd-catalyzed decarboxylative acylation of *N*-benzoylated carbazole with phenylglyoxylic acid **34b** *via* C1−H bond activation of **34a** affording **34c** in 41% yield. $Pd(TFA)_2$ was used as a catalyst in the presence of $(NH_4)_2S_2O_8$ as an oxidant (Scheme 20). The benzoyl group worked as a directing group in the C1−H acylation. Pivaloyl or *N*,*N*-dimethylcarbamoyl directing groups were found less effective for this reaction. A 6-membered palladacycle intermediate **I** was generated through the coordination of **34a** to the Pd(II) catalyst, which then reacts with phenylglyoxylic acid to furnish the dimeric Pd(III) or Pd(IV) intermediate **II** along with decarboxylation. Finally, C1-acylated carbazole **34c** is formed by reductive elimination, and Pd(II) species is regenerated to complete the catalytic cycle.

In 2021, the Dash group reported[37b] the regioselective Pd-catalyzed aerobic monoacylation of *N*-pyridylcarbazoles **35a** using toluene derivative **35b** as the acyl source, *N*-hydroxyphthalimide (NHPI) as a co-catalyst and oxygen as the sole oxidant (Scheme 20). A possible reaction mechanism for the regioselective Pd-catalyzed aerobic monoacylation of *N*-pyridylcarbazoles **35a** using toluene derivative was proposed. The initial step involves the generation of PINO radicals from NHPI and dioxygen. Then *in situ*-generated PINO radical abstracts hydrogen radical from toluene to form the benzylic radical, which, on reaction with molecular oxygen, forms the reactive benzoyl radical *via in situ* formation of benzaldehyde. Oxidative addition of benzoyl radical to cyclopalladated complex **III** followed by generation of intermediate Pd(IV) species and subsequent reductive elimination furnish the desired monoacylated product **35c** and the Pd(II) species is regenerated in the catalytic cycle.



Scheme 20. C1−H Acylation of carbazole.

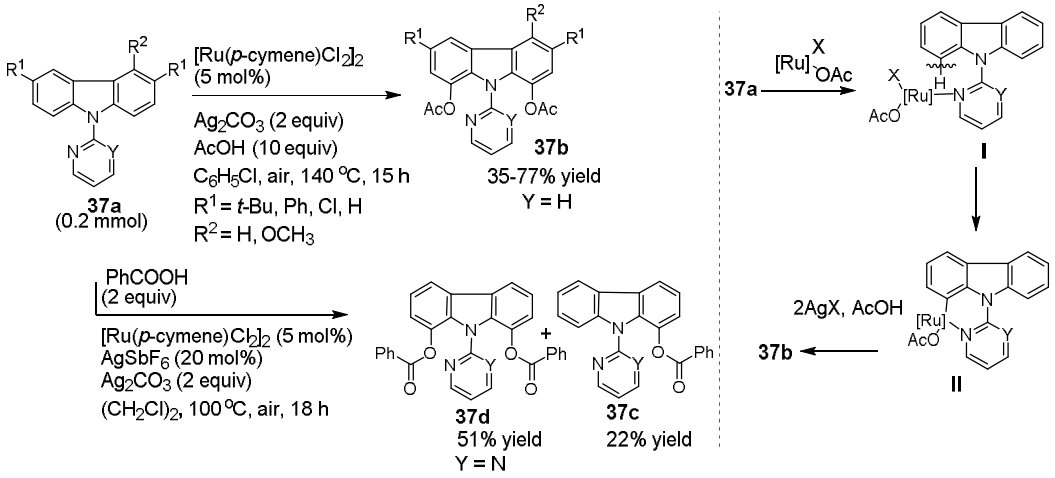
Subsequently, Dash and co-workers reported[37c] the directing group Pd-catalyzed C1−H and C8−H acylation of carbazoles **36a** using a variety of aromatic and aliphatic aldehydes as the acyl source in a regioselective manner (Scheme 21). Pyridyl moiety worked as a directing group and directed the acylation to occur at C1 and C8 positions. Mono acylated products is obtained using dibromo and diido *N*-pyridylcarbazole derivatives. Short reaction times and mild reaction conditions are the main advantages of this reaction. A plausible mechanism was proposed[37c] for the pyridyl moiety-directed 1,8-diacylation of carbazole **36a**. Aldehyde **36b** forms an acyl radical **36bb** in the presence of *t*-BuOOH. The compound **36a** with Pd(II) forms the corresponding palladacycle species, which undergoes a reaction with the acyl radical to give oxidative addition intermediate **I**, which then undergoes a reductive elimination to afford monoacylated carbazole derivative **II**. Subsequently, the carbazole derivative **III** undergoes the *ortho* cyclometalation, oxidative addition, and reductive elimination sequence as described above to produce the 1,8-diacylated carbazole derivative **36c** and Pd(II) catalyst is regenerated.



Scheme 21. C1−H Acylation of carbazole.

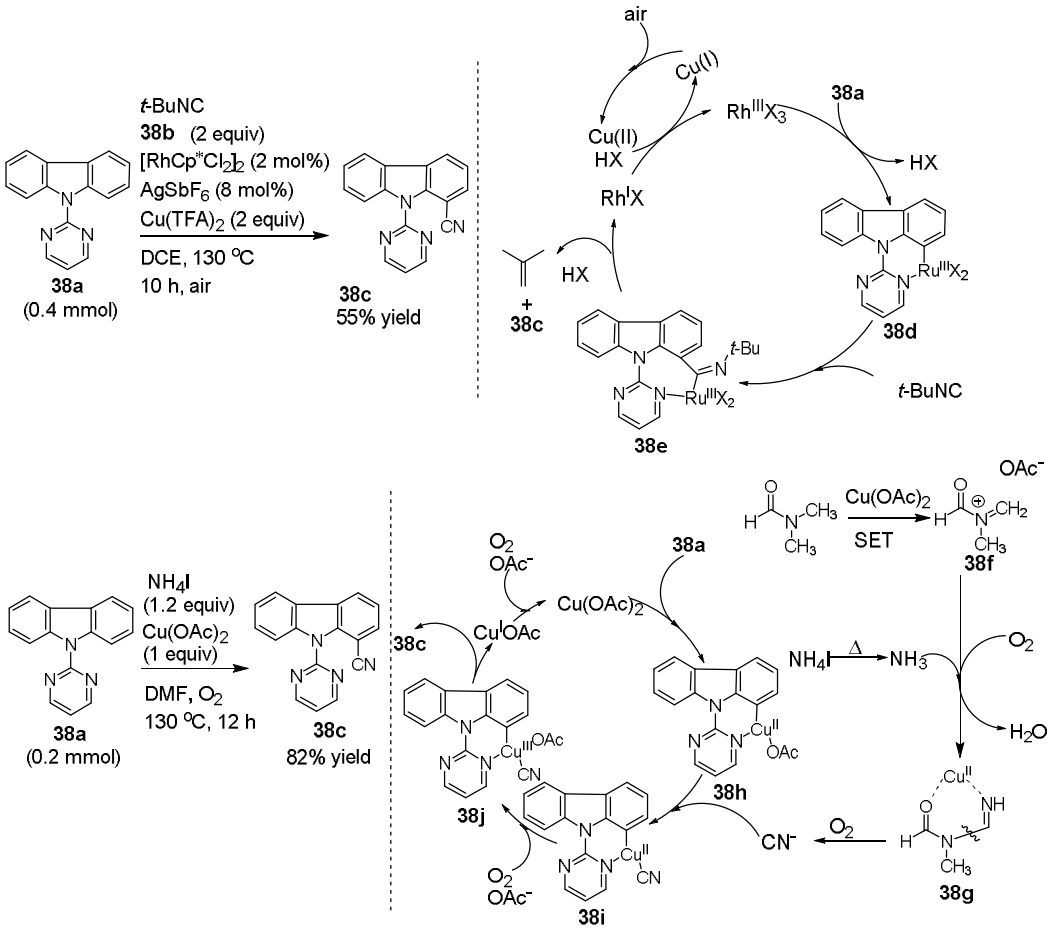
Miura and co-workers described[38a] the Ru-catalyzed regioselective C−H bond cleavage and C−O bond formation in 9-(pyridine-2-yl)carbazole scaffold (Scheme 22). Carbazole **37a** was treated with acetic acid (10 equiv), Ag_2CO_3 (2 equiv) salt, and $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) catalyst in chlorobenzene solvent at 140 °C for 15 h under air to furnish the corresponding C1- and C8-diacetoxylated products **37b**. Along this line, Punniyamurthy's group reported[38b] one example of site-selective C1- and C8-acyloxylation of

9-(pyrimidin-2-yl)-9*H*-carbazole with benzoic acid affording **37c** and **37d**. The rate-determining step for this transformation can be the C−H bond activation step, as suggested by kinetic isotope studies. Various directing groups, such as acetyl, pivaloyl, *N,N*-dimethylcarbamoyl and Boc were investigated and found to be less effective than the 2-pyrimidyl directing group. A plausible mechanism for the acetoxylation of **37a** was stated. Coordination of the pyridyl- or pyrimidyl-nitrogen of a substrate forming intermediate **I** trigger regioselective C−H bond cleavage at the neighboring position to yield a six-membered ruthenacycle intermediate **II**. Subsequently, oxidation of the Ru center by an Ag salt and reductive elimination may take place to produce **37b** and with regeneration of a catalytically active Ru species.



Scheme 22. C1−H Acetoxylation of carbazole.

In 2014, the Xu group reported[39a] a single example of a Rh-catalyzed regioselective C−H bond cyanation of 9-(pyrimidin-2-yl)-9*H*-carbazole **38a** with *t*-butyl isocyanide **38b** as the cyanide source to afford the carbazole **38c** containing the CN group at the C1 position and the reaction was promoted by the pyrimidyl directing group (Scheme 23). Although the detailed reaction mechanism remains to be clarified, a plausible pathway for this reaction was proposed. With the direction of pyrimidyl group, electrophilic rhodation at the C1 position affords a rhodacycle **38d**. Then the following insertion of isocyanide **38b** generates an intermediate **38e**, which undergoes *β t*-butyl elimination to give the product **38c** together with the expulsion of isobutene. The formed Rh(I) species is then re-oxidized by Cu(II), which could be derived from the oxidation of Cu(I) with oxygen and regenerating the Rh(III) catalyst in the catalytic cycle. Along this line, Cheng's group reported[39b] a single example of direct cyanation of 9-(pyrimidin-2-yl)-9*H*-carbazole **38a** with ammonium iodide and DMF as a cyanating agent under an O_2 atmosphere catalyzed by Cu. Other trials involving the $Pd(OAc)_2$/NaOAc or $[Cp^*RhCl_2]_2$/NaOAc as the catalytic system were found to be ineffective for this reaction. Several Cu sources such as $CuBr_2$, CuBr, $CuSO_4{\cdot}H_2O$, $Cu(OTf)_2$, and $Cu(OAc)_2$ were tested, and $Cu(OAc)_2$ was found to be the best choice. Also, the O_2 atmosphere is crucial for this reaction as the reaction was inhibited under N_2 atmosphere. A plausible mechanism for the transformation was proposed. $Cu(OAc)_2$ coordinates with the pyrimidyl N atom, the cleavage of the C1−H in **38a** affords the intermediate **38h**. Meanwhile, DMF is oxidized to iminium species **38f** by $Cu(OAc)_2$, proceeding with a single electron transfer step. Then, with the assistance of O_2, the reaction of **38f** and NH_3 leads to the intermediate **38g**, which releases CN *via* the cleavage of the C−N bond. This procedure was confirmed by the control experiments. Afterward, the replacement of AcO^- with CN^- leads to intermediate **38i**. Then, the intermediate **38i** was oxidized by O_2 to form Cu(III) the intermediate **38j**. Finally, the reductive elimination of Cu(III) intermediate **38j** releases **38c** along with the generation of Cu(I), which may be oxidized to Cu(II) by O_2 in the catalytic cycle.



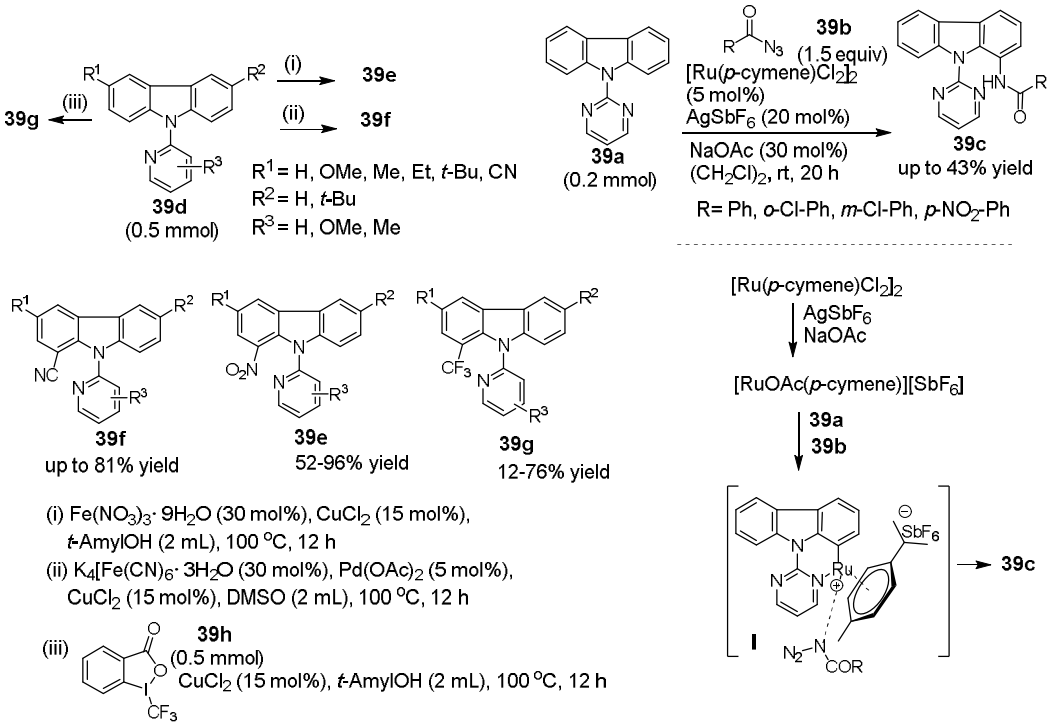
Scheme 23. C1−H Cyanation of carbazole.

The Punniyamurthy group reported[40a] the Ru-catalyzed pyrimidine-directed coupling of C−H bonds of carbazoles **39d** with acyl azides affording C1−H amidated carbazole derivatives **39c** (Scheme 24). The combination of $[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$ and NaOAc is found to be vital for this transformation and other directing groups, such as acetyl, pivaloyl, *N* ,*N*-dimethylcarbamoyl and Boc were also examined, which were found to be ineffective to afford the amidated product. The reaction of $[Ru(p\text{-cymene})Cl_2]_2$ with $AgSbF_6$ generates the cationic RuII species, which then reacts with **39a** and is followed by coordination of acyl azide **39b** generates the Ru-complex **I**. Then, the removal of N_2 and protodemetalation steps delivers **39c**. Hariharasarma and co-workers reported[40b] the pyridyl group-aided C1−H mononitration, and monocyanation of carbazoles **39d** affording **39e** and **39f**, respectively, and monotrifluoromethylation of **39d** with **39h** affording **39g**. This method enabled the direct functionalization of C1−H of carbazole which is challenging to access geometrically. The C3−H and C6−H positions were left unreacted, although these positions have high nucleophilic character wherein electrophilic substitutions are highly preferred. Direct cyanation did not generate the product without the use of $Pd(OAc)_2$ as the catalyst.

5.2. C−H Chalcogenation of carbazole

In 2015, the Law group reported[41a] a single example of direct phenyl-selenylation of 9-(pyrimidin-2-yl)-9*H*-carbazole in water using *N*-(phenylseleno)phthalimide (*N*-PSP) **40b** as the coupling

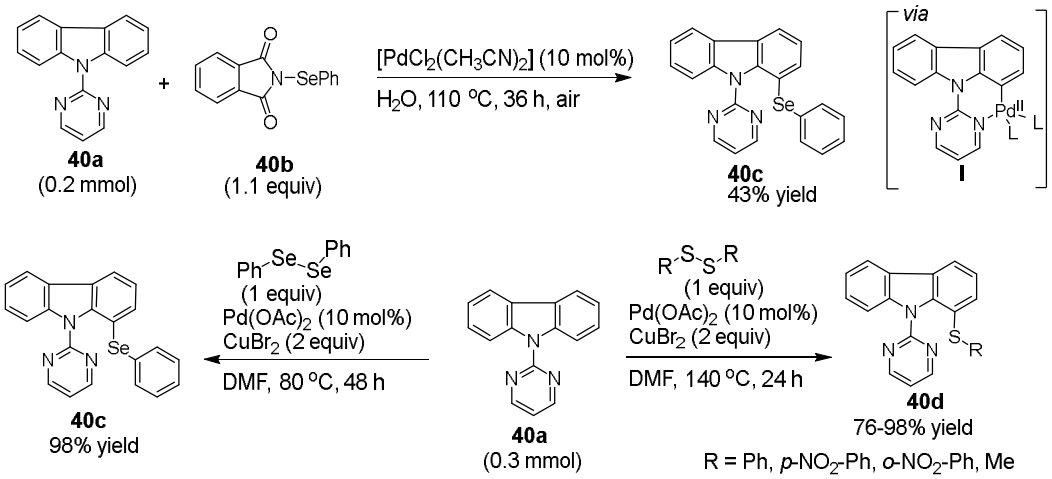
partner affording **40c** in 43% yield (Scheme 25). The main advantage of the reaction was the usage of water being a nontoxic, non-flammable, and renewable solvent in Csp^2–H bond activation without any oxidants, surfactants and other additives. The effects of the other additives, such as oxidants, bases, ligands and mixed solvents, were found to be ineffective in improving the conversion and selectivity. The conversion was adversely affected when polyoxyethylene lauryl ether as a surfactant was added to the reaction. The authors proposed the product formation through the plausible intermediate **I** which is a six-membered cyclopalladated complex formed by reacting **40a** with [$PdCl_2(CH_3CN)_2$] followed by oxidative addition of *N*-PSP to **I** to generate a Pd(IV) intermediate, followed by reductive elimination and**,** producing the desired product **40c** as well as the Pd(II) catalytic species. However, other pathways, such as the direct electrophilic aromatic substitution pathway involving Pd(II)–C bond cleavage and C–Se formation sequence or the Pd(II)/Pd(III) catalytic cycle, including the formation of a bimetallic Pd(III) complex cannot be completely ruled out.



Scheme 24. C1–H Amidation, nitration, trifluoromethylation and cyanation of carbazoles.

The Kambe group reported[41b] the intermolecular chalcogenation of 9-(pyrimidin-2-yl)-9*H*-carbazole **40a** with disulfides and diselenides *via* Pd-catalyzed selective C-H bond activation affording the corresponding C1–S or C1–Se containing carbazoles **40c** and **40d** (Scheme 25). Control experiments suggested that the Cu additive is essential for the conversion of C–Pd bonds to C–S and C–Se bonds in the presence of disulfides and diselenides, respectively. Subsequently, the same group reported[41c] the Cu(II)-mediated pyrimidyl group-directed C1–H thiolation of carbazole derivatives with disulfides (Scheme 26). Cu(I) and Cu(0) were found to be completely ineffective for this transformation; also, the addition of oxidants like $K_2S_2O_8$, DDQ and O_2 did not improve the yield. To understand the effect of the directing group, unsubstituted carbazole was reacted with disulfides under optimized conditions; without any directing group, a mixture of products, including C1–H and C8–H substituted product were obtained. Coordination of the Cu(II) to the nitrogen atom of the pyrimidyl ring of **40a** and an intramolecular one electron transfer

generates a Cu(I) complex, which then reacts with PhSSPh **41a** and $Cu(OAc)_2$ to form complex **I** or **II**. Then, the direct transfer of the PhS group from Cu to the aryl group *via* reductive elimination with concomitant deprotonation affords the C1−H thiolated carbazole derivative **41b**.



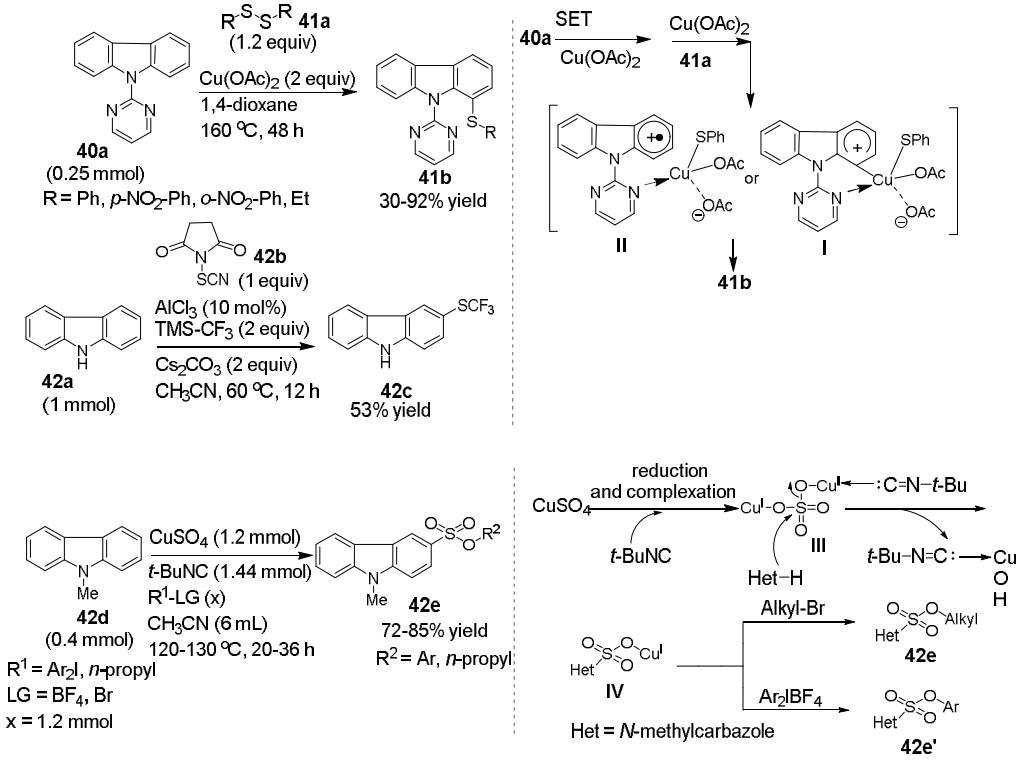
Scheme 25. C1−H Chalcogenation of carbazole.

Goossen and co-workers described[42a] a single example involving the C3−H trifluoromethylthiolation of carbazole motif **42a** catalyzed *via* $AlCl_3$-catalyzed C−H functionalization affording **42c**. The authors explained a straightforward and inexpensive approach by carrying out nucleophilic thiocyanations of alkyl halides or Sandmeyer thiocyanations of aryldiazonium salts, which were combined with Langlois-type exchange reactions. A one-pot, two-step synthetic protocol was developed by first reacting carbazole with *N*-thiocyanatosuccinimide (NTS) **42b** (1 equiv) and $AlCl_3$ (10 mol%) in acetonitrile at room temperature for 12 h followed by the addition of Cs_2CO_3 (2 equiv), TMS-CF_3 (2 equiv) at 60 °C for overnight to furnish the trifluoromethylthiol substituted carbazole **42c** in 53% yield (Scheme 26).

Xu and co-workers reported[42b] two examples of phenyl sulfonic esters from *N*-methyl carbazole using $CuSO_4$ as the sulfonating source through the activation effect of *t*-butyl isocyanide. Carbazole derivative **42e** was synthesized using **42d** (0.4 mmol), $CuSO_4$ (1.2 mmol), *t*-BuNC (1.44 mmol), CH_3CN (6.0 mL), Ar_2IBF_4 (1.2 mmol), *n*-propyl bromide (1.0 mL) under a nitrogen atmosphere at 120-130 °C for 20-36 h (Scheme 26). A plausible mechanism was proposed for the process, involving isocyanide-assisted reduction of Cu(II) to Cu(I). At the same time, isocyanide acts as a ligand and also helps in the dissociation of the robust O−S bond. It is assumed that *t*-BuNC initially reduced $CuSO_4$ to form complex **III**, where the isocyanide also acted as a ligand. The coordination of the isocyanide to the Cu center may stabilize the Cu(l) species and weaken the O−S bond, thus activating the sulfate anion. Then the complex **III** reacted with electron-rich heteroarene substrate to afford Cu(I) heteroaryl sulfonic intermediate **IV** *via* the Friedel-Crafts-type S_EAr reaction, which finally reacted with different electrophiles, such as alkyl halides or aryl iodonium salts, to give the corresponding alkyl or aryl sulfonates, respectively.

5.3. C−H Borylation, halogenation, perfluoroalkylation, and *N*-carbazolation of carbazole

The Sperry group described[43a] a five-step process that included sequential C1−H/C8−H and C3−H borylation reactions catalyzed by Ir for the synthesis of putative clausenal **43f** from carbazole **43a**. The Ir-catalyzed borylation reaction was carried out by using $[Ir(OMe)cod]_2$ as the catalyst with 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen) as a ligand and bis(pinacolato)diboron (B_2pin_2) to get desired borylated products **43b** and **43d** *via* **43c** (Scheme 27). In this process, the compound **43e** served as an intermediate for obtaining **43f**.



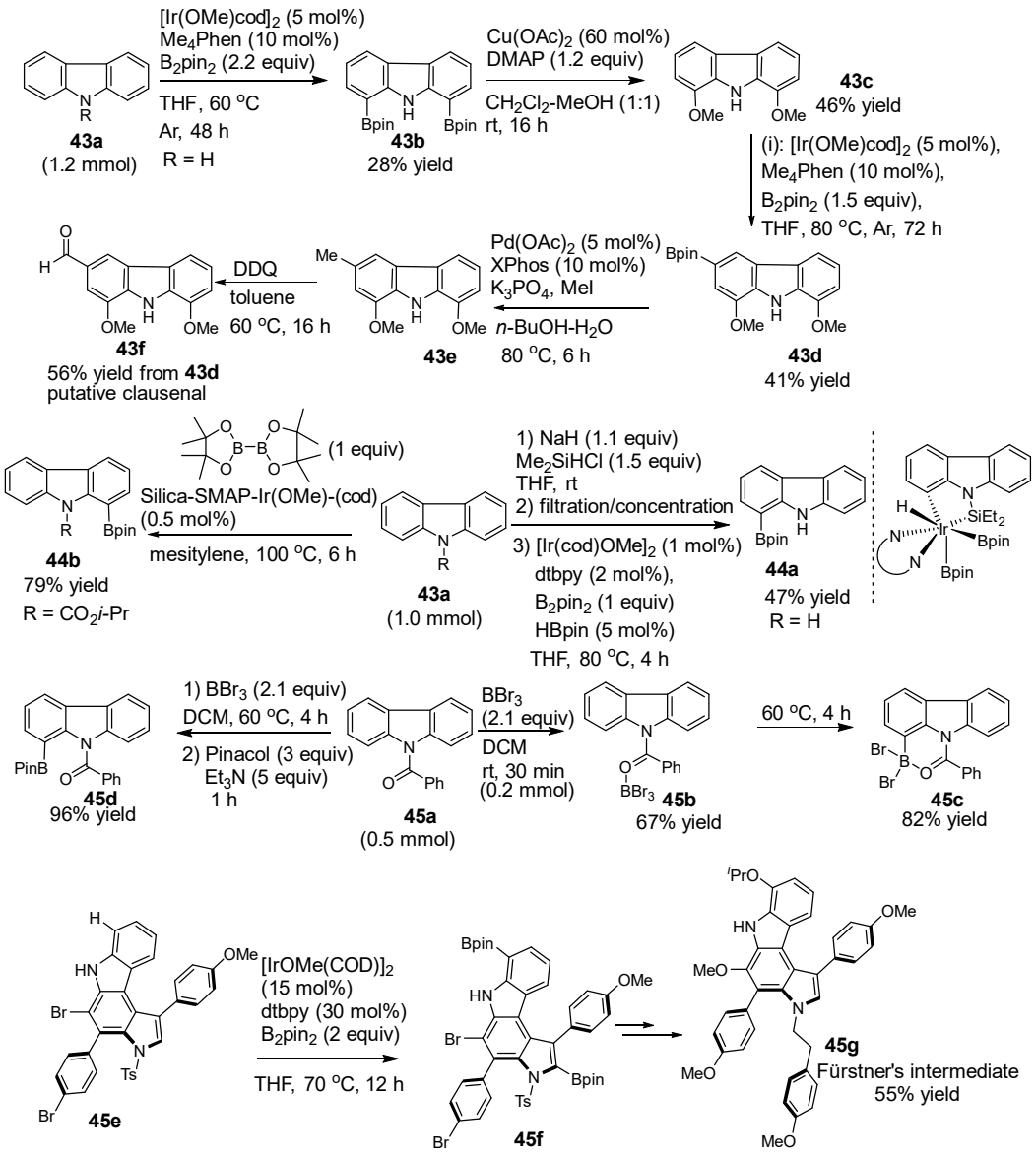
Scheme 26. C1−H/C3−H Chalcogenation of carbazole.

In 2010, Hartwig and co-workers revealed[43b] a single example of the silyl-directed borylation of carbazole *via* Ir catalysis. The authors described a one-pot protocol for carbazole borylation **43a** by installation of a silyl group using $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%) catalyst, Et_2SiH in toluene at rt. After evaporation of solvent, $[Ir(cod)Cl]_2$ (0.25 mol%) and dtbpy (0.5 mol%) catalytic system, B_2pin_2 (1 equiv), HBpin (5 mol%) in THF at 80 ºC assisted the subsequent C1−H borylation yielded the product **44a** in 47% yield (Scheme 27). Along this line, Sawamura and co-workers described[43c] the C1−H borylation of *N*-ester-functionalized carbazole scaffold catalyzed *via* silica-SMAP-Ir catalytic system to afford the C1−H borylated carbazole **44b**.

The Ingleson group disclosed[43d] the *N*-acyl-directed C1−H-borylation of carbazole using BBr_3 (Scheme 27). It was revealed that C−H borylation did not occur on *N*-pivaloyl carbazole using just BBr_3 (under heating conditions also), which was mainly attributed to the steric hindrance between the two proximal C−H bonds at the C1 and C8 position and the pivaloyl group results in the formation of large B−O−C−N dihedral angle in pivaloyl analogue **45b**. When *N*-benzoyl carbazole **45a** was allowed to react with BBr_3 at room temperature, C−H borylation did not occur, whereas a Lewis adduct **45b** was generated, which was confirmed by X-ray structure. However, heating of **45a** with BBr_3 resulted in the C−H borylation at the C1 position, and C−H borylated product **45c** was isolated and confirmed by X-ray structure and the boron center was subsequently protected *in situ* to furnish pinacol boronate ester **45d**. Yamaguchi's group reported[43e] the formal synthesis of dictyodendrins **B**, **C** and **E** *via* a multi-substituted indole **45e**. A C−H borylation of highly substituted pyrrolocarbazole skeleton **45f** served as a key step to assemble Fürstner's intermediate **45g** in the formal synthesis of dictyodendrins **B**, **C**, and **E**.

Shi's group developed[44a] a stable silicon reagent (octamethyl-1,4-dioxacyclohexasilane, ODCS) for the silacyclization of heteroarenes including carbazoles **46a** with varying complexity *via* a two-fold C−H activation process affording **46b**. The reactivity of OCDS is such that it results in activating two C−H bonds

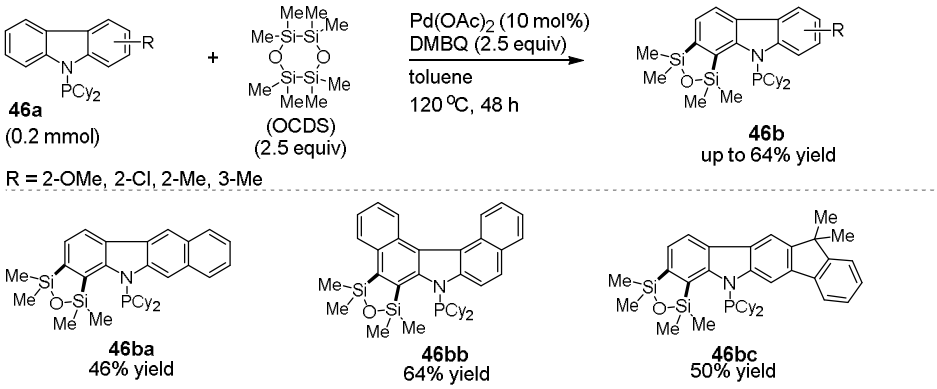
in (hetero)arenes which can be easily silylated to form benzoxadisilole compounds in the presence of a Pd catalyst, whereas such products were not generated using conventional silicon reagents (Scheme 28).



Scheme 27. C−H Borylation of carbazole.

Silacyclization of carbazoles **46b** were obtained by treating *N*-protected substituted carbazole **46a** with OCDS (2.5 equiv), $Pd(OAc)_2$ (10 mol%) catalyst and DMBQ (2.5 equiv) oxidant in toluene at 120 °C for 48 h under an argon atmosphere. A high level of steric control was observed when substituents were *ortho* (such as Me, OMe and groups at C1) to the reacting C−H bonds resulting in better regioselectivity. Highly π-extended heterocyclic skeletons, including 5*H*-benzo[*b*]carbazole, 7*H*-dibenzo[*c,g*]-carbazole and

5,11-dihydroindeno[1,2-*b*]carbazole also furnished the silacyclization products (*e.g.* **46ba**, **46bb**, and **46bc**) in good yields (Scheme 28).



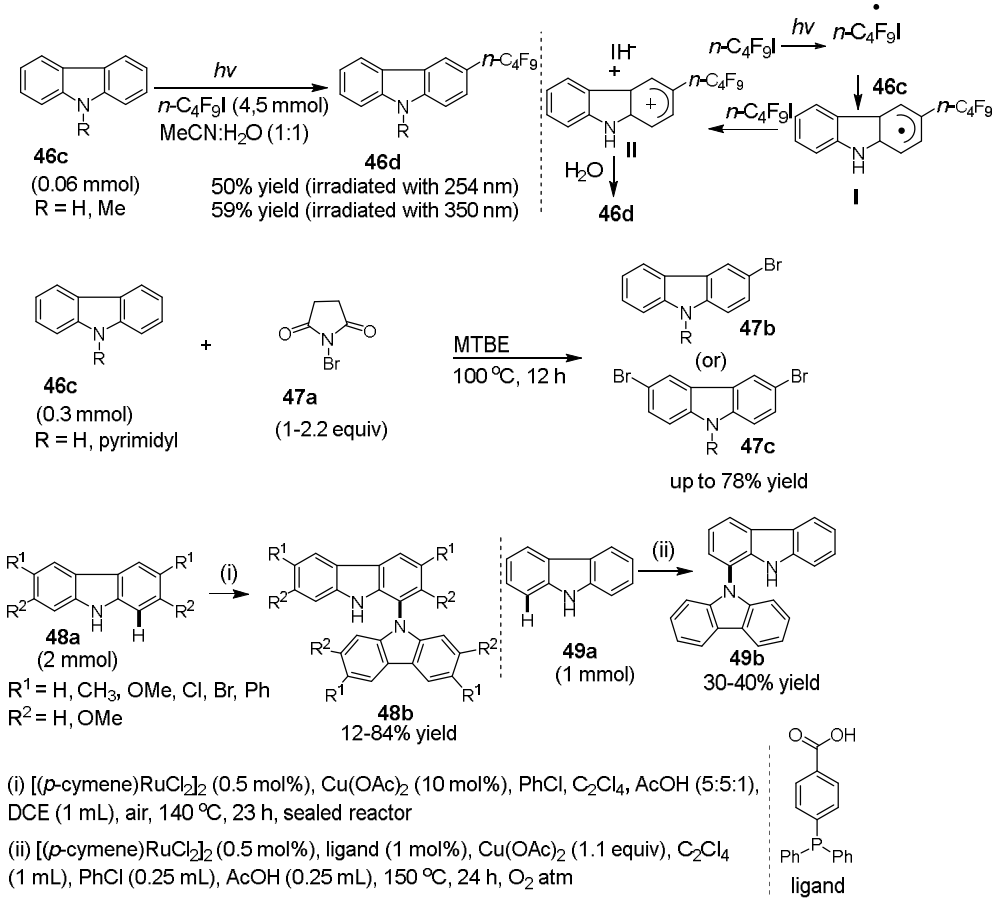
Scheme 28. C−H Silylation of carbazole.

In 2014, Postigo and co-workers disclosed[44b] the first example of direct C−H perfluoroalkylation of carbazole scaffold in aqueous media using a photochemical approach, surpassing the utilization of any transition metal reagents or organocatalyst. An argon-filled deoxygenated reaction mixture containing 9*H*-carbazole **46c** and *n*-C_4F_9I in MeCN-H_2O was irradiated with a 254 nm lamp and vigorously stirred for 4 h to furnish 3-(perfluorobutyl)-9*H*-carbazole **46d** in 50% yield. While protected, *N*-methyl-9*H*-carbazole **46c** was allowed to irradiate at 350 nm under similar reaction conditions to generate 9-methyl-3-(perfluorobutyl)-9*H*-carbazole **46d** in 59% yield (Scheme 29). At 254 nm irradiation, under conditions where most of the light is absorbed by *n*-C_4F_9I, homolysis of the F_9C_4–I bond produces perfluorobutyl radicals that add to the (di)benzo(hetero)arene to yield the radical adduct intermediate **I**. The radical adduct **I** undergoes a sequence of ET to *n*-C_4F_9I (to afford cation intermediate **II**, Wheland intermediate, oxidation triggered through the favorable Gibbs energy, *vide supra*) and then proton transfer (PT) steps to yield **46d**. Sharma and co-workers disclosed[45] a single example for the selective C3−H halogenation of carbazole scaffold through S_EAr (electrophilic aromatic substitution) type reaction under metal and additive-free conditions. It was suggested that *N*-protection with pyrimidyl moiety acted as a promoter group which afforded the product in good yields and regioselectivity. The reaction was carried out using carbazole **46c**, electrophilic source NBS **47a** in methyl *t*-butyl ether (MTBE) at 100 °C for 12 h to furnish the bromo substituted carbazoles **47b**/**47c** at C3 or C6 position.

In 2013, the Patureau group described[46a,b] the synergistic action of Ru and Cu catalysts resulting in direct C−H and N−H activation for the dehydrogenative *N*-carbazolation of carbazoles selectively at the C1 position (Schemes 29 and 30). Several mechanistic experiments were performed by the authors to understand the integrity of the reaction. The $Cu(OAc)_2$ and $[(p\text{-cymene})RuCl_2]_2$ catalysts were utilized to furnish the polynuclear dehydrogenative C−N carbazolation of carbazoles **48a** resulting in carbazole dimer **48b**. Additionally, Patureau and co-workers have reported[46c] a single example of synthesis of carbazole **49b** using **49a** (1 mmol) in the presence of $[(p\text{-cymene})RuCl_2]_2$ (0.5 mol%), ligand (1 mol%), $Cu(OAc)_2$ (1.1 equiv), C_2Cl_4 (1 mL), PhCl (0.25 mL), AcOH (0.25 mL) at 150 °C for 24 h (Scheme 30). Later, Patureau and co-workers described[47] the improved method for the formation of C1-*N* bi-carbazole product using Ru/Cu co-catalyzed dehydrogenative homo-coupling of carbazoles **50a**. $[\{Ru(p\text{-cymene})Cl_2\}_2]$ (0.5 mol%) (method A) catalyst was utilized earlier, which resulted in lower turn-over frequencies, thereby increasing the reaction time up to two weeks. Later, several ligands and catalysts were screened which suggested that two Ru pre-catalysts were able to result in the carbazole product **50b** up to 80% yield (Scheme 30).[47]

Koley and co-workers have reported[48] the Cu-catalyzed pyrimidine-directed C1−H diarylamination of carbazoles **51a** and hexahydrocarbazoles **51c** under an oxygen atmosphere (Scheme 30). Mechanistic investigations reveal that Cu plays a dual role. This method is a simple way to synthesize carbazole-based

triarylamine derivatives **51b**/**51d** *via* the C−H activation method. The reaction follows a radical pathway. Arenes bearing alkoxyl and halogen groups were well tolerated. When the same reaction was carried out in the absence of a Cu catalyst, no product was obtained. Aminyl radical acts as an important intermediate in this reaction. Electronically rich diaryl amines react preferentially over electronically neutral or electronically deficient substrates.



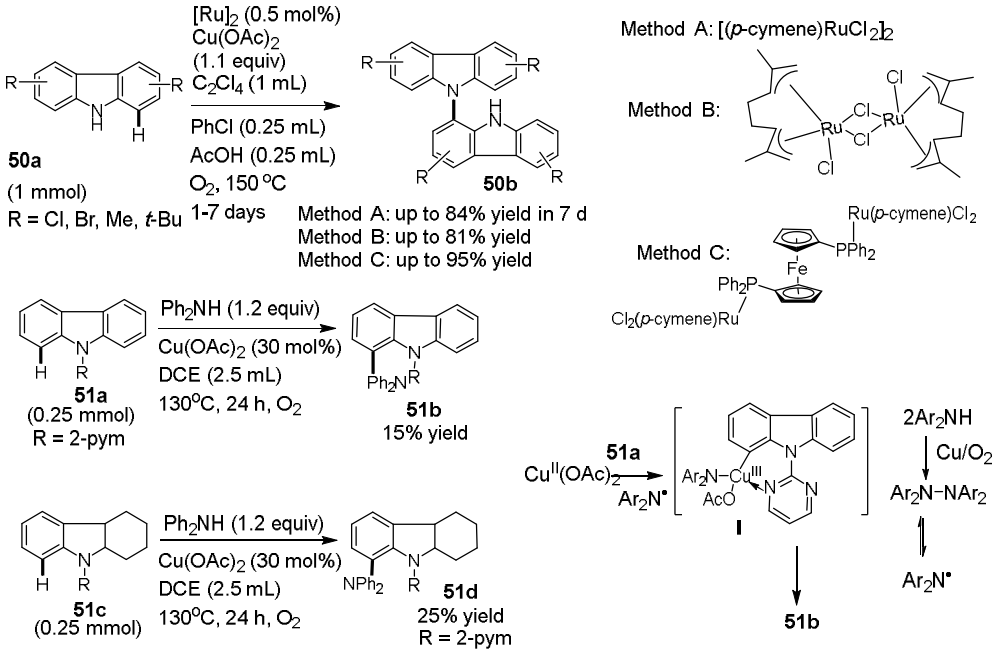
Scheme 29. C3−H Perfluoroalkylation and halogenation of carbazoleand direct C−H and N−H activation towards modified carbazoles *via* C−N coupling.

Based on the preliminary experimental results and previous reports, a plausible mechanism for this reaction was outlined (Scheme 30).[48] Carbazole **51a** chelates with Cu(II) to form an initial intermediate, which is then converted to another Cu(II) intermediate *via* chelation-assisted reversible C−H bond cleavage. Subsequently, tetraarylhydrazine formed *in situ* from diarylamine oxidizes the Cu(II) metallacycle to generate the Cu(III) intermediate **I**, which upon reductive elimination, furnishes the triarylamine product **51b** and Cu(I)OAc.

6. Oxidative cross-coupling with carbazole

In this section, we present the recent developments pertaining to oxidative cross-coupling involving C−H bonds of carbazole. The Kambe group reported[49] Rh-catalyzed intermolecular oxidative cross-coupling of C−H bond of 9-(pyrimidin-2-yl)-9*H*-carbazole with C−H bond thiophene or selenophene derivatives

(chalcogenophenes) *via* double C−H bond cleavage by using $[RhCp^*Cl_2]_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant (Scheme 31). A plausible reaction pathway was illustrated for the Rh-catalyzed intermolecular oxidative cross-coupling of the C−H bond of 9-(pyrimidin-2-yl)-9*H*-carbazole with C−H bond thiophene or selenophene **52b**. The Rh complex is activated by $AgSbF_6$ to generate the electrophilic cationic complex. The catalytic cycle starts initially where carbazole **52a** reacts with the thus formed Cp*Rh(III) to generate rhodacyclic intermediate **I** stabilized by *N*-Rh coordination. Subsequently, intermediate **I** react with chalcogenophene to provide intermediate **II**, which undergoes reductive elimination to give the cross-coupled product **52b** and an Rh(I) species, and the latter is oxidized by Cu(II) to complete the catalytic cycle.



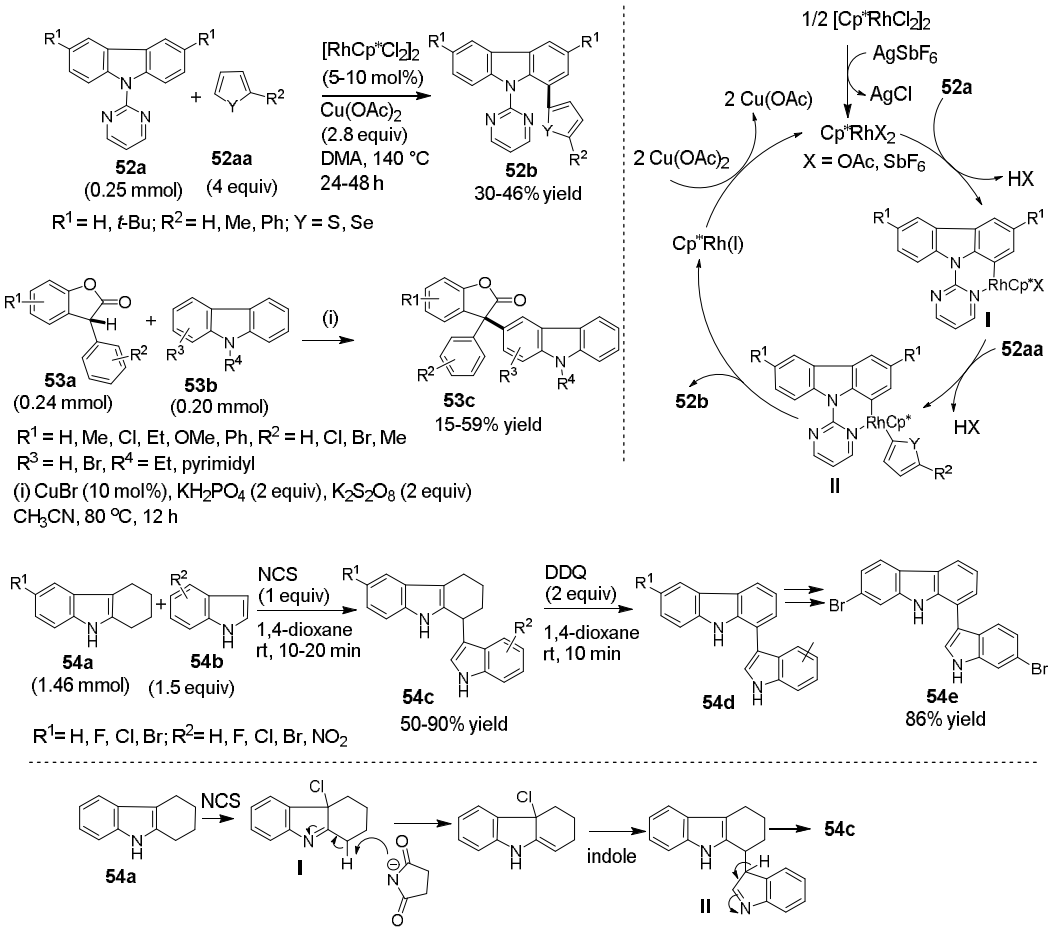
Scheme 30. Direct C−H and N−H activation towards modified carbazoles *via* C−N coupling.

The Kambe group reported[50] the synthesis of 3,3-diaryl benzofuranones **53c** having a three aryl quaternary center at C3 position *via* cross-dehydrogenative coupling of C3−H of carbazole **53b** and tertiary Csp^3−H of benzofuranones **53b**. CuBr was used as a catalyst and $K_2S_2O_8$ as an oxidizing agent; it was suggested by preliminary mechanistic studies that the reaction involves a Cu-catalyzed radical process (Scheme 31). The Nagarajan group reported[51] the synthesis of 1-(indol-3-yl)carbazole **54c** starting from tetrahydrocarbazole **54a** and **54b** by metal-free, oxidative cross-coupling using *N*-chlorosuccinimide as a mild oxidant followed by aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). This methodology was applied to synthesize a natural product 7-bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole **54e** *via* **54d** (Scheme 31). A proposed reaction mechanism was depicted that NCS reacts with tetrahydrocarbazole **54a** to form intermediates **III** and then **V**. Nucleophilic attack by indole to **V** then affords compound **VI**. Then, the compound **VI** upon aromatization conditions can furnish the 1-(indol-3-yl)carbazole (Scheme 31).

7. Intramolecular C−H cyclization involving carbazole

In this section, we present the recent developments pertaining to intramolecular C−H cyclization involving carbazole scaffold affording modified carbazoles. Patureau and co-workers developed[52] an intramolecular C−H oxidizing strategy to get fused carbazole moieties starting from simple naphthylamine

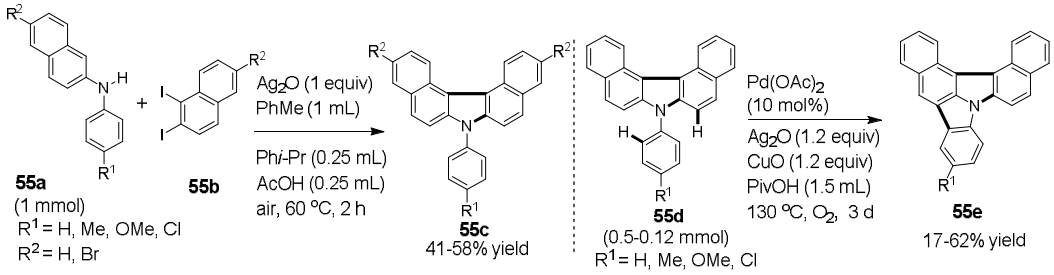
derivatives **55a** and **55b**. The authors also performed dehydrogenative ring closure of the *N*-aryl carbazole structures with significant properties. At first, the synthesis of **55c** was accomplished from the diarylamine system and subsequently, highly fused π-extended dibenzoindolocarbazole **55e** was synthesized *via* intramolecular dehydrogenative coupling by using carbazole derivative **55d** (0.5-0.12 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (1.2 equiv), CuO(1.2 equiv), PivOH (1.5 mL), under O_2 at 130 °C for 3 days (Scheme 32).



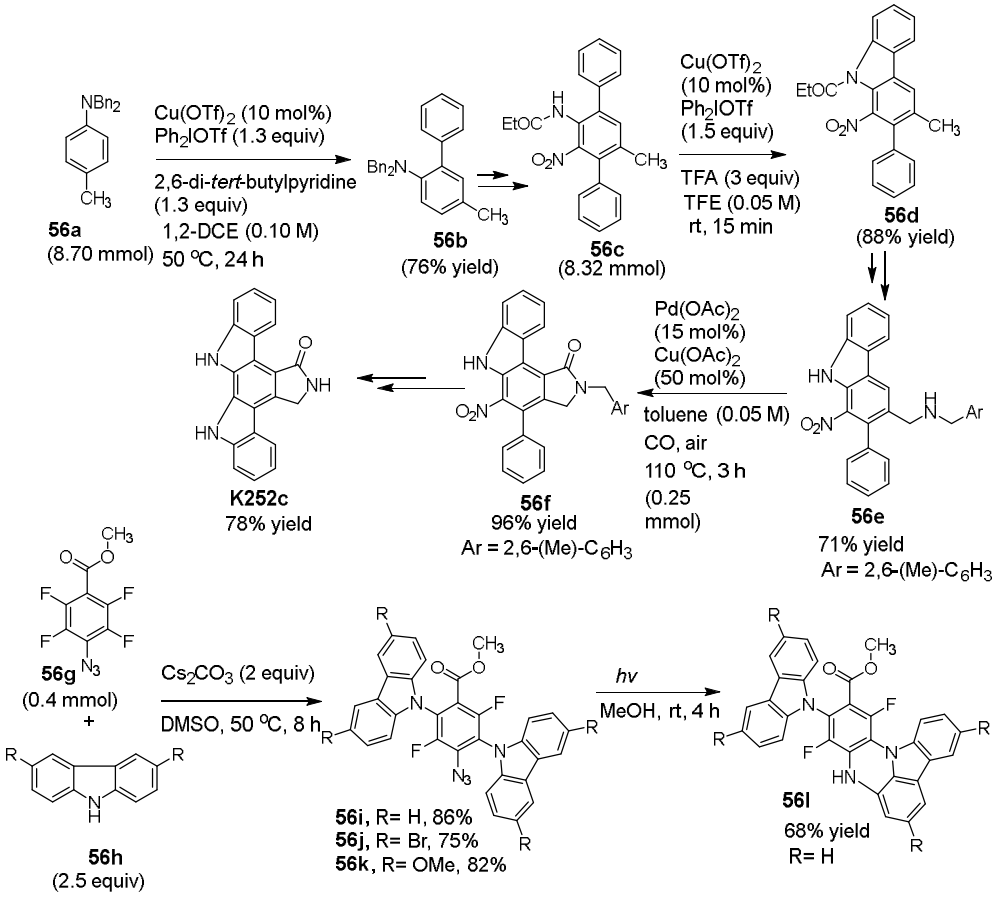
Scheme 31. Oxidative cross-coupling with C−H bond of carbazoles.

Gaunt and co-workers demonstrated[53a] a concise synthetic protocol for the construction of indolocarbazole alkaloid K-252c (staurosporinone) *via* a sequential C−H functionalization strategy. The strategy involves a direct C−H functionalization reaction comprising Cu-catalyzed C−H arylation followed by C−H amination and a Pd-catalyzed C−H carbonylation (Scheme 33). The synthesis was initiated from the readily available dibenzyl *p*-toluidine **56a,** which was subjected to the first C−H functionalization reaction using $Cu(OTf)_2$ (10 mol%), Ph_2IOTf (1.3 equiv), 2,6-di-*t*-butylpyridine (1.3 equiv) in DCE (0.10 M) at 50 °C for 24 h to generate *ortho*-selective arylated product **56b** in 76% yield. Then, the Cu-catalyzed *meta*-arylation was conducted by switching the benzylic substituents to a carbonyl group, followed by the formation of a teraryl intermediate using $CuOTf_2$. On further transforming the functional groups, the resulting intermediate **56c** was treated with $CuOTf_2$ (10 mol%), $PhI(TFA)_2$ (1.5 equiv) and trifluoroacetic acid (3 equiv) in TFE at room temperature for 15 min to afford **56d**. Next, the Cu-catalyzed oxidative C−H

amination strategy furnished the carbazole **56e** in 71% yield. Subsequently, the γ-lactam motif was installed in **56e** *via* Pd-catalyzed C−H carbonylation using $Pd(OAc)_2$ (15 mol%) and $Cu(OAc)_2$ in toluene under a CO atmosphere at 110 °C for 3 h affording **56f**. Further subsequent reactions on **56f** resulted in the formation of K252c in 78% yield.



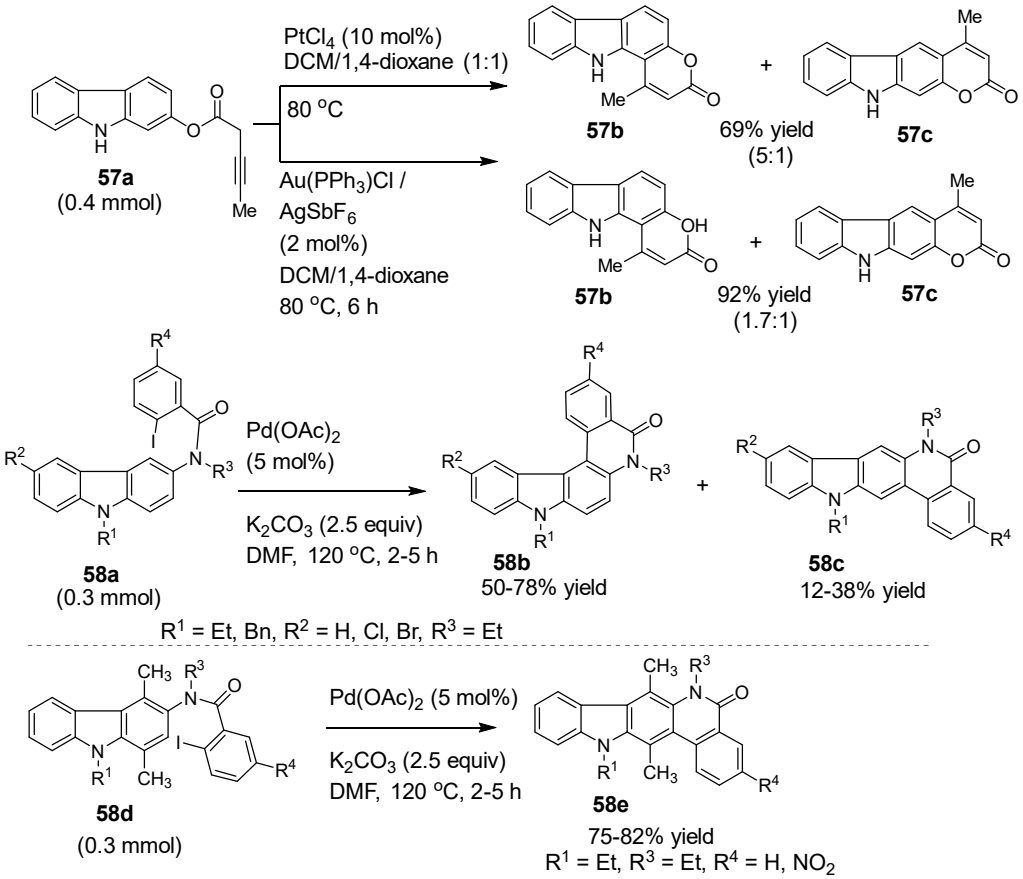
Scheme 32. Intramolecular C−H coupling reactions affording modified carbazole.



Scheme 33. Intramolecular C−H carbonylative cyclization reactions affording modified carbazole **56f** and synthesis of K252c.

Perfluroaryl azides are generally non-fluorescent, which can be turned on by photochemical conversion to the corresponding fluorescent carbazole structure. In 2019, The Yan group developed[53b] a novel fluorescence turn-on strategy based on photoinitiated intramolecular C−H insertion of perfluoroaryl nitrenes into neighbouring aromatic rings. At first, compounds **56i-k** were assembled from **56g** and **56h** and then compound **56i** was selected as a model fluorogen, which was irradiated at 350 nm in MeOH for 4 h to afford the carbazole **56i** *via* the intramolecular insertion in 68% yield (Scheme 33).

The Sames group described[54a] a single example of intramolecular C−H hydroarylation of carbazole alkynolate esters **57a**, which was catalyzed by $PtCl_4$ and $Au(PPh_3)Cl/AgSbF_6$. (Scheme 34) It was revealed that $PtCl_4$ catalyst exhibited higher regioselectivity affording **57b**/**57c** (in a ratio of 5:1) as compared to the $Au(PPh_3)Cl/AgSbF_6$ system affording **57b**/**57c** (in a ratio 1.7:1), thereby suggesting that less active catalyst is more selective towards the more sterically hindered product **57b**, illustrating the importance of electronic factors involved in this transformation.

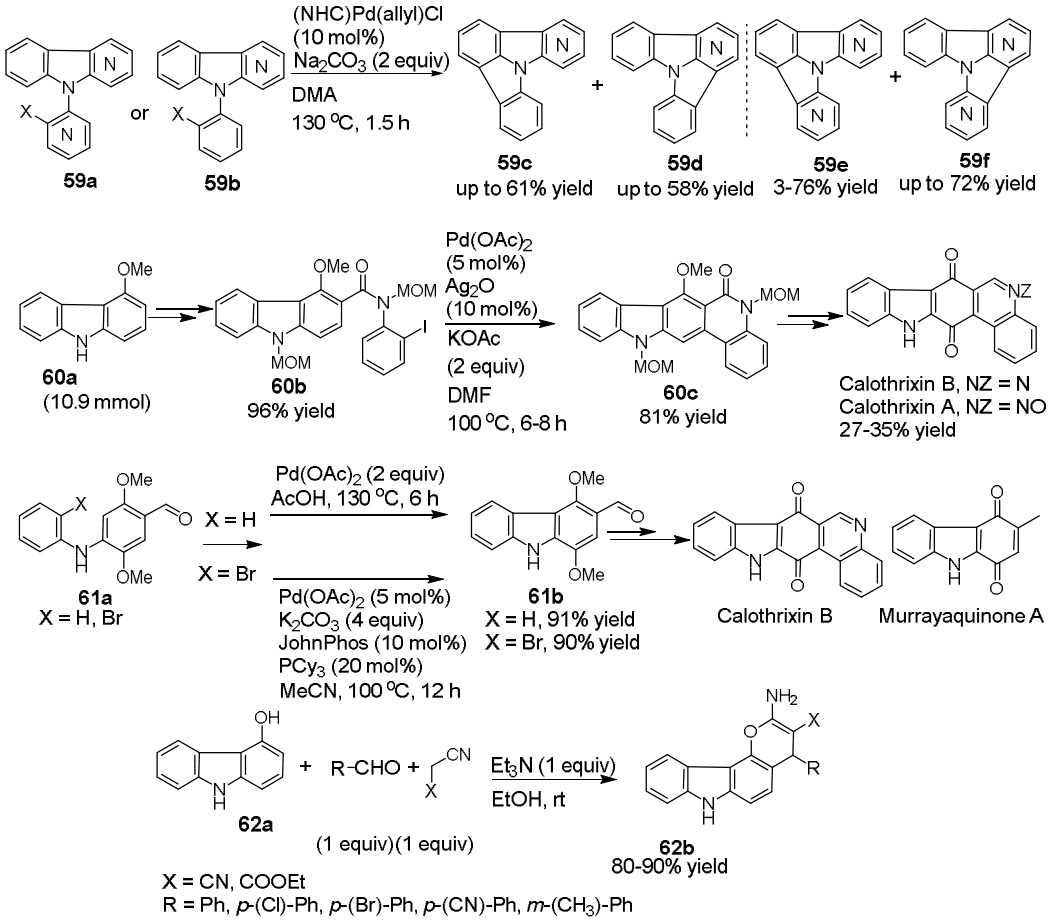


Scheme 34. Intramolecular C−H functionalization on carbazoles towards modified carbazoles.

In 2010, Nagarajan and co-workers described[54b] a synthetic pathway for the synthesis of quino[2,3-*c*] and quino[3,2-*b*]carbazoles *via* Pd-catalyzed intramolecular *ortho* arylation (Scheme 34). Various *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-iodobenzamide **58a** which were prepared from 9-ethyl-3-aminocarbazole and 2-iodobenzoyl chloride. Then, the intramolecular cyclization was carried out using $Pd(OAc)_2$ (5 mol%) catalyst, K_2CO_3 (2.5 equiv) base in the presence of DMF solvent at 120 °C for 2 h to afford the quinocarbazoles in good to moderate yields. The versatility of the reaction was confirmed by synthesizing

various substituted quinocarbazoles under optimized conditions, resulting in facile cyclization to give isomeric products **58b** and **58c**. A similar protocol was extended to the substituted 1,4-dimethylcarbazoloiodobenzamides **58d** using a similar Pd-catalyzed reaction condition to generate **58e** in good yields.

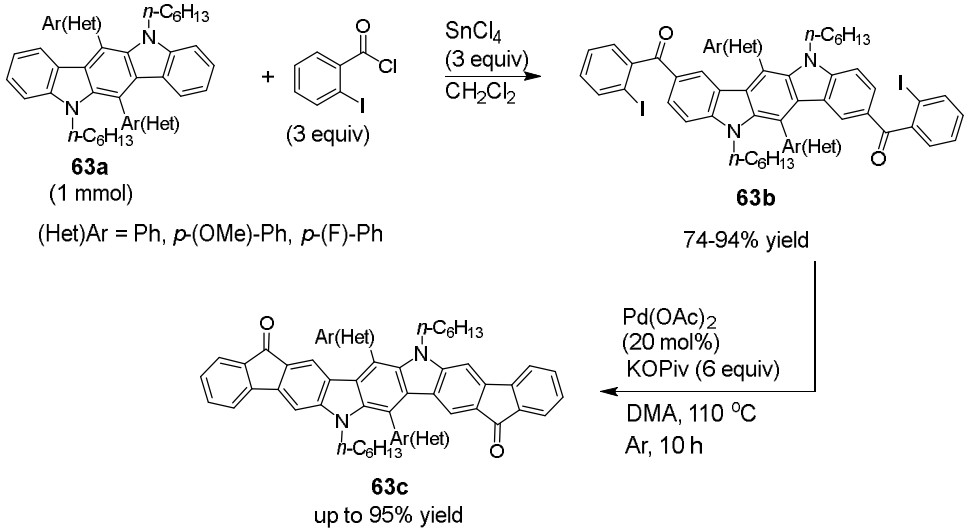
The Kautny group reported[55a] the synthesis of azaindolo[3,2,1-*jk*]carbazoles **59c-f** from the corresponding substrates **59a** and **59b** *via* Pd-catalyzed ring-closing C−H activation method (Scheme 35). Incorporating pyridine moiety into the planar indolo[3,2,1-*jk*]carbazoles backbone had a substantial influence, according to the produced materials, comprehensive photo-physical and electrochemical characterization. Additionally, the nitrogen location influenced intermolecular hydrogen bonding and, thus, solid-state alignment significantly. The Nagarajan group reported[55b] the total synthesis of bioactive indolo[3,2-*j*]phenanthridine calothrixin A and B starting from 4-methoxycarbazole **60a** *via* Pd-catalyzed intramolecular C−H activation of bis-*N*-protected compound **60b** as the key step. The presence of Ag_2O was found to be vital for Pd-catalyzed cross-coupling reaction between aryl iodide and Csp^2 of carbazole skeleton affording **60c**, which is the precursor to indolo[3,2-*j*]phenanthridine calothrixin A and B (Scheme 35).



Scheme 35. Intramolecular C−H functionalization on carbazoles towards modified carbazoles.

Furthermore, Kaliyaperumal *et al.* reported[55c] the synthesis of carbazoles alkaloids calothrixin B and murrayaquinone A in excellent yields utilizing the Pd-catalyzed intramolecular C−H functionalization reaction affording **61b**, involving **61a** as starting substrate. In turn, **61b** is the precursor of calothrixin B and murrayaquinone A. The Bhadra group reported[55d] the synthesis of pyrano[3,2-*c*]carbazole derivatives **62b** by a simple one-pot, three-component reaction of aromatic aldehydes, malononitrile-ethyl cyanoacetate and 4-hydroxycarbazole **62a**. The synthesized derivatives were further investigated as anti-tumor agents that inhibit tubulin polymerization and induce apoptosis. The colchicine binding site of tubulin polymer was selectively occupied by all the lead compounds, as demonstrated by molecular docking studies (Scheme 35).

The Irgashev group reported[56] the synthesis of fused nine-ring systems of the indolo[3,2-*b*]carbazole family **63c** *via* an efficient two-step strategy based on the double Friedel-Crafts acylation of 5,11-dihexyl-6,12-di(hetero)aryl-substituted 5,11-dihydroindolo[3,2-*b*]carbazoles **63a** with 2-iodobenzoyl chloride in the presence of $SnCl_4$, followed by regioselective double Pd-catalyzed intramolecular C–H arylation involving **63b** (Scheme 36). Without the use of any additional ligands or additives, double Pd-cyclization has been effectively accomplished by utilizing Pd(II) acetate as the catalyst and excess potassium pivalate as the base. For several of the discovered compounds, physicochemical studies have been carried out to determine their optical, redox, and thermal stability.

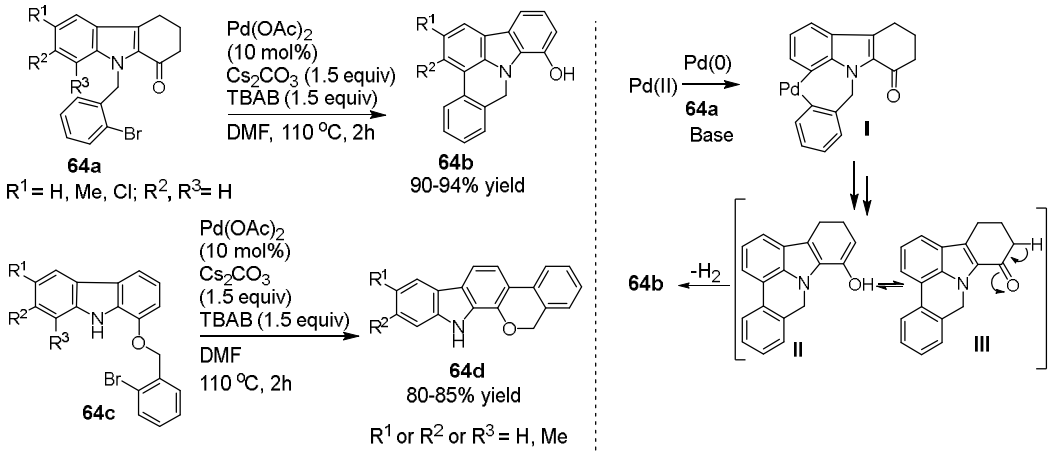


Scheme 36. Intramolecular C−H functionalization on carbazoles towards modified carbazoles.

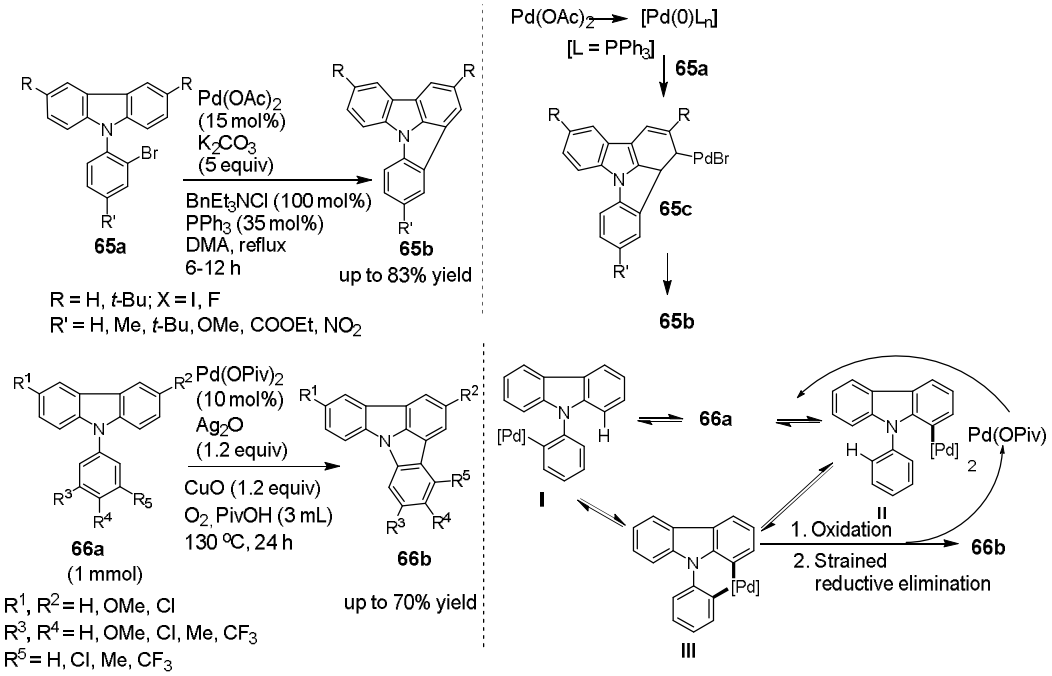
The Prasad group developed[57] an efficient method for the synthesis of indolo[3,2,1-*d,e*]phenanthridines **64b** and isochromeno[3,4-*a*]carbazoles **64d** under ligand-free conditions *via* Pd-catalyzed intramolecular Heck-type C−H functionalization reaction involving corresponding substrates **64a** and **64c** (Scheme 37). The coupling reaction was carried out using 10 mol% of $Pd(OAc)_2$ as a catalyst, Cs_2CO_3 as a base, and tetrabutylammonium bromide (TBAB) as an additive under nitrogen atmosphere in anhydrous DMF as a solvent. Several other bases like Et_3N, K_2CO_3, Ag_2CO_3, and KOAc were examined for this reaction, and Cs_2CO_3 was found to be the most effective. The reaction did not proceed without any additive, which signified that additive TBAB plays an essential role in cyclization. The reaction pathway affording **64b** involves the intermediates **I**, **II** and **III**.

Subsequently, the Liu group reported[58] the synthesis of indolo[3,2,1-*jk*]carbazoles **65b** *via* Pd-catalyzed intramolecular C−H cyclization of *N*-(2-bromoaryl)carbazoles **65a** (Scheme 38). The reaction was carried out using $Pd(OAc)_2$ as a catalyst, K_2CO_3 as a base and $BnEt_3NCl$ as an additive in refluxed *N,N*-dimethylacetamide (DMA) with PPh_3 as a ligand. K_2CO_3 was found to be more efficient than various other bases like Na_2CO_3, $NaHCO_3$, $KHCO_3$ and NEt_3. The proposed mechanism for Pd-catalyzed cyclization

toward indolo[3,2,1-*jk*]-carbazoles undergoes the oxidative addition of **65a** with Pd to form aryl-Pd intermediate **I**, followed by addition to the double bond of carbazole ring to give intermediate **65c**. The *β*-hydrogen elimination is triggered by the attack of bases to aromatic protons to form compound **65b**.



Scheme 37. Intramolecular C–H functionalization on carbazoles towards modified carbazoles.



Scheme 38. Intramolecular C–H functionalization on carbazoles towards modified carbazoles.

Next, Patureau and co-workers reported[59] the ring closure of strained phenylcarbazoles **66a** *via* the Pd-catalyzed C–H activation. The modified carbazole **66b** was synthesized using **66a** (1 mmol), $Pd(OPiv)_2$ (10 mol%), Ag_2O (1.2 equiv), CuO (1.2 equiv), PivOH (3 mL) and O_2 (1 atm) at 130 °C for 24 h (Scheme 38). The electronic disposition of the substrates affects the reaction in such a way that highly electron-rich

and highly electron-poor substrates were found to be unreactive. Unsymmetrical substrates, whether at the phenyl moiety or the carbazole moiety, gave moderate C−H regioisomeric selectivity. These results unambiguously indicated[59] that Pd is involved in the reversible C−H activation steps, presumably in a classical concerted metalation deprotonation (CMD) mechanism involving pivalate ligands. The other components, however, the Ag and Cu salts, and O_2, are more likely involved in the later steps of the catalytic cycle. Interestingly, the apparent correlation between oxidation strength (Ag-Cu-O_2 triple oxidizing system) and reaction efficiency suggests that the final strained reductive elimination step must be preceded by or simultaneous to a high oxidation event at Pd in intermediate **III**. The latter high oxidation step, either alone or combined with the reductive elimination, is probably the rate-limiting, which is also consistent with the very strained and rigid nature of the product.

Furthermore, Miura and co-workers reported[60] an interesting method for the synthesis of carbazole-based nitrogen containing polycyclic aromatic compounds **67b**, **67f**, and **67g** having highly extended conjugation using an oxidizing system of Pd(II)/Ag(I) *via* double intramolecular C−H/C−H coupling of corresponding substrates **67a** and **67e** (Scheme 39). The authors also isolated singly cyclized product **67d** using 1,2-bis(3,6-di-*t*-butyl-9*H*-carbazol-9-yl)benzene **67c**. All the products exhibit fluorescence and are also expected to be useful as electron donors. Kautny and co-workers have reported[61] the formation of three regioisomeric thienopyrrolo[3,2,1-*jk*]carbazoles **68b**, **68d**, and **68f** *via* a convenient intramolecular ring-closing C−H activation approach involving corresponding substrates **68a**, **68c,** and **68e**.

8. Annulation reaction involving C−H bond of carbazole towards modified carbazole

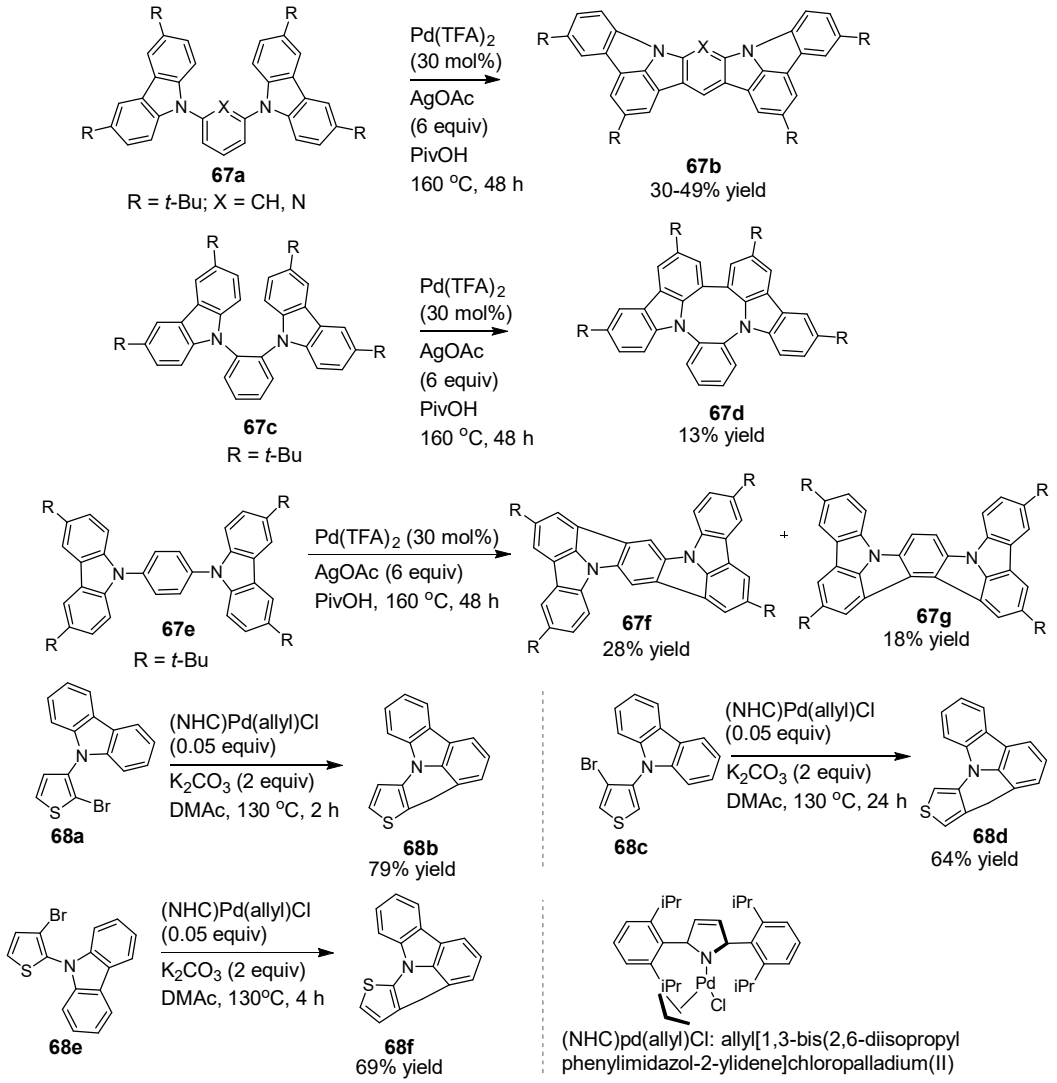
In this section, we present the recent developments concerning the synthesis of modified carbazoles *via* annulative C−H cyclization involving carbazole scaffold. The Wang group reported[62] the synthesis of a single example of carbazole-fused azepine by C−H/N−H activation of readily available alkynes **69b** and carbazole scaffold **69a** using $Pd(OAc)_2$ as a catalyst with stoichiometric amounts of AgOAc (oxidant) in a mixture of solvent of MeCN/1,4-dioxane (v/v=1:1) (Scheme 40). Performing the reaction under a nitrogen atmosphere was essential for the better yield of products because a moderate yield (55%) of the product was obtained when the reaction was carried out in the presence of air. A plausible mechanism to account for product formation was proposed. The palladation of carbazole **69a** involving a *syn*-addition to diphenylacetylene **69b** is believed to generate a vinyl Pd intermediate. Then the vinyl Pd intermediate generated from **69a** is added with another acetylene unit **69b** to afford a butadienyl Pd intermediate. Next, an intramolecular palladation of butadienyl Pd intermediate is believed to generate a palladabenzocycloheptatriene intermediate, which then undergoes reductive elimination to yield the product benzazepine **69c**. In 2017, the Wang group reported[63] the synthesis of substituted carbazoles and 4-*H*-oxepino[2,3,4,5-*def*]carbazoles **70b** through Rh-catalyzed [4+2]-cycloaddition with an internal alkyne and tandem [4+2]- and [5+2]-cycloaddition of **70a** with two molecules of alkynes, respectively. The hydroxyl group of substituted carbazole **70b** acted as an efficient directing group for further Rh-catalyzed annulative C−H functionalization to afford **70c**.

Chatani and co-workers developed[64] a nickel/NHC system for carrying out regioselective oxidative annulation in carbazole moiety **71a** *via* 8-aminoquinoline directing group-assisted double C−H bond activation followed by subsequent alkyne insertion affording modified carbazole **71c** (Scheme 40). The *N*-methyl protected carbazole possessing 8-aminoquinoline directing group **71a** (0.25 mmol) and diphenylacetylene **71b** (5 equiv) were treated with [$NiBr_2$(dme)] (10 mol%) catalyst, SlMes·HCl ligand (20 mol%), *t*-BuOK (22 mol%) in toluene at 160 °C for 3 h under a nitrogen atmosphere, which gave the corresponding modified carbazole **71c** in 73% yield. Chatani *et al.* propsoed[64] a plausible mechanism for the formation of carbazole **71c** through the 8-aminoquinoline directing group-assisted double C−H bond activation followed by subsequent alkyne insertion reaction.

9. C−H Functionalization of tetrahydrocarbazole

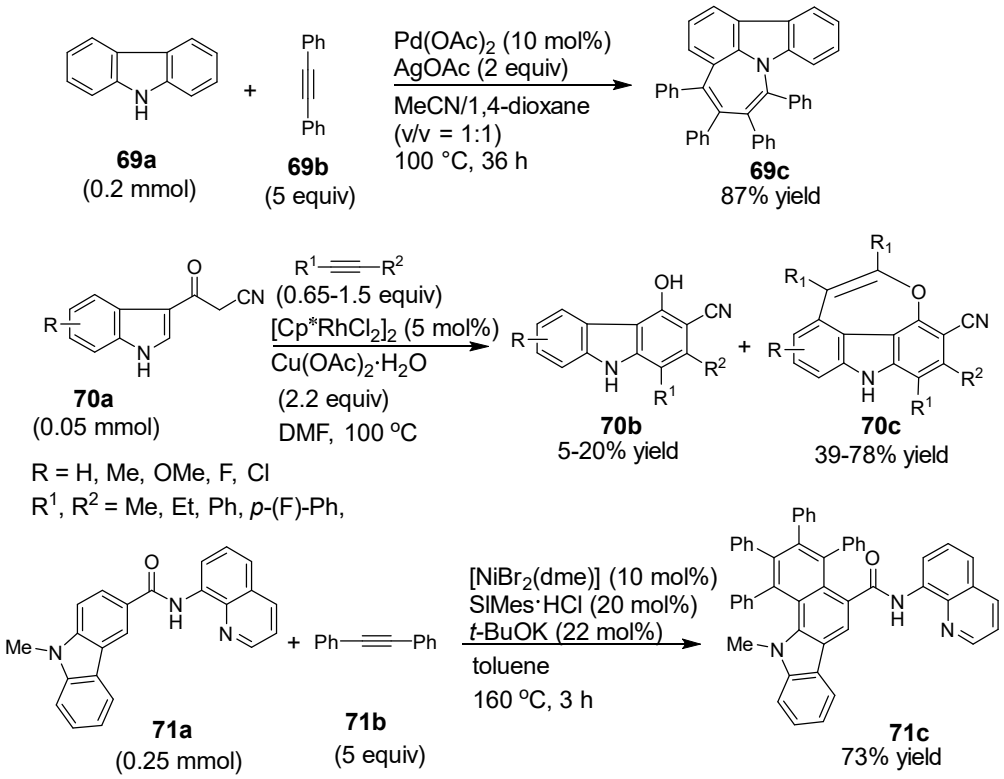
In this section, we present the recent developments pertaining to C−H functionalization reactions involving tetrahydrocarbazole scaffolds affording modified tetrahydrocarbazoles. In 2019, the Hong group revealed[65a] a few examples of Cu-catalyzed regioselective Csp^3−H azidation of tetrahydrocarbazoles.

Tetrahydrocarbazoles **72a** were treated with azidoiodinane reagent **72b** using CuBr (10 mol%) in ethyl acetate at room temperature to afford the modified tetrahydrocarbazoles **72c** (yield up to 70%) (Scheme 41).

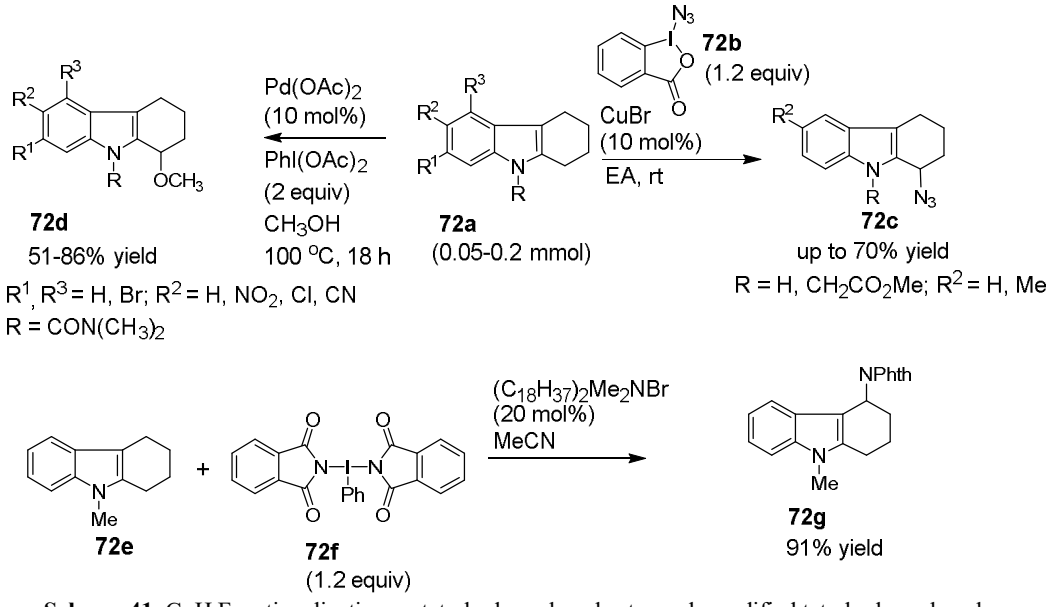


Scheme 39. Intramolecular C−H functionalization on carbazoles towards modified carbazoles.

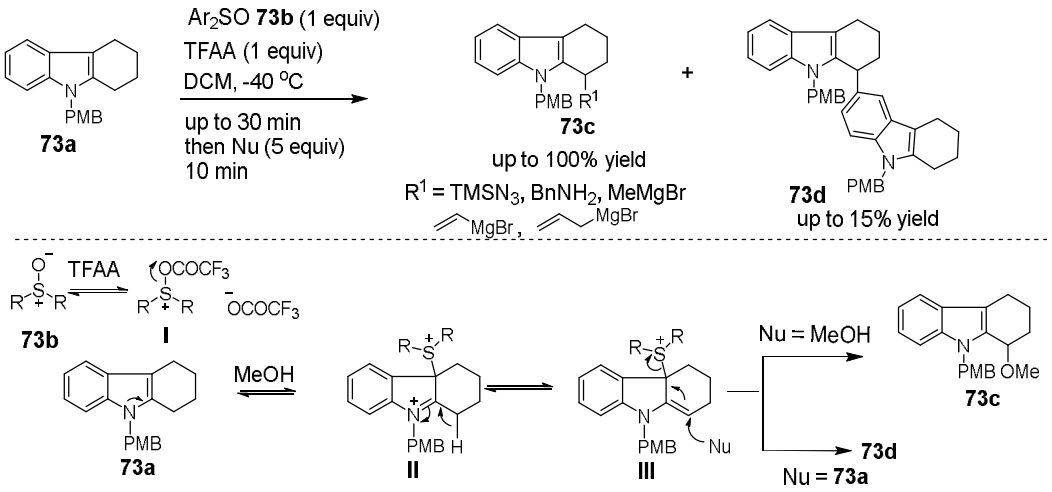
Lupton and co-workers reported[65b] the Csp^3−H oxidation of dimethyl carbamoyl tetrahydrocarbazoles **72a** using $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2 equiv) in CH_3OH to provide modified tetrahydrocarbazoles **72d** (Scheme 42). The generality of this reaction is broad with respect to tetrahydrocarbazoles; however, this reaction is not suited to alternate ring sizes and non-cyclic structures. Replacing methanol with ethanol and benzyl alcohol gave the desired ethers. Allyl alcohol gave a moderate yield due to the readily oxidized allyl functionality. Muñiz *et al.* described[65c] a C−H amination and C−N bond forming reaction of **72e** with **72f** through an electrophilic bromine redox catalysis affording the tetrahydrocarbazole motif **72g** installed with NPhth group.



Scheme 40. Annulative C−H functionalization on carbazoles towards modified carbazoles.

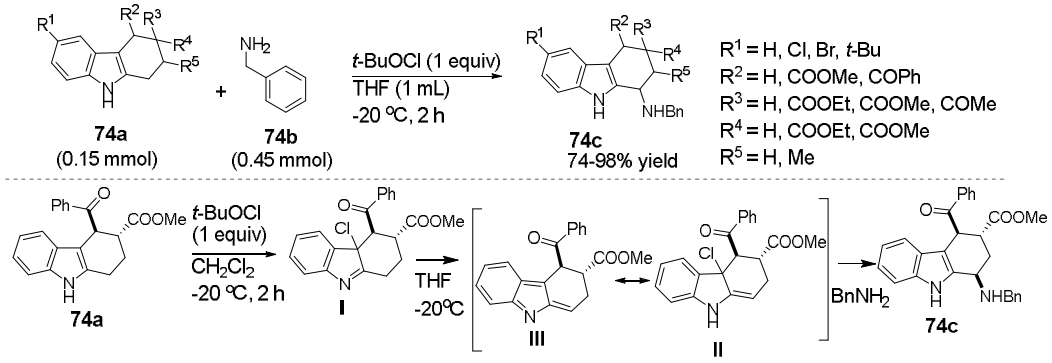


Scheme 41. C−H Functionalization on tetrahydrocarbazoles towards modified tetrahydrocarbazoles.



Scheme 42. C−H Functionalization on tetrahydrocarbazoles towards modified tetrahydrocarbazoles.

Zu and co-workers reported[67a] a mild and operationally simple method for the direct C−H functionalization at the C1 position of the tetrahydrocarbazoles using benzylamine (Scheme 43). Tetrahydrocarbazoles **74c** were synthesized using **74a** (0.15 mmol), **74b** (0.45 mmol), *t*-BuOCl (1.0 equiv), and THF (1 mL) at −20 °C for 2 h. A variety of tetrahydrocarbazoles underwent effective coupling with benzylamine. In addition to the benzyl amine, cyclic and acyclic secondary amines were used as effective coupling partners. Oxygen-based nucleophiles were also able to participate in this reaction. To probe whether the chloroindolenine **I** was the first formed intermediate leading to the desired coupling product **74c**, control experiments were carried out by the authors. The reaction between **74a** and *t*-butyl hypochlorite in dichloromethane led exclusively to the formation of chloroindolenine intermediate **I**. When the intermediate **I** was subjected to the standard reaction condition for the oxidative coupling with benzyl amine in THF, **74c** was obtained in good yield, indicating that the chloroindolenine **I** was indeed an intermediate *en route* to the product **74c**. The observed diastereoselectivity might be attributed to the axial attack of the nucleophilic reagents from the opposite side of the most hindered substituted group. Nagarajan *et al.* described[67b] a metal-free, mild oxidative cross-coupling protocol for the synthesis of 1-indolyl tetrahydrocarbazoles to afford 1-(indol-3-yl)carbazoles. *N*-Chlorosuccinimide was used as a mild oxidant for the functionalization of the 1-position of tetrahydrocarbazoles using indoles, which underwent the aromatization of which furnished 1-(indol-3-yl)carbazoles.

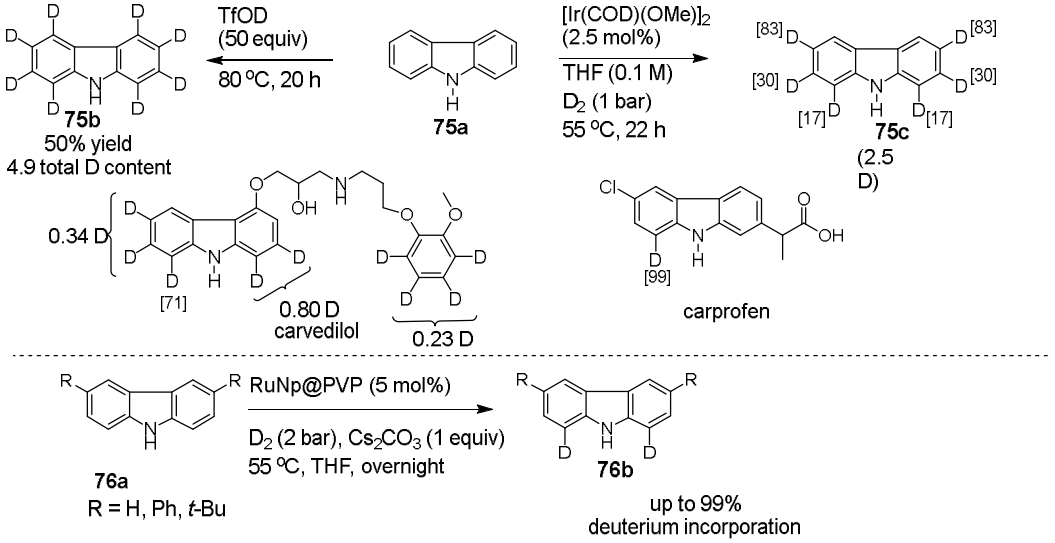


Scheme 43. C−H Functionalization on tetrahydrocarbazoles towards modified tetrahydrocarbazoles.

A naturally occurring dibromo 1-(indol-3-yl)carbazole alkaloid was also synthesized by using the oxidative cross-coupling methodology (Scheme 43).

10. C−H Deuteration in carbazole

In this section, we present the recent developments pertaining to deuteration of C−H bonds of carbazoles affording deuterated carbazoles. The Pieter group disclosed[68a] an easy and effective protocol for the incorporation of deuterium and tritium atoms on pharmaceutical related substructures including carbazoles using air-stable Ir precatalyst $[Ir(COD)\text{-}OMe]_2$. This protocol possessed a high functional group tolerance bearing compatibility with halogen (Cl, Br, F) and nitrile-containing compounds, which are usually difficult to label using HIE methods (Scheme 44). The reaction was initiated using carbazole **75a**, which was treated with precatalyst $[Ir(COD)(OMe)]_2$ (2.5 mol%) in THF (0.1 M) at 55 °C under 1 bar D_2 gas for 22 h to furnish deuterated carbazole **75c**. Two carbazole derivatives, carvedilol and carprofen, were deuterated. Thibaudeau *et al.* revealed[68b] a single example of polydeuteration on carbazole motif promoted through superacid-mediated late-stage reactions. Carbazole **75a** was reacted with TfOD (50 equiv) at 80 °C for 20 h to obtain product **75b** with high overall D incorporation (Scheme 44). The utilization of TfOD from commercial sources is a relatively expensive source of deuterium, therefore, authors attempted to prepare *in situ* TfOD by reacting an equimolar mixture of D_2O and triflic anhydride for 3 h at 80 °C. Pieters and co-workers explained[69] the deuteration of carbazole and its derivatives using hydrogen isotopic exchange assisted *via* Ru nanoparticles. Carbazole derivatives **76a** were treated with RuNp@PVP (5 mol%) catalyst, D_2 (2 bar), and Cs_2CO_3 at 55 °C in THF overnight, resulting in deuterated carbazole derivatives **76b** in excellent yields. It was suggested that deuteration with high isotopic enrichment was achieved using milder conditions, and the addition of base enhanced the chemoselectivity, efficacy of deuterium incorporation, and quantitative yields, which was confirmed through DFT studies.

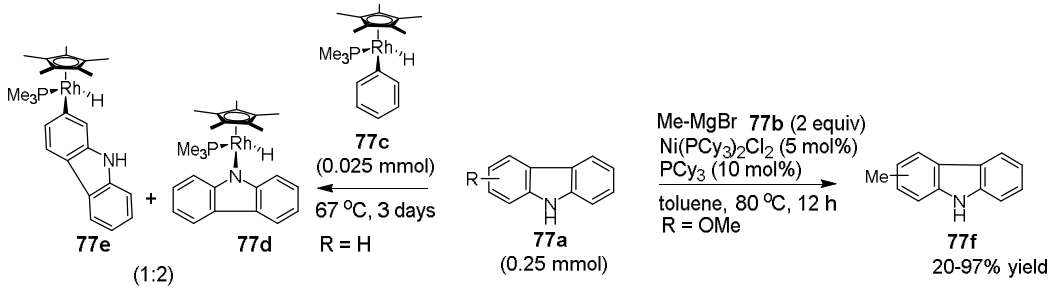


Scheme 44. C−H Deuteration of carbazoles towards deuterated carbazoles.

11. Miscellaneous reactions involving C−H functionalization of carbazoles

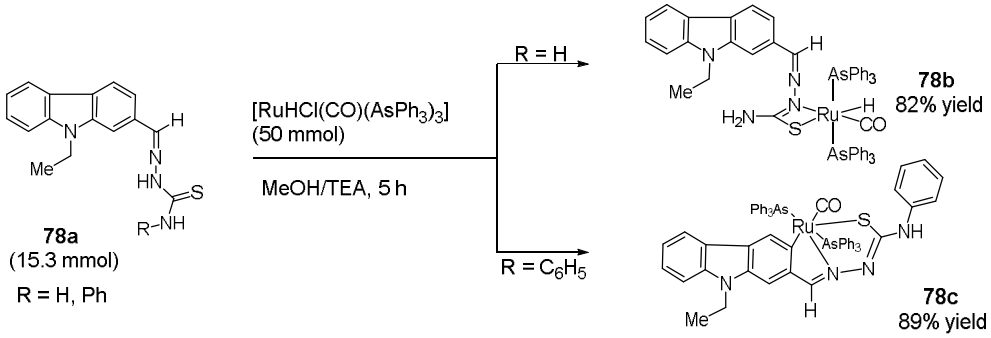
In this section, we present the recent developments pertaining to the synthesis of modified carbazoles *via* the C−H/C−O bond activation of carbazoles. Das's group developed[70] a method for C−O bond activation of methoxy-substituted carbazoles **77a** by nickel-catalyzed cross-coupling reaction between methoxy-substituted carbazoles and MeMgBr **77b**. The reaction did not work well with different metal catalysts like Pd or Co. The reaction was carried out in the presence of different ligands like dppf, XPhos, PPh_3, PCy_3, out of which PCy_3, was found to be the best ligand furnishing the product **77f** in 95% yield

(Scheme 45). The optimized protocol was extended to the total synthesis of the anti-cancer compound ellipticine. Jones's group reported[71] the thermolysis reaction of $(C_5Me_5)Rh(PMe_3)PhH$ **77c** at 67 °C with carbazole **77a** for 3 days, which yielded C−H and N−H insertion products **77e** and **77d**. Major product was assigned as $(C_5Me_5)Rh(PMe_3)$(*N*-carbazole)H **77d**, from insertion into the N-H bond of **77a** (Scheme 45).



Scheme 45. Modified carbazoles C−H or C−O activation reactions.

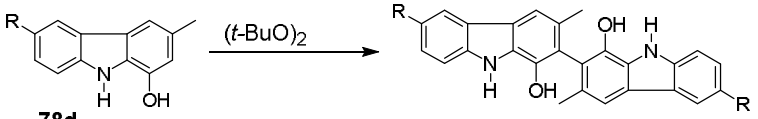
In 2016, the Ramesh group reported[72] the synthesis of two Ru complexes **78b** and **78c** starting from substituted carbazole thiosemicarbazone derivatives **78a** by treating them with an equimolar amount of $[RuH(CO)(Cl)(AsPh_3)_3]$ in refluxing methanol in the presence of a base (NEt_3). The complexes were characterized by elemental analysis, spectral techniques (FT-IR, UV-vis, NMR and ESI-MS), and X-ray crystallography. Thiosemicarbazone ligands differ in their coordination mode due to differences in the steric nature of the substituents present in the thiosemicarbazone moiety (Scheme 46).

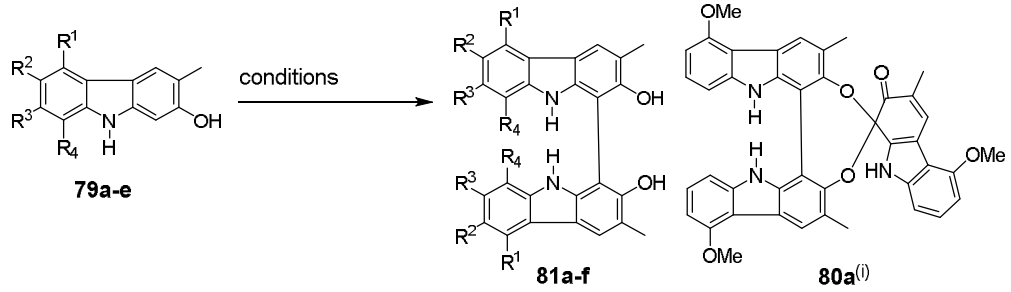


Scheme 46. Organometallic complex-based carbazoles.

There have been efforts aimed at realizing the synthesis of bis carbazoles and bis carbazole alkaloids *via* the oxidative C–C coupling of carbazoles possessing various substituents in the presence of transition metal catalysts and metal-free oxidants.[73-75] Youn *et al.* reported[74] the construction of carbazole alkaloids including dimeric *O*-demethylmurrayafoline A **78e** and bisclausenol **78f** from 1-hydroxycarbazole **78d**, which was constructed *via* Pd-catalyzed aerobic C−H amidation method (Scheme 47). Knölker *et al.* described the synthesis of 1,1'- and 2,2'-bicarbazole alkaloids by Fe(III)-catalyzed oxidative coupling of various 2- and 1-hydroxycarbazoles. Knölker *et al.* accomplished[75] the first syntheses of the bis carbazole alkaloid motifs **81a-f**, **83a,b**, **84b** (Scheme 48). Accordingly, compounds including biscarbalexines A–C **81a,b,e**, bis glybomine B **81c**, 2,2'-dihydroxy-7,7'-dimethoxy-3,3'-dimethyl-1,1'-bicarbazole **81d** were obtained from their corresponding substrates **79a-e** involving oxidative coupling. Notably, in one of the trials involving the oxidative coupling of **79a** afforded the product **81a** along with the product **80a**. Additionally, the compound **81d** was subjected to the BBr_3-mediated demethylation to afford compound **81f** (Scheme 47). Along this line, bispyrayafoline C **83a** and bisisomahanine **83b** were obtained from their corresponding substrates pyrayafoline C **82a** and pyrayafoline D **82b** *via* the oxidative coupling method

(Scheme 48). The Fe-catalyzed coupling of koenigine **84a** was also found to yield 8,8"-biskoenigine **84b**. Additionally, oxidative coupling of 1-hydroxycarbazoles was found to afford bisclausenol and this approach was used to complete the first total syntheses of bismurrayafoline B and D.[75]





79a: carbalexin A: R^1 = OMe, R^2,R^3,R^4 = H
79b: carbalexin C: R^2 = OMe, R^1,R^3,R^4 = H
79c: glybomine B: R^2 = OMe, R^1 = prenyl, R^3,R^4 = H
79d: 2-hydroxy-7-methoxy-3-methylcarbazole: R^3 = OMe, R^2,R^1,R^4 = H
79e: carbalexin B: R^4 = OMe, R^2,R^3,R^1 = H

81a: biscarbalexin A: R^1 = OMe, R^2,R^3,R^4 = H[(i)]
81b: biscarbalexin C: R^2 = OMe, R^1,R^3,R^4 = H[(ii)]
81c: bisglybomine B: R^2 = OMe, R^1 = prenyl, R^3,R^4 = H[(iii)]
81d: 2,2'-dihydroxy-7,7'-dimethoxy-3,3'-dimethyl-1,1'-bicarbazole: R^3 = OMe, R^2,R^1,R^4 = H[(iv)]
81e: biscarbalexin B: R^4 = OMe, R^2,R^3,R^1 = H[(v)]
81f (obtained from **81d**): R^3 = OH, R^2,R^1,R^4 = H[(vi)]

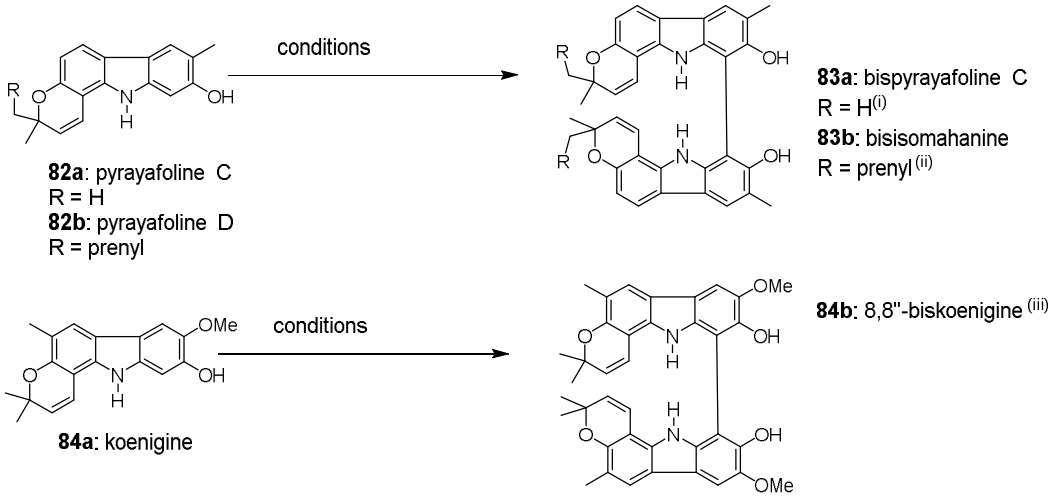
conditions:
(i): 0.1 equiv $[CuOH{\cdot}TMEDA]_2Cl_2$, CH_2Cl_2, RT, air, 45 min; 53% yield along with **80a**: 29% yield.
(ii): 3.0 mol% $F_{16}PcFe$, 10 mol% MsOH, CH_2Cl_2, RT, air, 80 min; 92% yield.
(iii): 2.0 mol% $F_{16}PcFe$, HOAc, RT, air, 10 min; 63% yield.
(iv) 3.0 mol% $F_{16}PcFe$, HOAc, RT, air, 30 min; 61% yield.
(v) 2.0 mol% $F_{16}PcFe$, HOAc, RT, air, 30 min; 54% yield.
(vi) **81d**, 4.0 equiv BBr_3, CH_2Cl_2, -78 °C, 2 h, 0 °C, 4 h, RT, 44 h; 40% yield.

Scheme 47. Construction of biscarbazoles-based alkaloids.

12. Conclusion

In summary, in this review we have delineated some of the recent developments in the area pertaining to the modification of the carbazole skeleton *via* the transition metal-catalyzed C–H activation/functionalization method. The C–H bonds present in the carbazole motif were replaced with functional groups affording functionalized carbazoles. The transition metal-catalyzed C–H activation and functionalization served as a valuable synthetic transformation for modifying the carbazole motif, which is considered as one of the privileged scaffolds in various branches of chemical science. Thus, introducing functional groups with ease in carbazole affording modified and different classes of carbazoles would strengthen the library of carbazole scaffolds. There are various reviews that describe the available classical methods including aromatic substitution reactions affording modified carbazoles. This review is focused on

revealing the developments in the area pertaining to the modification of the carbazole skeleton involving the transition metal-catalyzed C−H activation/functionalization of C−H bonds present at different positions in the carbazole skeleton affording functionalized carbazoles. Knowing carbazoles are a privileged class of nitrogen-containing heterocycles and given their importance, newer protocols including the C−H functionalization will keep emerging as a valuable tool for synthesizing functionalized carbazole derivatives.



conditions:
(i): 1.0 mol% $F_{16}PcFe$, HOAc, RT, air, 10 min; 93% yield.
(ii) 1.0 mol% $F_{16}PcFe$, HOAc, RT, air, 20 min; 93% yield.
(iii) 0.1 equiv $VO(acac)_2$, CH_2Cl_2, RT, O_2, 1.75 h; 72% yield.

Scheme 48. Construction of biscarbazoles-based alkaloids.

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References

1. Selected reviews/papers dealing with carbazoles and their applications, see: a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193-3328. b) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967-1976. c) Xubin, F.; Lei, F.; Shaohua, G. *Chin. J. Org. Chem.* **2012**, *32*, 1217-1231. d) Zhang, W.; Ready, J. M. *Nat. Prod. Rep.* **2017**, *34*, 1010-1034. e) Banerjee, A.; Kundu, S.; Bhattacharyya, A.; Sahu, S.; Maji, M. S. *Org. Chem. Front.* **2021**, *8*, 2710-2771. f) Mandal, T.; Dash, J. *Org. Biomol. Chem.* **2021**, *19*, 9797-9808. g) Aggarwal, T.; Sushmita; Verma, A. K. *Org. Biomol. Chem.* **2019**, *17*, 8330-8342. h) Obora, Y. *Tetrahedron Lett.* **2018**, *59*, 167-172. i) Graebe, C.; Glaser, C. *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 12-15. j) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099-6121.
2. Selected reviews/papers dealing with bio-active carbazoles, see: a) Głuszyńska, A. *Eur. J. Med. Chem.* **2015**, *94*, 405-426. b) Caruso, A.; Ceramella, J.; Iacopetta, D.; Saturnino, C.; Mauro, M. V.; Bruno, R.; Aquaro, S.; Sinicropi, M. S. *Molecules* **2019**, *24*, 1912. c) Issa, S.; Prandina, A.; Bedel, N.; Rongved, P.; Yous, S.; Borgne, M. L.; Bouaziz, Z. *J. Enzyme Inhib. Med. Chem.* **2019**, *34*, 1321-1346. d) Caruso, A.; Barbarossa, A.; Carocci, A.; Salzano, G.; Sinicropi, M. S.; Saturnino, C. *Appl. Sci.* **2021**, *11*, 6192-1346. e) Spandana, Z.; Sreenivasulu, R.; Rao, M. V. B. *Lett. Org. Chem.* **2019**, *16*, 662-667. f) Wang, G.; Sun, S.; Guo, H. *Eur. J. Med. Chem.* **2022**, *229*, 113999. g) Venkatesh, Y.; Rajesh, Y.; Karthik, S.; Chetan, A. C.; Mandal, M.; Jana, A.; Singh, N. D. P. *J. Org. Chem.* **2016**, *81*, 11168-11175. h) Wang, W.; Li, J.; Yao, J.; Wang, T.; Li, S.; Zheng, X.; Duan, L.; Zhang, W. *J. Antimicrob. Chemother.* **2017**, *72*, 3122-

3130. i) Ghobadian, R.; Nadri, H.; Moradi, A.; Bukhari, S. N. A.; Mahdavi, M.; Asadi, M.; Akbarzadeh, T.; Khaleghzadeh-Ahangar, H.; Sharifzadeh, M.; Amini, M. *Bioorg. Med. Chem.* **2018**, *26*, 4952-4962. j) Fang, L.; Chen, M.; Liu, Z.; Fang, X.; Gou, S.; Chen, L. *Bioorg. Med. Chem.* **2016**, *24*, 886-893. k) Thiratmatrakul, S.; Yenjai, C.; Waiwut, P.; Vajragupta, O.; Reubroycharoen, P.; Tohda, M.; Boonyarat, C. *Eur. J. Med. Chem.* **2014**, *75*, 21-30. l) Meng, F.; Liu, Y.; Yu, X.; Lin, W. *New J. Chem.* **2016**, *40*, 7399-7406. m) Sadeghian, B.; Sakhteman, A.; Faghih, Z.; Nadri, H.; Edraki, N.; Iraji, A.; Sadeghian, I.; Rezaei, Z. *J. Mol. Struc.* **2020**, *1221*, 128793. n) You, X.; Zhu, D.; Lu, W.; Sun, Y.; Qiao, S.; Luo, B.; Du, Y.; Pi, R.; Hu, Y.; Huang, P.; Wen, S. *RSC Adv.* **2018**, *8*, 17183-17190. o) Diaz, P.; Horne, E.; Xu, C.; Hamel, E.; Wagenbach, M.; Petrov, R. R.; Uhlenbruck, B.; Haas, B.; Hothi, P.; Wordeman, L.; Gussio, R.; Stella, N. *Eur. J. Med. Chem.* **2018**, *159*, 74-89.

3. a) Qiu, Z.; Nakamura, S.; Fujimoto, K. *Org. Biomol. Chem.* **2019**, *17*, 6277-6283. b) Yang, Z.; Zhao, N.; Sun, Y.; Miao, F.; Liu, Y.; Liu, X.; Zhang, Y.; Ai, W.; Song, G.; Shen, X.; Yu, X.; Sun, J.; Wong, W.-Y. *Chem. Commun.* **2012**, *48*, 3442-3444. c) Martin, A. D.; Robinson, A. B.; Thordarson, P. *J. Mater. Chem. B*, **2015**, *3*, 2277-2280. d) Ren, Y.; Zhao, J.; Shi, Y.; Chen, C.; Chen, X.; Lv, C. *J. Pharm. Biomed. Anal.* **2017**, *142*, 1-6. e) Marcher, B.; Chapoy, L. L.; Christensen, D. H. *Macromolecules* **1988**, *21*, 677-686. f) Zhao, H.; Sanda, F.; Masuda, T. *J. Polym. Sci. A Polym. Chem.* **2007**, *45*, 253-261.
4. Selected reviews dealing with applications of carbazoles in materials chemistry, see: a) Jiang, H. *Asian J. Org. Chem.* **2014**, *3*, 102-112. b) Yin, J.; Ma, Y.; Li, G.; Peng, M.; Lin, W. *Coord. Chem. Rev.* **2020**, *412*, 213257. c) Dumur, F. *Eur. Polym. J.* **2020**, *125*, 109503. d) Wex, B.; Kaafarani, B. R. *J. Mater. Chem.* **2017**, *5*, 8622-8653. e) Ledwon, P. *Org. Electron.* **2019**, *75*, 105422. f) Manickam, M.; Iqbal, P.; Belloni, M.; Kumar, S.; Preece, J. A. *Isr. J. Chem.* **2012**, *52*, 917-934. g) Adhikari, R. M.; Neckers, D. C.; Shah, B. K. *J. Org. Chem.* **2009**, *74*, 3341-3349.
5. a) Graebe, C.; Ullmann, F. *Justus Liebigs Ann. Chem.* **1896**, *291*, 16-17. b) Bremer, O. *Justus Liebigs Ann. Chem.* **1934**, *514*, 279-291. c) Borsche, W. *Justus Liebigs Ann. Chem.* **1908**, *359*, 49-80. d) Drechsel, E. *J. Prakt. Chem.* **1888**, *38*, 65-74. e) Wang, Z., *Comprehensive Organic Name Reactions and Reagents*. **2010**, DOI:10.1002/9780470638859.conrr120.
6. Selected papers on carbazoles *via* C-H amination; a) Nack, W. A.; Chen, G. *Synlett* **2015**, *26*, 2505-2511. b) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 1597-1600. c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.: Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184-16186. d) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560-14561. e) Monguchi, Y.; Okami, H.; Ichikawa, T.; Nozaki, K.; Maejima, T.; Oumi, Y.; Sawama, Y.; Sajiki, H. *Adv. Synth. Catal.* **2016**, *358*, 3145-3151. f) Bal, A.; Maiti, S.; Mal, P. *J. Org. Chem.* **2018**, *83*, 11278-11287. g) Polley, A.; Varalaxmi, K.; Jana, R. *ACS Omega* **2018**, *3*, 14503-14516. h) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 8605-8608. i) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996-6005. j) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738-3741.
7. For selected reviews on C-H functionalization, see: a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826-834. b) Hirano, K.; Miura, M. *Chem. Lett.* **2015**, *44*, 868-873. c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147-1169. d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624-655. e) Wang, W.; Lorion, M. M.; Shah, J.; Kapdi, A. R.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 14700-14717. f) Rej, S.; Das, A.; Chatani, N. *Coord. Chem. Rev.* **2021**, *431*, 213683. g) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578-10599. h) Yoshino, T.; Matsunaga, S. *Adv. Synth. Catal.* **2017**, *359,* 1245-1262. i) Higham J. I.; Bull, J. A. *Org. Biomol. Chem.* **2020**, *18*, 7291-7315. j) Banerjee, A.; Sarkar, S.; Patel, B. K. *Org. Biomol. Chem.* **2017**, *15*, 505-530. k) Bag, S.; Maiti, D. *Synthesis* **2016**, *48*, 804-815. l) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009. m) Uttry, A.; van Gemmeren, M. *Synthesis* **2020**, *52*, 479-488. n) Arockiam, P. B.; Bruneau C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879-5918. o) Besset, T.; Poisson T.; Pannecoucke, X. *Chem. Eur. J.* **2014**, *20*, 16830-16845. p) Sinha, S. K.; Guin, S.; Maiti, S.; Biswas, J. P.; Porey S.; Maiti, D. *Chem. Rev.* **2022**, *122*, 5682-5841. For themed issues on C-H activation, see: q) Crabtree, R. H.; Lei, A. *Chem. Rev.* **2017**, *117*, 8481-8482. r) C–H

Functionalization in organic synthesis; Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855-1856.

8. a) Zu, B.; Guo, Y.; Ke, J.; He, C. *Synthesis* **2021**, *53*, 2029-2042. b) Talukdar, K.; Shah, T. A.; Sarkar, T.; Roy, S.; Maharana, P. K.; Punniyamurthy, T. *Chem. Commun.* **2021**, *57*, 13221-13233. c) Babu, S. A.; Padmavathi, R.; Suwasia, S.; Dalal, A.; Bhattacharya, D.; Singh, P.; Tomar, R. *Stud. Nat. Prod. Chem.* **2021**, *71*, 311-399. d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936. e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654-2672. f) Yang, K.; Song, M.; Liu, H.; Ge, H. *Chem. Sci.* **2020**, *11*, 12616-12632. g) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. Asian J.* **2016**, *11*, 168-192. h) Yorimitsu, H.; Yoshimura, A.; Misaki, Y. *Synthesis* **2020**, *52*, 3326-3336. i) Manikandan, R.; Jeganmohan, M. *Chem. Commun.* **2017**, *53*, 8931-8947. j) Saito, H.; Yamamoto, K.; Sumiya, Y.; Liu, L.-J.; Nogi, K.; Maeda, S.; Yorimitsu, H. *Chem. Asian J.* **2020**, *15*, 2442-2446. k) Manoharan, R.; Jeganmohan, M. *Asian J. Org. Chem.* **2019**, *8*, 1949-1969. l) Das, R.; Kumar, G. S.; Kapur, M. *Eur. J. Org. Chem.* **2017**, 5439-5459. m) Babu, S. A.; Aggarwal, Y.; Patel, P.; Tomar, R. *Chem. Commun.* **2022**, *58*, 2612-2633. n) Maraswami M.; Loh, T.-P. *Synthesis* **2019**, *51*, 1049-1062. o) Patel, O. P. S.; Nandwana, N. K.; Legoabe, L. J.; Das, B. C.; Kumar, A. *Adv. Synth. Catal.* **2020**, *362*, 4226-4255. p) Babu, S. A.; Padmavathi, R.; Aggarwal, Y.; Kaur, R. and Suwasia, S. (2022). Pd-Catalyzed Csp^3–H Activation by Native Directing Groups. *In Handbook of CH-Functionalization*, D. Maiti, Ed., **2022**, https://doi.org/10.1002/9783527834242.chf0006. q) Dutta, S.; Bhattacharya, T.; Geffers, F. J.; Bürger, M.; Maiti, D.; Werz, D. B. *Chem. Sci.* **2022**, *13*, 2551-2573.
9. For selected reviews on the bidentate directing group (DG)-aided C-H functionalization, see: a) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788-1887. b) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743. c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053-1064. d) Liu, B.; Romine, A. M.; Rubel, C. Z.; Engle, K. M.; Shi, B.-F. *Chem. Rev.* **2021**, *121*, 14957-15074. e) Yadav, M. R.; Rit, R. K.; Majji, S.; Sahoo, A. K. *Asian. J. Org. Chem.* **2015**, *4*, 846-864. f) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, 47, 6603-6743. g) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635-645. h) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775-8806. i) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett*. **2016**, *57*, 819-836. j) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450-4459. k) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191-206.
10. a) Negishi, E.-I. *Angew. Chem. Int. Ed.* **2011**, *50*, 6738-6764. b) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722-6737. c) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146-151. d) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085. e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489. f) Sestelo, J. P.; Sarandeses, L. A. 2020 25, 4500. g) de Meijere, A.; Bräse, S.; Oestreich, M. *Metal-catalyzed cross-coupling reactions and more*; 1st ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2014. h) Molnár, A. *Palladium-catalyzed coupling reactions*; 1st ed.; Wiley-VCH: Weinheim, Germany, 2013.
11. For selected papers on directing group (DG)-aided C-H functionalization, see: a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972. b) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192-5196. c) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387-3390. d) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790-4793. e) Hoshiya, N.; Kondo, M.; Fukuda, H.; Arisawa, M.; Uenishi, J.; Shuto, S. *J. Org. Chem.* **2017**, *82*, 2535-2544. f) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc*. **2016**, *138*, 10750-10753. g) Zeng, W.; Nukeyeva, M.; Wang, Q.; Jiang, C. *Org. Biomol. Chem.* **2018**, *16*, 598-608. h) Song, J.; Chen, W.; Zhao, Y.; Li, C.; Liang, G.; Huang, L. *RSC Adv.* **2016**, *6*, 54984-54992. i) Seki, A.; Takahashi, Y. *Tetrahedron Lett.* **2021**, *74*, 153130. j) Zhang, S.-K.; Yang, X.-Y.; Zhao, X.-M.; Li, P.-X.; Niu, J.-L.; Song, M.-P. *Organometallics* **2015**, *34*, 4331-4339. k) Ghouilem, J.; Tran, C.; Grimblat, N.; Retailleau, P.; Alami, M.; Gandon, V.; Messaoudi, S. *ACS Catal.* **2021**, *11*, 1818-1826. l) Aihara, Y.; Chatani, N. *ACS Catal.* **2016**, *6*, 4323-4329. m) Xiong, H.-Y.; Cahard, D.; Pannecoucke, X.; Besset, T. *Eur. J. Org. Chem.* **2016**, 3625-3630. n) Gou, Q.; Zhang, Z.-F.; Liu, Z.-C.; Qin, J. *J. Org. Chem.* **2015**, *80*, 3176-3186. o) Pradhan, S.; De, P. B.; Punniyamurthy, T. *J. Org. Chem.* **2017**, *82*, 4883-4890. p) Song, H.; Li,

Y.; Yao, Q.-J.; Shi, B.-F. *Org. Chem. Front.* **2022**, *9*, 4823-4828. q) Milbauer, M. W.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2022**, *144*, 21030-21034. r) Bay, K. L.; Yang, Y.-F.; Houk, K. N. *J. Organomet. Chem.* **2018**, *864*, 19-25. s) Hu, Y.; Wang, M.; Li, P.; Li, H.; Wang, L. *Asian J. Org. Chem.* **2019**, *8*, 171-178.

12. For selected papers of our lab on bidentate DG-aided C-H functionalization, see: a) Reddy, C.; Bisht, N.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81,* 12143-12168. b) Padmavathi, R.; Sankar, R.; Gopalakrishnan, B.; Parella, R.; Babu, S. A. *Eur. J. Org. Chem.* **2015**, 3727-3742. c) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82,* 7123-7150. d) Bisht, N.; Babu, S. A.; Tomar, R. *Asian J. Org. Chem.* **2020**, *9*, 1225-1233. e) Naveen; Rajkumar, V.; Babu, S. A.; Gopalakrishnan, B. *J. Org. Chem.* **2016**, *81*, 12197-12211. f) Banga, S.; Kaur, R.; Babu, S. A. *Eur. J. Org. Chem.* **2021**, 3641-3656. g) Padmavathi, R.; Babu, S. A. *Asian J. Org. Chem.* **2019**, *8*, 899-908. h) Dalal, A.; Babu, S. A. *Synthesis* **2021**, *53*, 3307-3324. i) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82,* 6550-6567. j) Gopalakrishnan, B.; Mohan, S.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81,* 8988-9005. k) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80,* 12379-12396. l) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80,* 2339-2355. m) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15,* 3238-3241. n) Singh, P.; Dalal, A.; Babu, S. A. *Asian J. Org. Chem.* **2019**, *8*, 877-886. o) Tomar, R.; Kumar, A.; Dalal, A.; Bhattacharya, D.; Singh, P. Babu, S. A. *Asian J. Org. Chem.* **2022**, *11*, e202200311. p) Bisht, N.; Singh, P.; Babu, S. A. *Synthesis* **2022**, *54*, 4059-4094. q) Bisht, N.; Babu, S. A.; Tomar, R. *Asian J. Org. Chem.* **2022**, *11*, e202200589.
13. For reviews see: a) Yang, J. *Org. Biomol. Chem.* **2015**, *13*, 1930-1941. b) Dey, A.; Agasti, S.; Maiti, D. *Org. Biomol. Chem.* **2016**, *14*, 5440-5453. For seminal publications see: c) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593-1597. d) Leow, D.; Li, G.; Mei, T.-S.; Yu, J. -Q. *Nature* **2012,** *486*, 518-522. e) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334-338. f) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712-717. g) Cho, J. -Y.; Tse, M. K.; Holmes, D.; Maleczka Jr, R. E.; Smith, M. R. *Science* **2002**, *295*, 305-308. h) Dey, A.; Maity, S.; Maiti, D. *Chem. Commun*. **2016**, *52*, 12398-12414.
14. a) Wu, X.-T.; Xiao, E.-K.; Ma, F.; Yin, J.; Wang, J.; Chen, P.; Jiang, Y.-J. *J. Org. Chem*. **2021**, *86*, 6734-6743. b) Hallberg, A.; Martin, A. R. *J. Heterocycl. Chem.* **1984**, *21*, 837-840. c) Katritzky, A. R.; Rewcastle, G. W.; Vazquez de Miguel, L. M. *J. Org. Chem.* **1988**, *53*, 794-799.
15. a) Qi, Z.-C.; Lou, Q.-X.; Niu, Y.; Yang, S.-D. *Chem. Commun.* **2021**, *57*, 2021-2024. b) For direct 1,2-substitution see: Wang, D.; Li, M.; Chen, X.; Wang, M.; Liang, Y.; Zhao, Y.; Houk, K. N.; Shi, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 7066-7071. c) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*, 10807-10813.
16. Feng, Y.; Holte, D.; Zoller, J.; Umemiya, S.; Simke, L. R.; Baran, P. S. *J. Am. Chem. Soc.* **2015,** *137*, 10160-10163.
17. a) Leitch, J. A.; Heron, C. J.; McKnight, J.; Kociok-Köhn, G.; Bhonoah, Y.; Frost, C. G. *Chem. Commun.* **2017**, *53,* 13039-13042. b) Pocock, I. A.; Alotaibi, A. M.; Jagdev, K.; Prior, C.; Burgess, G. R.; Male, L.; Grainger, R. S. *Chem. Commun.* **2021**, *57*, 7252-7255.
18. a) Rzayev, J.; Zhang, Z.; Durand, N.; Soulé, J.-F. *Org. Lett.* **2022**, *24*, 6755-6760. b) Jo, H.; Park, J.; Choi, M.; Sharma, S.; Jeon, M.; Mishra, N. K.; Jeong, T.; Han, S.; Kim, I. S. *Adv. Synth. Catal.* **2016**, *358*, 2714-2720. c) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem. Eur. J.* **2014**, *20*, 17653-17657.
19. a) Verma, S. K.; Punji, B. *Chem. Asian. J.* **2022**, *17*, e202200103. b) Cho, E. H.; Akhtar, M. S.; Aslam, M.; Thombal, R. S.; Li, X.; Shim, J.-J.; Lee, Y. R. *Org. Biomol. Chem.* **2022**, *20*, 6776-6783. c) Han, S. H.; Choi, M.; Jeong, T.; Sharma, S.; Mishra, N. K.; Park, J.; Oh, J. S.; Kim, W. J.; Lee, J. S.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 11092-11099. d) Zhou, X.; Yu, S.; Qi, Z.; Kong, L.; Li, X. *J. Org. Chem.* **2016**, *81*, 4869-4875.
20. a) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 438-446. b) Uemura, T.; Yamaguchi, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 3162-3165. c) Kaur, R.; Singh, H.; Babu, S. A. *Synthesis* **2023**, *55*, 3535-3567.
21. a) Jana, S.; Empel, C.; Pei, C.; Aseeva, P.; Nguyen, T. V.; Koenigs, R. M. *ACS Catal.* **2020**, *10,* 9925-9931. b) Jana, S.; Empel, C.; Nguyen, T. V.; Koenigs, R. M. *Chem. Eur. J.* **2021**, *27*, 2628-2632.

22. a) Karmakar, U.; Hwang, H. S.; Lee, Y.; Cho, E. J. *Org. Lett.* **2022**, *24*, 6137-6141. b) Arredondo, V.; Hiew, S. C.; Gutman, E. S.; Premachandra, I. D. U. A.; Van Vranken, D. L. *Angew. Chem. Int. Ed*. **2017**, *56*, 4156-4159.
23. He, F.; Koenigs, R. M. *Org. Lett.* **2021**, *23*, 5831-5835.
24. Zhao, H.; Shen, P.; Sun, D.; Zhai, H.; Zhao, Y. *J. Org. Chem.* **2021**, *86*, 9189-9199.
25. Chu, J.-H.; Wu, C.-C.; Chang, D.-H.; Lee, Y.-M.; Wu, M.-J. *Organometallics* **2013**, *32*, 272-282.
26. a) Reddy, K. H. V.; Kumar, R. U.; Reddy, V. P.; Satish, G.; Nanubolu, J. B.; Nageswar, Y. V. D. *RSC Adv.* **2016**, *6*, 54431-54434. b) Reddy, G. M.; Rao, N. S. S.; Satyanarayana, P.; Maheswaran, H. *RSC Adv.* **2015**, *5*, 105347-105352.
27. Qi, Z.-C.; Lou, Q.-X.; Niu, Y.; Yang, S.-D. *Chem. Commun.* **2021**, *57*, 2021-2024.
28. Maeda, B.; Mori, G.; Sakakibara, Y.; Yagi, A.; Murakami, K.; Itami, K. *Asian J. Org. Chem.* **2021**, *10*, 1428-1431.
29. a) Urones, B.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 1120-1123. b) Guo, D.; Li, B.; Gao, W.; Zhang, W., Wang, Y.; Zhao, J. *Synlett* **2021**, *32*, 800-804.
30. Jia, J.; Shi, J.; Zhou, J.; Liu, X.; Song, Y.; Xu, H. E.; Yi, W. *Chem. Commun.*, **2015**, *51*, 2925-2928.
31. Tanaka, R.; Ochiai, S.; Sakai, A.; Usuki, Y.; Kang, B.; Shinada, T.; Satoh, T. *Chem. Asian J.* **2023**, *18*, e202201210.
32. a) Xu, L.; Zhang, C.; He, Y.; Tan, L.; Ma, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 321-325. b) Zhang, L.-Q.; Yang, S.; Huang, X.; You, J.; Song, F. *Chem. Commun*. **2013**, *49*, 8830-8832.
33. a) Morita, T.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 4384-4387. b) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, *551*, 489-493. c) Samala, S.; Shin, J.; Shim, J. Y.; Yoo, E. J. *Asian J. Org. Chem*. **2017**, *6*, 998-1002.
34. a) Li, T.; Wang, Z.; Qin, W.-B.; Wen, T.-B. *ChemCatChem.* **2016**, *8*, 2146-2154. b) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. *J. Org. Chem*. **2015**, *80*, 1946-1951.
35. Fang, S.; Jiang, G.; Li, M.; Liu, Z.; Jiang, H.; Wu, W. *Chem. Commun.* **2019**, *55,* 13769-13772.
36. Sharma, S.; Shin, Y.; Mishra, N. K.; Park, J.; Han, S.; Jeong, T.; Oh, Y.; Lee, Y.; Choi, M.; Kim, I. S. *Tetrahedron* **2015**, *71*, 2435-2441.
37. a) Kim, M.; Mishra, N. K.; Park, J.; Han, S.; Shin, Y.; Sharma, S.; Lee, Y.; Lee, E.-K.; Kwak, J. H.; Kim, I. S. *Chem. Commun.* **2014**, *50*, 14249-14252. b) Maiti, S.; Mandal, T.; Dash, B. P.; Dash, J. *J. Org. Chem.* **2021**, *86*, 1396-1407 6. c) Maiti, S.; Burgula, L.; Chakraborti, G.; Dash, J. *Eur. J. Org. Chem.* **2017**, 332-340.
38. a) Okada, T.; Nobushige, K.; Satoh T.; Miura, M. *Org. Lett.* **2016**, *18*, 1150-1153. b) De, P. B.; Banerjee, S.; Pradhan, S.; Punniyamurthy, T. *Org. Biomol. Chem.* **2018**, *16*, 5889-5898.
39. a) Hong, X.; Wang, H.; Qian, G.; Tan, Q.; Xu, B. *J. Org. Chem.* **2014**, *79*, 3228-3237. b) Xu, S.; Teng, J.; Yu, J.-T.; Sun, S.; Cheng, J. *Org. Lett.* **2019**, *21*, 9919-9923.
40. a) Banerjee, S.; De, P. B.; Pradhan, S.; Shah, T. A.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2019**, *7*, 1677-1684. b) Reddy, G. M.; Rao, N. S.; Hariharasarma, M. *Asian J. Org. Chem.* **2017***, 6*, 59-62.
41. a) Jin, W.; Zheng, P.; Wong, W.-T.; Law, G.-L. *Asian J. Org. Chem.* **2015**, *4*, 875-878. b) Qiu, R.; Reddy, V. P.; Iwasaki, T.; Kambe, N. *J. Org. Chem.* **2015**, *80*, 367-374. c) Zhu, L.; Cao, X.; Qiu, R.; Iwasaki, T.; Reddy, V. P.; Xu, X.; Yin, S.-F.; Kambe, N. *RSC Adv.* **2015**, *5*, 39358-39365.
42. a) Jouvin, K.; Matheis, C.; Goossen, L. J. *Chem. Eur. J.* **2015**, *21*, 14324-14327. b) Hong, X.; Tan, Q.; Liu, B.; Xu, B. *Angew. Chem. Int. Ed.* **2017***, 56*, 3961-3965.
43. a) Liyu, J.; Sperry, J. *Tetrahedron Lett.* **2017**, *58*, 1699-1701. b) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068-4069. c) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem*. **2010**, *75*, 3855-3858. d) Iqbal, S. A.; Cid, J.; Procter, R. J.; Uzelac, M.; Yuan, K.; Ingelson, M. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 15381-15385. e) Kabuki, A.; Yamaguchi, J. *Synthesis* **2022**, *54*, 4963-4970.
44. a) Wang, D.; Li, M.; Chen, X.; Wang, M.; Liang, Y.; Zhao, Y.; Houk, K. N.; Shi, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 7066-7071. b) Lantaño, B.; Barata-Vallejo, S.; Torviso, M. R.; Bonesi, S. M.; Argüello, J. E.; Postigo, A. *J. Fluor. Chem.* **2014**, *161*, 149-155.
45. Gupta, S. S.; Manisha; Kumar, R.; Dhiman, A. K.; Sharma, U. *Org. Biomol.Chem.* **2021**, *19*, 9675-9687.

46. a) Rank, C. K.; Wall, T.; Dietrich, F.; Vidovic, M.; Klein, M. P.; Sun, Y.; Niedner-Schatteburg, G.; Gerhards, M.; Patureau, F. W. *Eur. J. Inorg. Chem.* **2018**, 1394-1398. b) Biafora, A.; Patureau, F.W. *Synlett* **2014**, *25*, 2525-2530. c) Louillat, M.-L.; Patureau, F. W. *Org. Lett.* **2013**, *15*, 164-167.
47. Jones, A. W.; Rank, C. K.; Becker, Y.; Malchau, C.; Funes-Ardoiz, I. Maseras, F.; Patureau, F. W. *Chem. Eur. J.* **2018**, *24*, 15178-15184.
48. Kumar, M.; Sharma, R.; Raziullah; Khan, A. A.; Ahmad, A.; Dutta, H. S.; Koley, D. *Org. Lett.* **2020**, *22*, 2152-2156.
49. Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. *Org. Lett.* **2013**, *15*, 1290-1293.
50. Tang, Z.; Liu, Z.; Tong, Z.; Xu, Z.; Au, C.-T.; Qiu, R.; Kambe, N. *Org. Lett.* **2019**, *21*, 5152-5156.
51. Ranjani, G.; Nagarajan, R. *Org. Lett.* **2019**, *21*, 675-678.
52. Rank, C. K.; Jones, A. W.; Wall, T.; Di Martino-Fumo, P.; Schröck, S.; Gerhards, M.; Patureau, F. W. *Chem. Commun.* **2019**, *55*, 13749-13752.
53. a) Fox, J. C.; Gilligan, R. E.; Pitts, A. K; Bennett, H. R.; Gaunt, M. J. *Chem. Sci.* **2016**, *7*, 2706-2710. b) Xie, S.; Proietti, G.; Ramström, O.; Yan, M. *J. Org. Chem*. **2019**, *84*, 14520-14528.
54. a) Vadola, P. A.; Sames, D. *J. Org. Chem*. **2012**, *77*, 7804-7814. b) Sreenivas, D. K.; Nagarajan, R. *Tetrahedron* **2010**, *66*, 9650-9654.
55. a) Kader, T.; Stöger, B.; Fröhlich, J.; Kautny, P. *Chem. Eur. J.* **2019**, *25*, 4412-4425. b) Ramkumar, N.; Nagarajan, R. *J. Org. Chem.* **2013**, *78*, 2802-2807. c) Kaliyaperumal, S. A.; Banerjee, S.; U K, S. K. *Org. Biomol. Chem.* **2014**, *12*, 6105-6113. d) Padmaja, P.; Koteswara Rao, G.; Indrasena, A.; Subba Reddy, B. V.; Patel, N.; Shaik, A. B.; Reddy, N.; Dubey, P. K.; Bhadra, M. P. *Org. Biomol. Chem.* **2015**, *13*, 1404-1414.
56. Irgashev, R. A.; Kazin, N. A.; Kim, G. A.; Rusinov, G. L.; Charushin, V. N. *RSC Adv.* **2016**, *6*, 70106-70116.
57. Yamuna, E.; Zeller, M.; Rajendra Prasad, K. J. *Tetrahedron Lett.* **2011**, *52*, 6030-6033.
58. Lv, J.; Liu, Q.; Tang, J.; Perdih, F.; Kranjc, K. *Tetrahedron Lett.* **2012**, *53*, 5248-5252.
59. Jones, A.W.; Louillat-Habermeyer, M.-L.; Patureau, F.W. *Adv. Synth. Catal.* **2015**, *357*, 945-949.
60. Taniguchi, T.; Itai, Y.; Nishii, Y.; Tohnai, N.; Miura, M. *Chem. Lett.* **2019**, *48*, 1160-1163.
61. Bader, D.; Fröhlich, J.; Kautny, P. *J. Org. Chem.* **2020**, *85*, 3865-3871.
62. Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem. Int. Ed*. **2013**, *52*, 1768-1772.
63. Zhou, T.; Li, B.; Wang, B. *Chem. Commun.* **2017**, *53*, 6343-6346.
64. Castro, L. C. M.; Obata, A.; Aihara, Y.; Chatani, N. *Chem. Eur. J.* **2016**, *22*, 1362-1367.
65. a) Huang, L.; Xun, X.; Zhao, M.; Xue, J.; Li, G.; Hong, L. *J. Org. Chem*. **2019**, *84*, 11885-11890. b) Nakano, Y.; Lupton, D.W. *Chem. Commun.* **2014**, *50*, 1757-1760. c) Bergès, J.; García, B.; Muñiz, K. *Angew. Chem. Int. Ed.* **2018**, *5579*, 15891-15895.
66. Tayu, M.; Higuchi, K.; Inaba, M.; Kawasaki, T. *Org. Biomol. Chem.* **2013**, *11*, 496-502.
67. a) Jiang, L.; Xie, X.; Zu, L. *RSC Adv.* **2015**, *5*, 9204-9207. b) Ranjani, G.; Nagarajan, R. *Org. Lett.* **2019**, *21*, 675-678.
68. a) Daniel-Bertrand, M.; Garcia-Argote, S.; Palazzolo, A.; Marin, I. M.; Fazzini, P.-F.; Tricard, S.; Chaudret, B.; Derdau, V.; Feuillastre, S.; Pieters, G. *Angew. Chem. Int. Ed.* **2020**, *59*, 21114-21120. b) Appert, E.; Martin-Mingot, A.; Karam, O.; Zunino, F.; Michelet, B.; Bouazza, F.; Thibaudeau, S. *Chem. Eur. J.* **2022**, *28*, e202201583.
69. Pfeifer, V.; Certiat, M.; Bouzouita, D.; Palazzolo, A.; Garcia-Argote, S.; Macron, E.; Buisson, D.-A.; Lesot, P.; Maron, L.; Chaudret, B.; Tricard, S.; del Rosal, I.; Poteau, R.; Feuillastre, S.; Pieters, G. *Chem. Eur. J.* **2020**, *26*, 4988-4996.
70. Rasheed, Sk.; Rao, D. N.; Das, P. *Asian J. Org. Chem.* **2016**, *5,* 1499-1507.
71. Jones, W. D.; Dong, L.; Myers, A. W. *Organometallics* **1995**, *14*, 855-861.
72. Kumar, R. R.; Ramesh, R.; Małecki, J. G. *New J. Chem.* **2016**, *40*, 10084-10093.
73. Mallick, S.; Maddala, S.; Kollimalayan, K.; Venkatakrishnan, P. *J. Org. Chem.* **2019**, *84,* 73-93.
74. Youn, S. W.; Kim, Y. H.; Jo, Y. H. *Adv. Synth. Catal.* **2019**, *361*, 462-468.
75. Brütting, C.; Fritsche, R. F.; Kutz, S. K.; Börger, C.; Schmidt, A. W.; Kataeva, O.; Knölker, H.-J. *Chem. Eur. J.* **2018**, *24*, 458-470.