Construction of the indole nucleus through C-H functionalization reactions

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Abstract

This review article summarizes C-H functionalization-based synthesis of indoles and related structures (e.g. carbazoles and indolines) with an emphasis on literature after 2000. The discussion is organized into four broadly defined sections: a) *via* nitrene or carbene insertion into a C-H bond; b) *via* direct coupling of two sp^2 carbon centers; c) *via* transition-metal catalyzed C-H amination and d) other strategies.

Keywords: C-H functionalization, indole, carbazole, indoline

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1. Introduction

The indole subunit is ubiquitous in naturally occurring compounds as well as designer therapeutic agents. Numerous methods have been developed for its synthesis.[1] Notably, in the past two decades, contemporary transition metal catalyzed cross-coupling reactions have enabled

some very powerful strategies for the construction of indole and related ring systems. For example, a wide range of indoles can be efficiently assembled from *ortho*-haloanilines and alkynes through a Pd-catalyzed Sonogashira coupling followed by a base-mediated cyclization.[2]

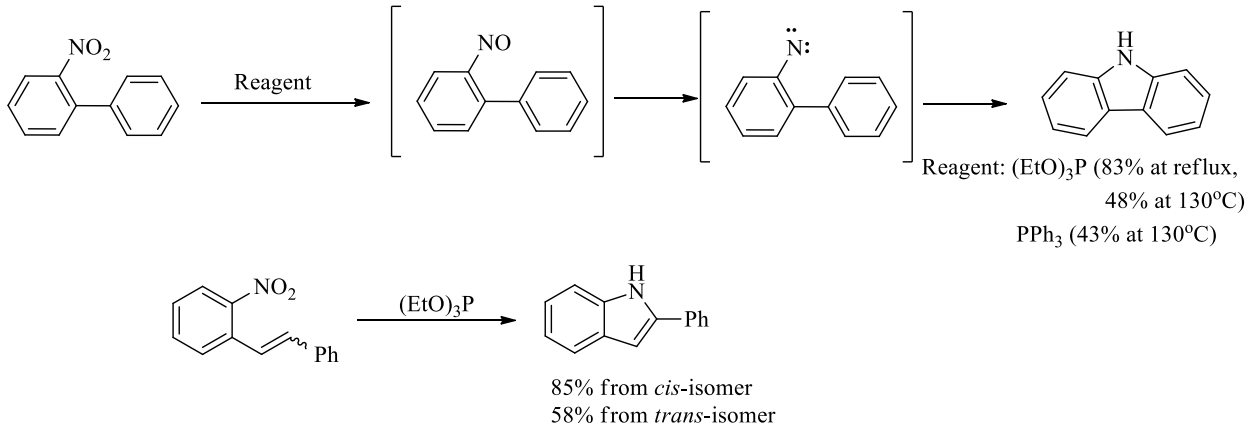
In recent years, C-H activation/functionalization[3] has received increased attention as an alternative strategy for indole synthesis due to the fact that it offers improved atom and step-economy compared to the traditional cross-coupling-based methods where extra steps are needed for pre-activation of the aromatic rings. We intend to provide the readers with a review focused on the synthesis of indoles and related structures (e.g. carbazoles and indolines) *via* C-H functionalization with an emphasis on literature after 2000.

Methods discussed herein contain at least one presumed or proved C-H bond functionalization step. In some cases, the exact mechanism is not yet clear and mechanisms other than C-H activation might also be possible. This review article will be organized into four broadly defined sections: a) *via* nitrene or carbene insertion into a C-H bond; b) *via* direct coupling of two sp^2 carbon centers; c) *via* transition-metal catalyzed C-H amination and d) other strategies.

2. Nitrene or Carbene Insertion into a C-H Bond

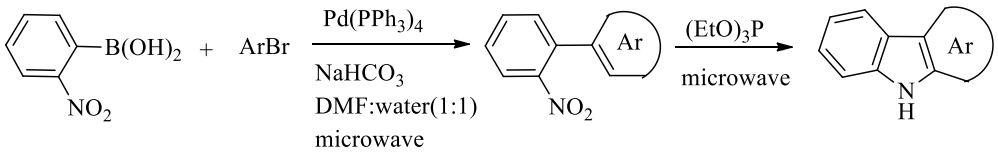
Indole synthesis through nitrene insertion has been known for many years as exemplified by the classical Cadogan, Sundberg and Hemetsberger indole syntheses.[1b]

Cadogan first reported the reductive cyclization of 2-nitrosobiphenyl compounds to carbazoles using triethyl phosphite or triphenylphosphine (Scheme 1).[4] The C-H insertion of a nitrene intermediate generated by reduction of nitroso-compound was proposed for the conversion. Shortly after, the same group discovered that 2-nitrobiphenyls also underwent reductive cyclization to carbazoles with trivalent phosphorous reagents, through the intermediacy of the nitroso-compound.[5] Notably, under the same conditions (refluxing triethyl phosphite), nitrostilbenes were also cyclized to 2-phenyl indole in good yield.

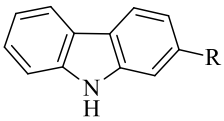


Scheme 1

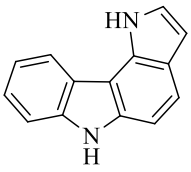
Recently, Dehaen *et al*. applied microwave to this reaction and found that the reaction time could be significantly reduced (Scheme 2). For cyclization of 2-nitrobiphenyl to the corresponding carbazole, the reaction time was shortened from 9 h to 10-20 min, although the yield was slightly down, from 83% to 74%.[6]



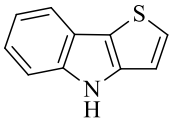
Selected Examples:



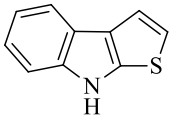
R = H (74%); Me (71%); OMe (68%); NMe2 (63%); Cl (74%); CN (68%); COMe (74%); COOMe (71%)



67%



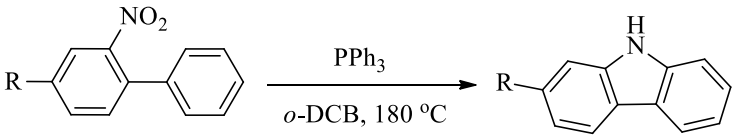
78%



76%

Scheme 2

While triethyl phosphite-mediated reductive cyclization reactions are generally successful, the product obtained is often contaminated by the *N*-ethylated derivatives, most likely from the alkylation of the product by the triethyl phosphate byproduct generated in the reaction mixture. Triphenyl phosphine was briefly examined by Cadogan and coworkers for carbazole synthesis from 2-nitrobiphenyl.[5] Freeman *et al*. refined and expanded this reaction by using triphenylphosphine in refluxing *o*-dichlorobenzene (*o*-DCB, Scheme 3).[7] The use of PPh_3 as the reducing reagent avoided the unwanted *N*-ethylation of carbazoles. However, it was noted that substrates with acidic protons (e.g. carboxylic acids and phenols) were not suitable for this reaction.

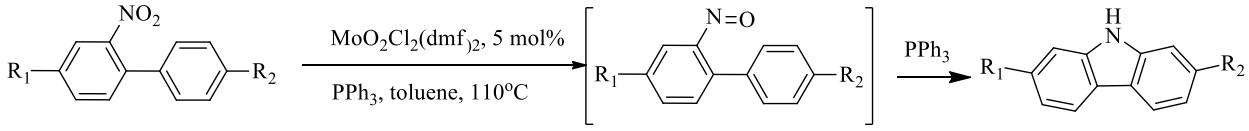


R = MeO (91%); F (91%); CF_3 (85%); CN (75%); CHO (78%) COMe (81%); COPh (99%); COOMe (90%)

Scheme 3

Sanz *et al*. reported a dioxomolybdenum (VI)-catalyzed reductive cyclization of nitroaromatics in the presence of triphenylphosphine at lower temperatures (Scheme 4).[8] Heating

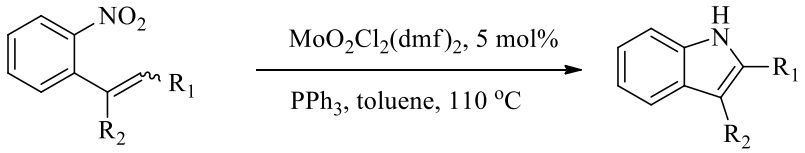
2-nitrobiphenyls in toluene (110 ºC, 16 h) with triphenylphosphine and a catalytic amount of $MoO_2Cl_2(dmf)_2$ (5 mol%) afforded carbazoles. The proposed mechanism for this reaction involves the initial molybdenum catalyzed reduction of nitroaromatics to nitroso compounds which are then further reduced by triphenylphosphine to form nitrenes (or nitrenoids) that undergo C-H insertion to give carbazoles.



R^2 = H, R_1 = H (86%); OMe (78%); CHO (70%); COMe (81%);
F (73%); CO_2Et (87%); OH (33%); CO_2H (30%)
R_2 = *t*-Bu, R_1 = *t*-Bu (80%)

Scheme 4

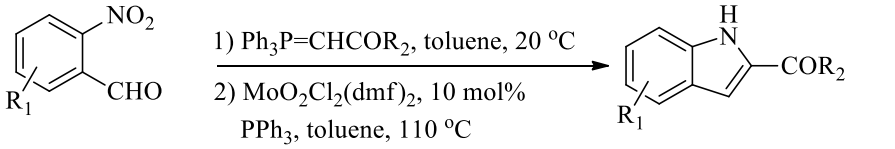
This procedure tolerates a wide variety of functional groups. Even substrates with acidic protons such as phenols and carboxylic acids gave products in modest (30-33%) yields (For this type of substrates, no carbazole or indole products were obtained under Freeman's conditions).[7] Analogously, *o*-nitrostyrenes were converted into indoles in good yields (Scheme 5).



R_2 = H, R_1 = Ph (64% for *E*, 80% for *Z*, 73% for *E*/*Z* = 4/1);
n-C_5H_{11}(80% for *E*/*Z* = 1/2.3); Me (77% for *E*/*Z* = 4/1);
CO_2Et (75% for *E*/*Z* = 10/1)
R_2 = Me, R_1 = CO_2Et (84% for *E*/*Z* = 1.5/1)

Scheme 5

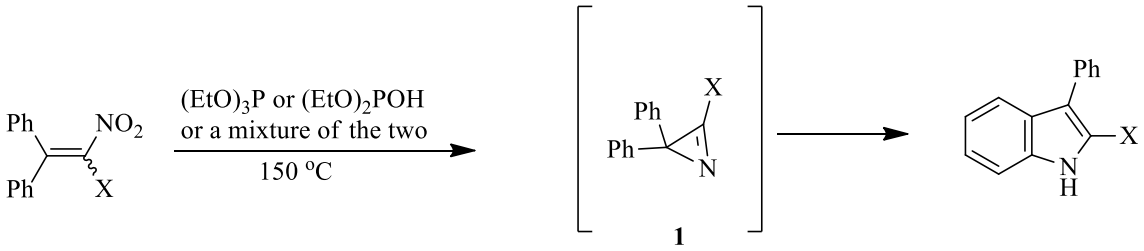
It was demonstrated that this reaction could be telescoped with a Wittig reaction (using 10 mol% catalyst and 24 h reaction time) to synthesize substituted indoles from commercially available *o*-nitroarylaldehydes in a one-pot fashion (Scheme 6). Polymer-bound triphenylphosphine has also been employed in this reductive cyclization reaction for easier isolation of the product (four examples). Reactions with the polymer-bond reagent required longer reaction times, but gave similar yields.



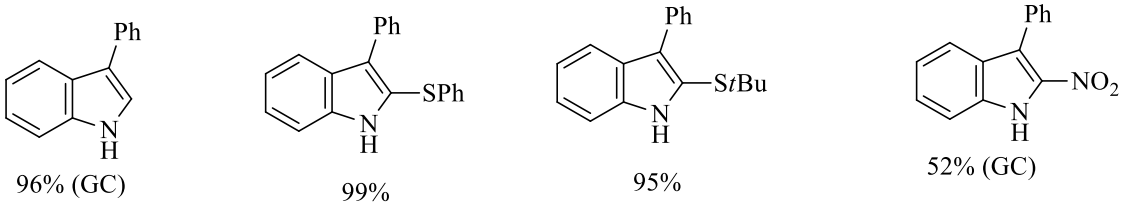
R_2 = OEt, R_1 = H (71%); 4-Cl (85%); 5-Cl (15%); 6-Cl (50%); 5,6-(OCH_2O) (81%); 7-OMe (45%)
R_2 = Me, R_1 = H (63%); 4-Cl (93%); 5-Cl (39%); 6-Cl (55%); 5,6-(OCH_2O) (78%)

Scheme 6

Aryl substituted nitro alkenes were also subjected to phosphite reduction conditions to prepare indoles as shown below (Scheme 7).[9] The presumed reactive intermediate was the 2*H*-azirine **1** derived from the nitrene insertion onto the neighboring double bond. Thermal rearrangement of 2*H*-azirines gave rise to the formation of indoles. Sulfide and nitro groups were tolerated in these reactions.

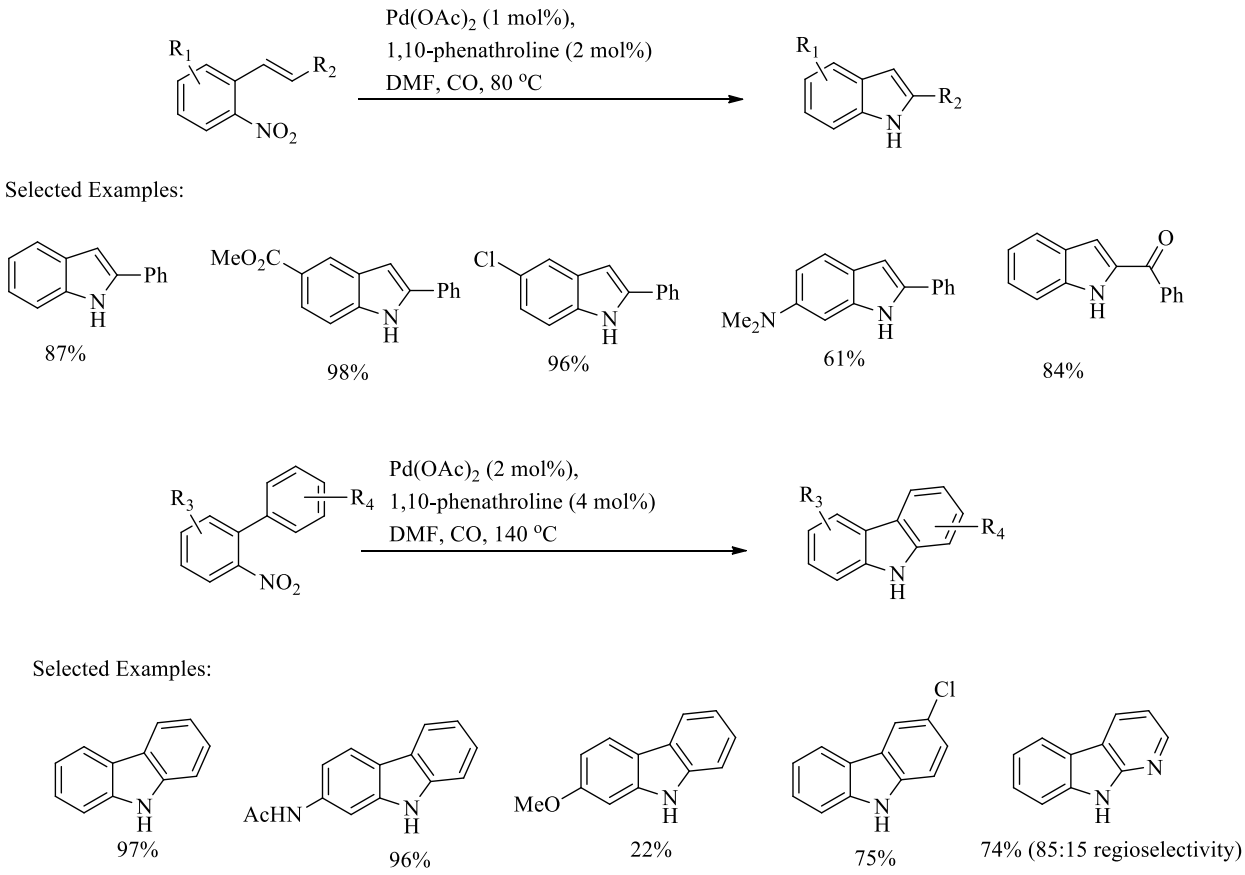


Selected Examples:



Scheme 7

Carbon monoxide has been employed as the reducing agent for cyclization of nitro aromatics into indole cores. It was generally accepted that these reactions proceeded through a transient nitrene intermediate.[10] However, in certain cases, mechanistic data supported an electrocyclization pathway. Nonetheless, transition-metal catalyzed reductive *N*-heterocyclization of nitroaromatics with carbon monoxide represents an efficient method for indole synthesis. Literature related to this reaction prior to 2006 has been reviewed.[11] A few recent representative examples are summarized (Scheme 8).

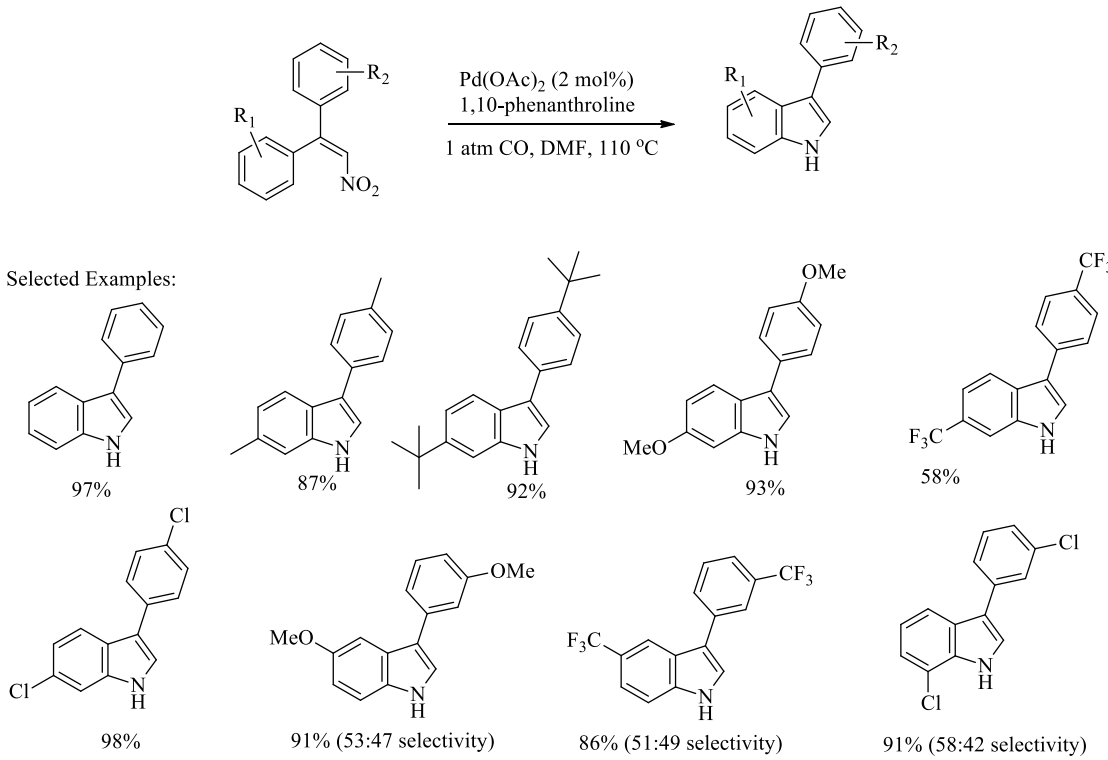


Scheme 8

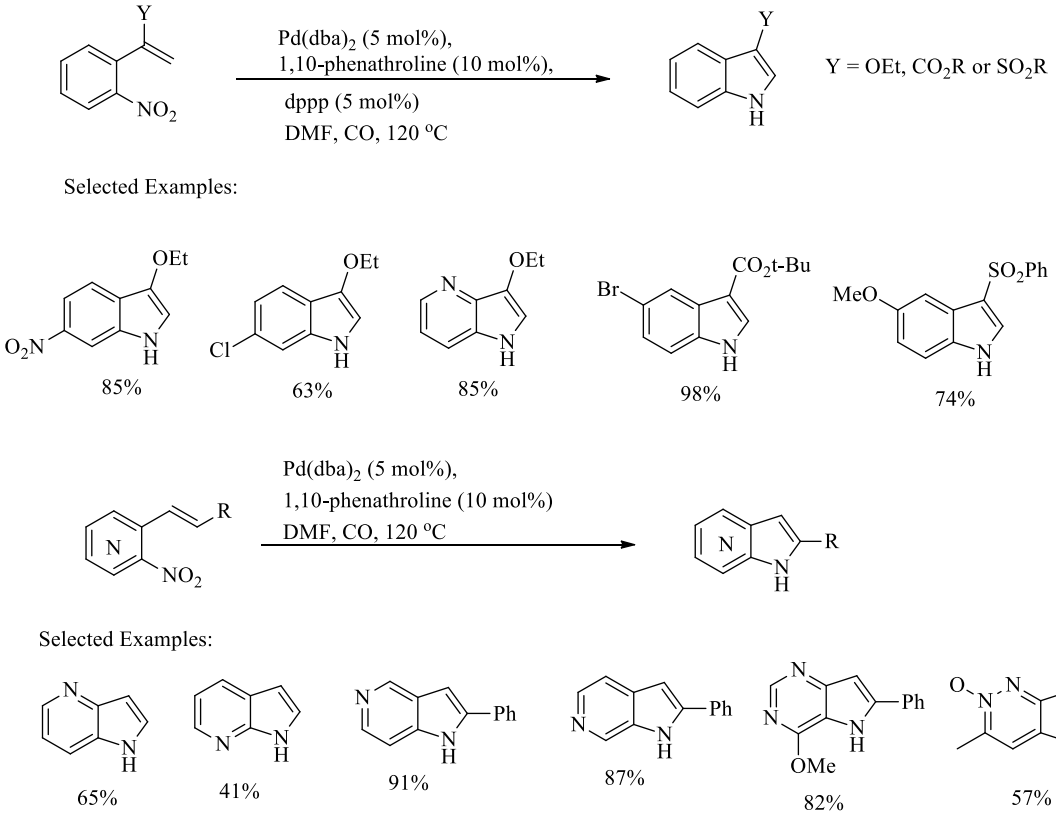
Davies *et al.* found that *ortho*-vinyl or *ortho*-aryl nitroarenes underwent reductive cyclization to give indoles or carbazoles in good to excellent yields (Scheme 8).[12] Their conditions involved the use of a catalytic amount of $Pd(OAc)_2$, carbon monoxide, 1,10-phenathroline as the ligand and DMF as the solvent.

Dong and Hsieh employed similar conditions for nitroalkene cyclizations and obtained indole products in good to excellent yields (Scheme 9).[13] For *meta*-substituted starting materials, very little regioselectivities were observed. The reaction was not attempted on unsymmetrically substituted substrates ($R_1 \neq R_2$).

Söderberg's group has long been interested in reductive cyclization of nitro compounds into indole derivatives. For example, they have developed conditions to prepare 3-alkoxy and 3-carboxy-indoles from nitroarene precursors as shown in Scheme 10.[14] Recently, they further extended such a reaction to azaindole synthesis starting from various nitro-heteroaromatics.[15]

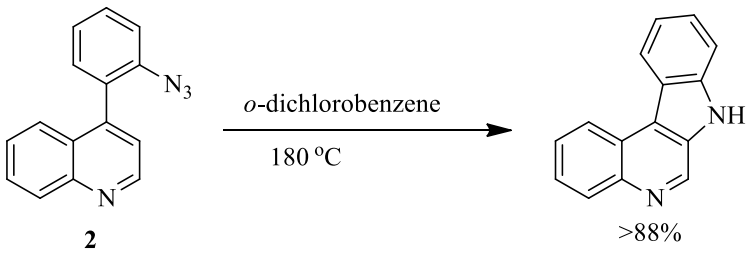


Scheme 9



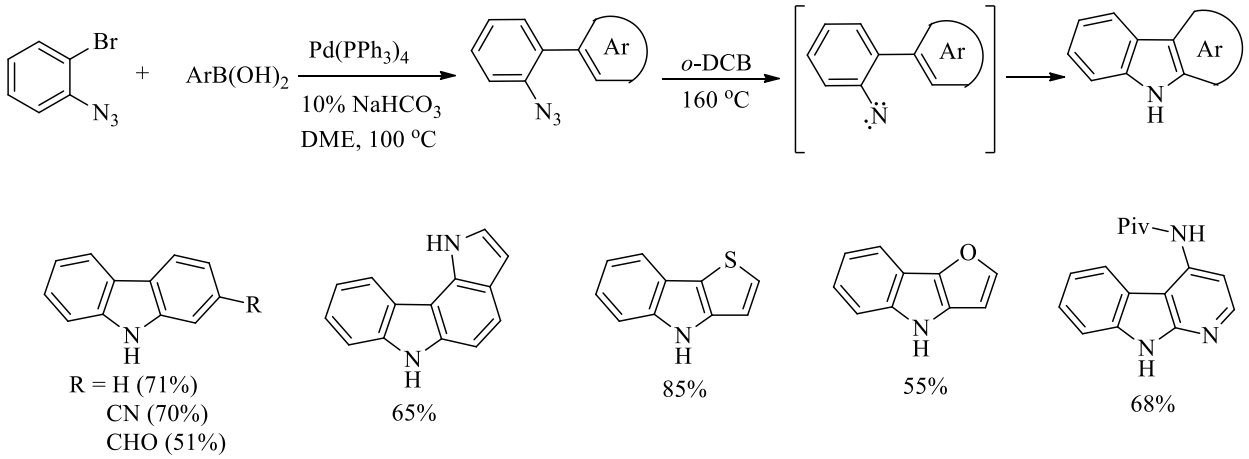
Scheme 10

Nitrenes can also be generated from an azide precursor as illustrated in Sundberg[16] and Hemetsberger indole syntheses.[17] The required azido substrates can be prepared by using, for example, a sequence involving an initial Suzuki coupling of aryl halides and protected aminoboronic acid followed by diazotation and substitution with NaN_3.[18] Heating compound **2** in *o*-dichlorobenzene at 180 °C resulted in the formation of the cyclized product in good yield (Scheme 11). It is generally believed that the reaction proceeds *via* a nitrene intermediate formed by thermolysis of the azide functionality.



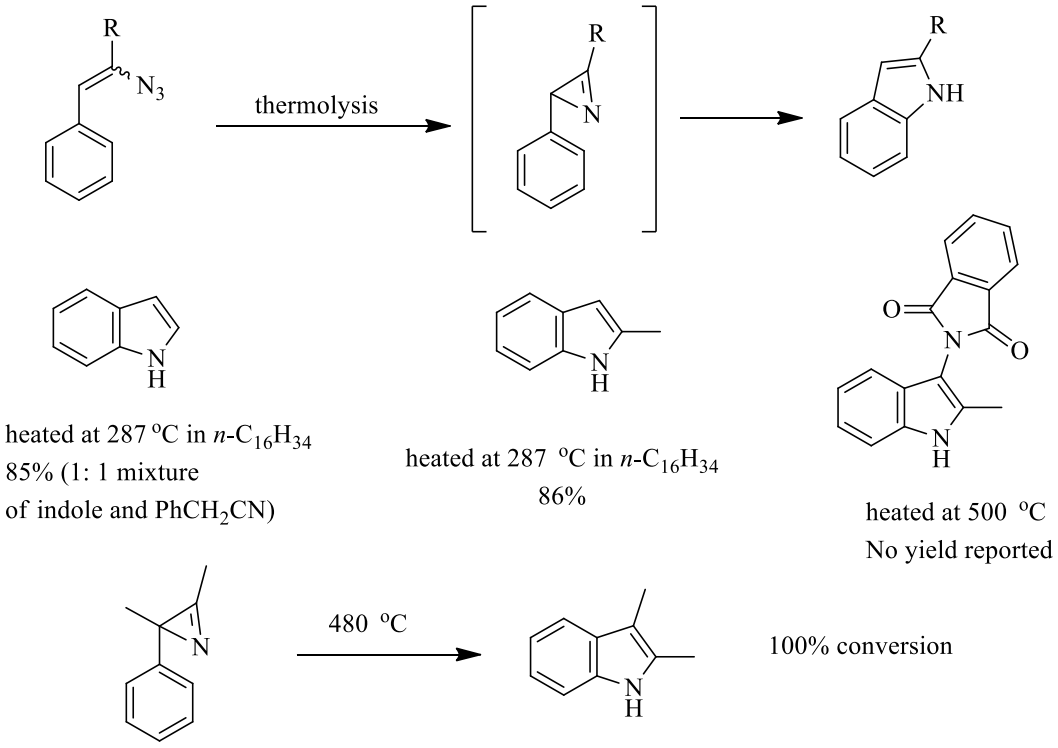
Scheme 11

Sapi et al. reported the direct Suzuki cross-coupling of 2-azidobromobenzene (prepared quantitatively from 2-bromoaniline) with arylboronic acids to form azido-biaryl compounds (Scheme 12).[19] Thermal decomposition (160 °C in *o*-dichlorobenzene) of the azido-biaryl compounds yielded a range of indole-containing heterocycles, including an α-carboline, in modest to good yields.



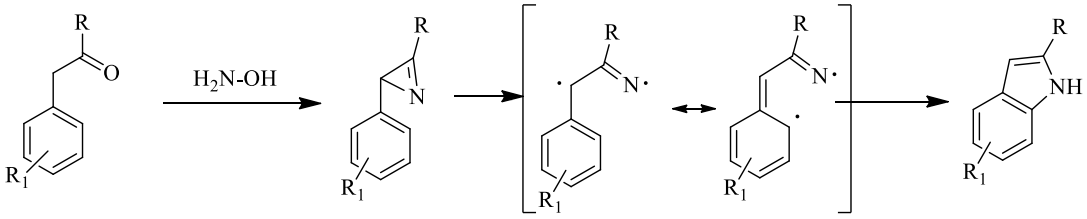
Scheme 12

Vinyl azides are also known to undergo thermal decomposition to provide 2*H*-azirines that can isomerize to indole derivatives, through either a nitrene intermediate or a radical process. Some early examples were carried out at pyrolysis temperatures (290 -500 °C) as shown in Scheme 13.[20]

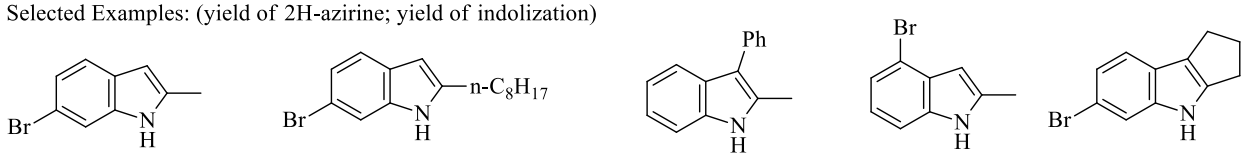


Scheme 13

Taber and coworkers[21] expanded the scope of the above 2*H*-azirine thermolysis to prepare 2-alkyl-substituted indoles (Scheme 14). The 2*H*-azirines were synthesized from aryl-alkyl ketones through the Neber reaction. Then thermal rearrangement furnished substituted indoles in good to moderate yields. The mechanism for the thermolysis was examined and experimental data supported a π-participation radical mechanism rather than the traditional nitrene mechanism.



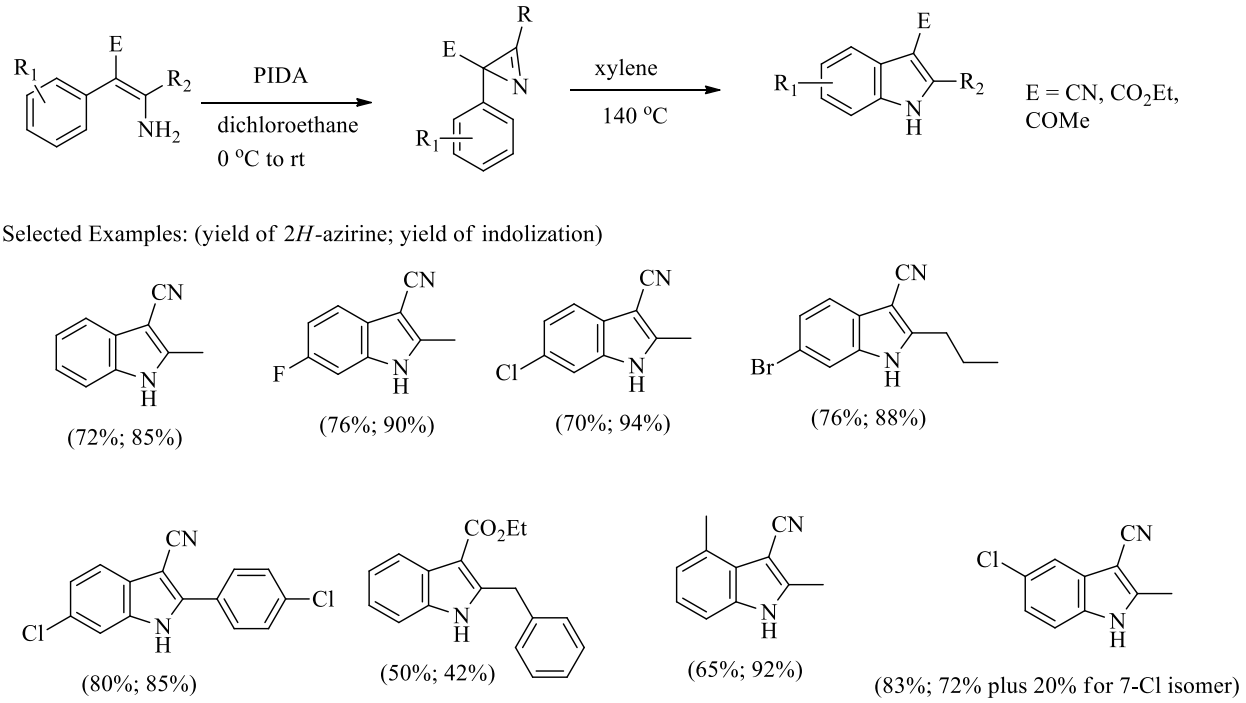
Selected Examples: (yield of 2H-azirine; yield of indolization)



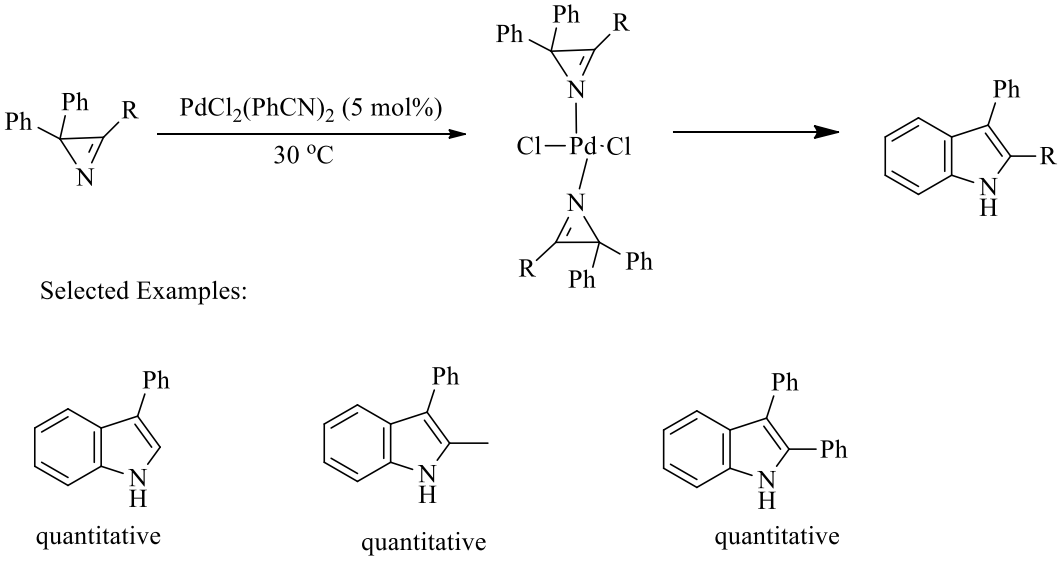
(78%; 88%) (70%; 86%) (91%; 89%) (78%; 84%) (41% two steps)

Scheme 14

2*H*-Aziridines can also be prepared from enamines. Du, Zhao, *et al.*[22] showed that treatment of substituted enamines with phenyliodine (III) diacetate (PIDA) in dichloroethane at 0 °C to room temperature led to the facile formation of 2*H*-azirines in good yields (Scheme 15). Thermal rearrangements afforded a range of indole products.



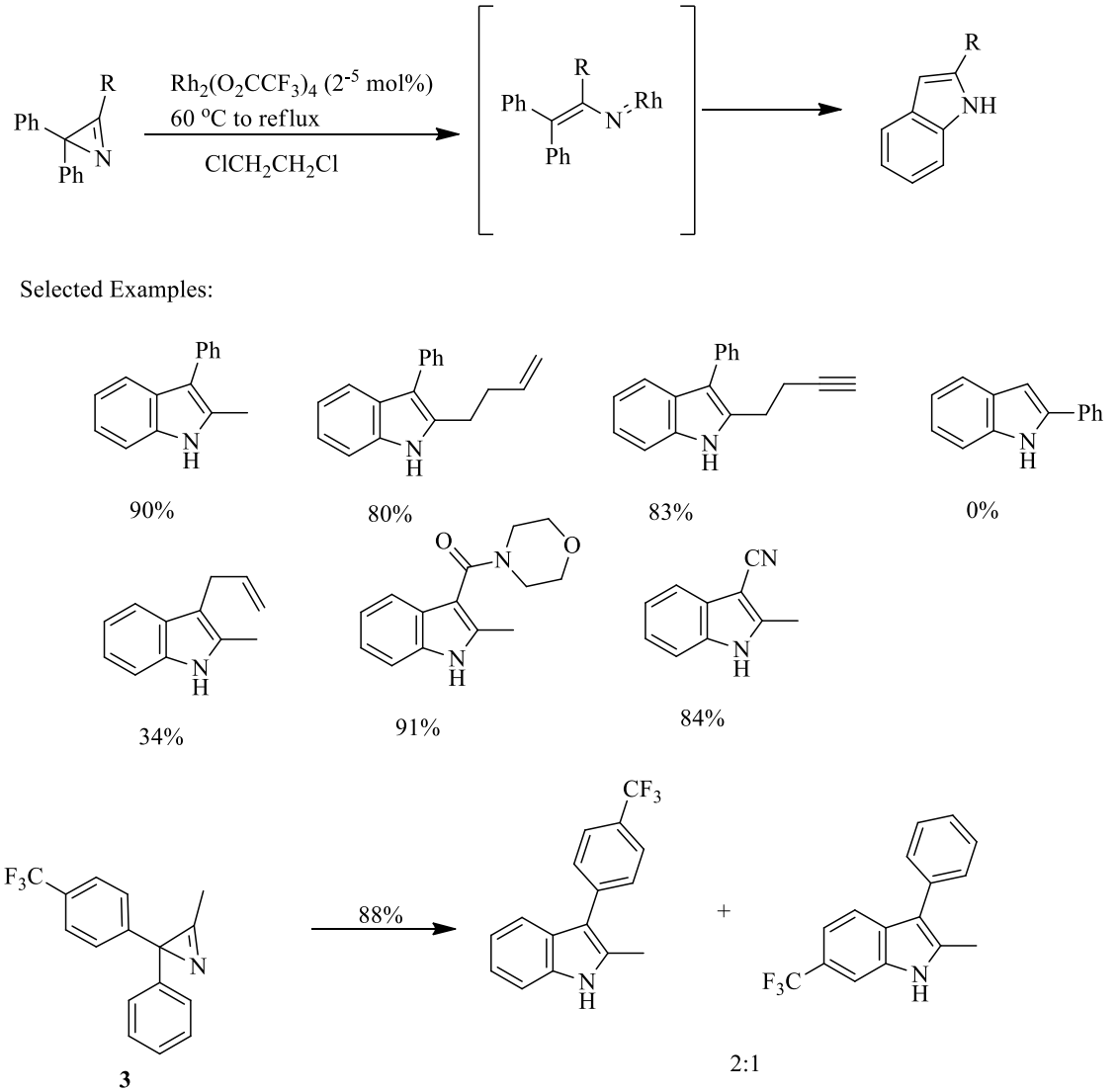
Scheme 15



Scheme 16

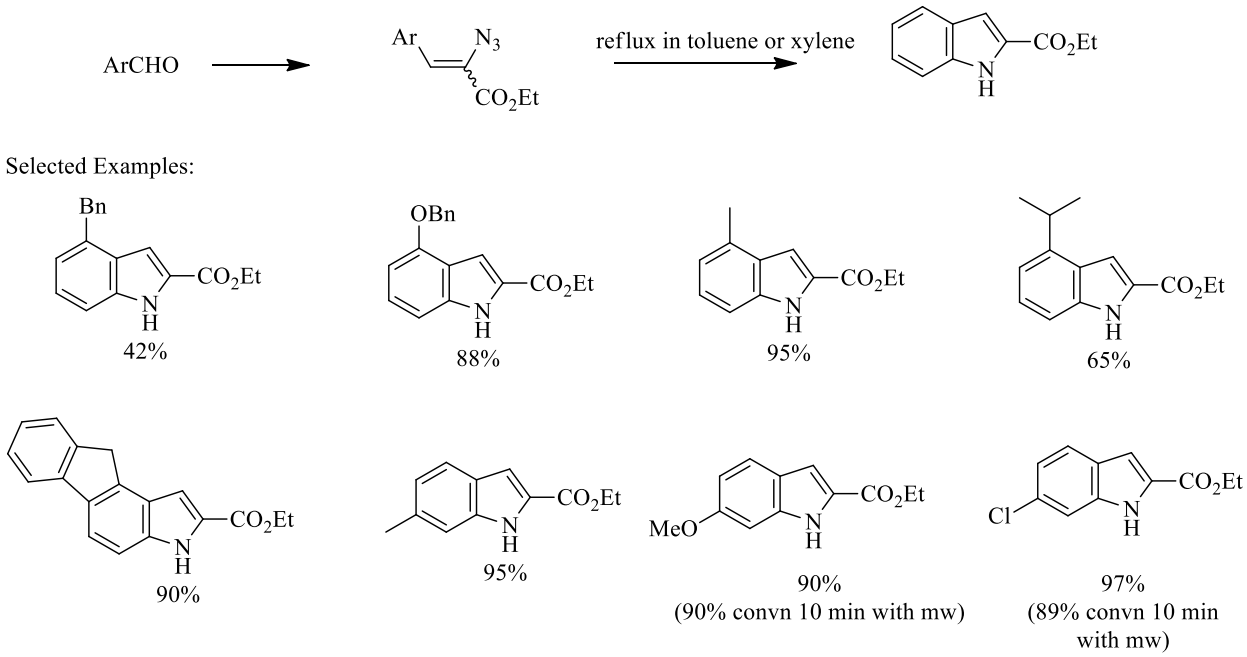
Transition metals have been employed to catalyze 2*H*-azirine rearrangements under milder conditions. Taniguchi and coworkers found that 2*H*-azirines readily transformed into indoles at nearly room temperature (30 ºC) in quantitative yields with the catalysis of $PdCl_2(PhCN)_2$ (5 mol%).[23] The authors also identified the active Pd (II) species to be a bis-2*H*-azirine complex as shown in Scheme 16.

Narasaka *et al*.[24] explored the same transformation *via* a presumed Rh-nitrenoid species. They reasoned that Rh complexes could provide effective stabilization to the nitrene intermediate (Scheme 17). They found that $Rh_2(OCOCF_3)_4$ catalyzed isomerization of 2-aryl-2*H*-azirines to form the Rh nitrenes that subsequently underwent C-H insertion to give various 2,3-disubstituted indoles under mild conditions. Rearrangement of compound **3** containing two different aryl groups was also examined and a 2:1 mixture of two indole products was obtained, favoring the C-H insertion onto the more electron-rich aryl ring.



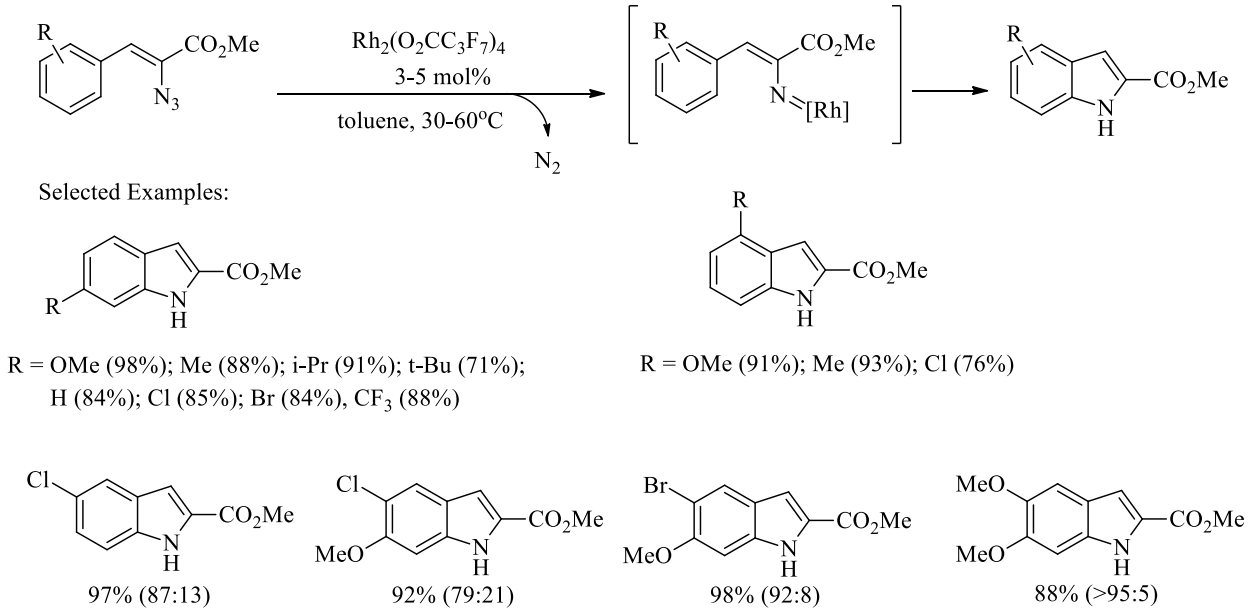
Scheme 17

In a typical Hemetsberger synthesis[25,26] the starting vinyl azides were conveniently synthesized by the condensation of aromatic aldehydes with ethyl azidoacetate (Scheme 18). Then refluxing these substrates in toluene or xylene resulted in the rearrangement to 2-carboxyindoles in good yields. Recently, Laufer *et al.* applied microwave technique to Hemetsberger reaction and obtained excellent conversions within only minutes of irradiation at 200 °C.[27]



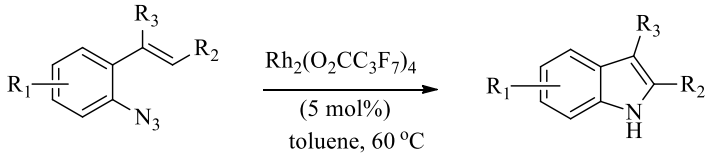
Scheme 18

Driver's group discovered that dirhodium(II) carboxylates were able to catalyze the conversion of vinyl azides into indoles and other *N*-heterocycles at 30-60 °C through the intermediacy of a rhodium nitrenoid, therefore realizing Hemetsberger indole synthesis under mild conditions (Scheme 19).[28] Without the Rh catalyst, the reaction usually required much higher temperature (e.g. 145 °C) to complete. Substrates with both electron-donating and electron-withdrawing aryl substituents were tolerated. A variety of 2-carboxyindoles were synthesized from vinyl azides using rhodium (II) perfluorobutyrate as the catalyst (Scheme 19). For *meta*-substituted substrates, the major isomer resulted from the nitrene insertion onto the less-hindered C-H bond on the benzene ring.



Scheme 19

Driver and coworkers subsequently reported a related, Rh-catalyzed Sundberg indole synthesis starting from aryl azides (Scheme 20).[29] The reaction proceeded well at 60 °C, a temperature much lower than the original thermal conditions. It was observed that the nature of the R_2 substituent was critical for the success of the reaction. When R_2 = aryl, good to excellent yields of indoles were obtained. On the other hand, for substrates with an alkyl R_2 group, only low to moderate yields of indole products were formed. In certain cases, Rh octanoate proved to be a more effective catalyst for R_2-alkyl starting materials. It was also shown that $Rh_2(O_2CC_3F_7)_4$ or $Rh_2(O_2CC_7H_{15})_4$ (5 mol%) were able to catalyze carbazole formation from *ortho*-aryl azidoaromatics.[30]



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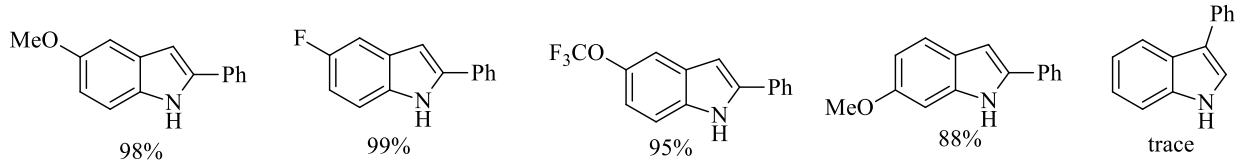

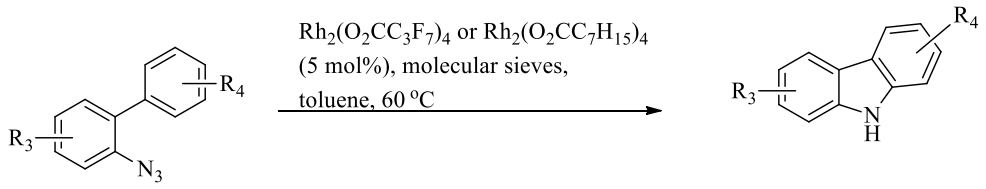

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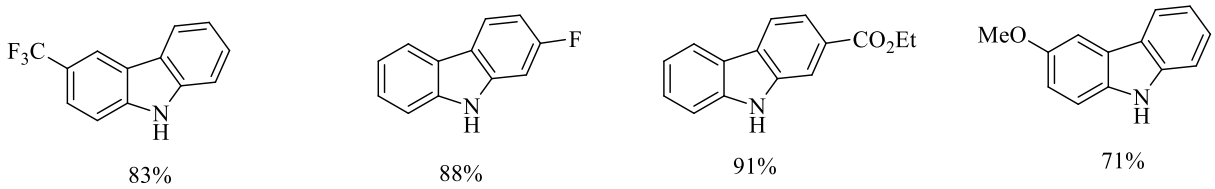
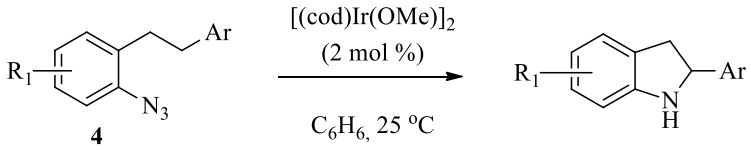


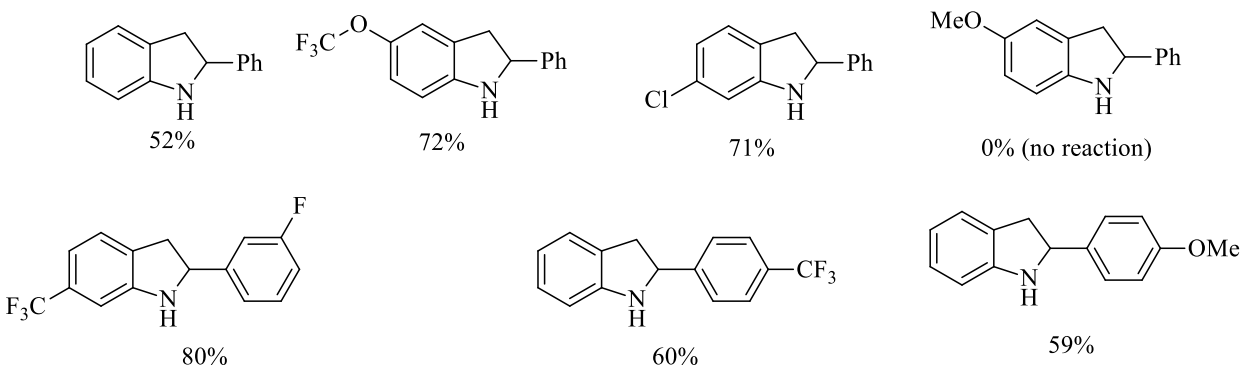
Scheme 20

The same group discovered that cyclization of aryl azides can also be catalyzed by iridium to afford indole, indoline and carbazole products (Scheme 21).[31] Treatment of aryl azide **4** with catalytic $[(cod)Ir(OMe)]_2$ furnished the indoline in high yield at room temperature *via* the activation of an sp3 benzylic C-H bond. It was noted that the reaction was sensitive to the electronic nature of the aromatic ring: electron-withdrawing substituents facilitated the reaction. The same Ir catalyst system can be applied to aryl azides with an additional unsaturation on the side chain to prepare indoles and carbazoles in good yields. More recently, Lin and Jia found that $RuCl_3$ could also efficiently catalyze both Sundberg and Hemetsberger indole/carbazole formation at 85 to 105 °C.[32] The reaction mechanism was explored by experimental and computational studies.

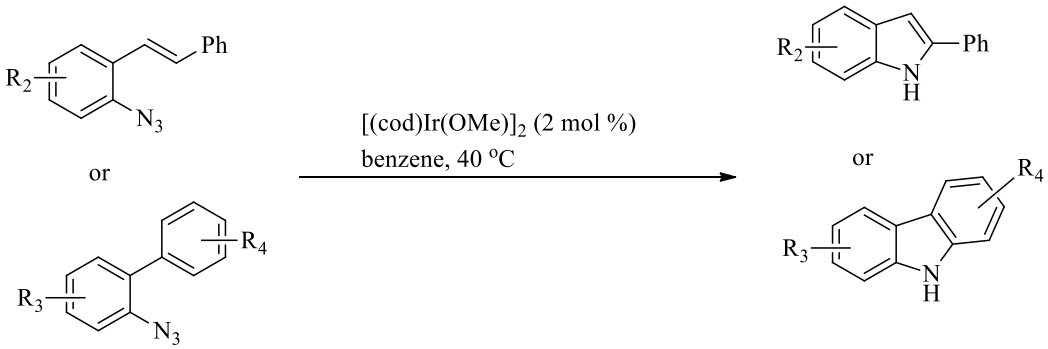
Indoline Synthesis:



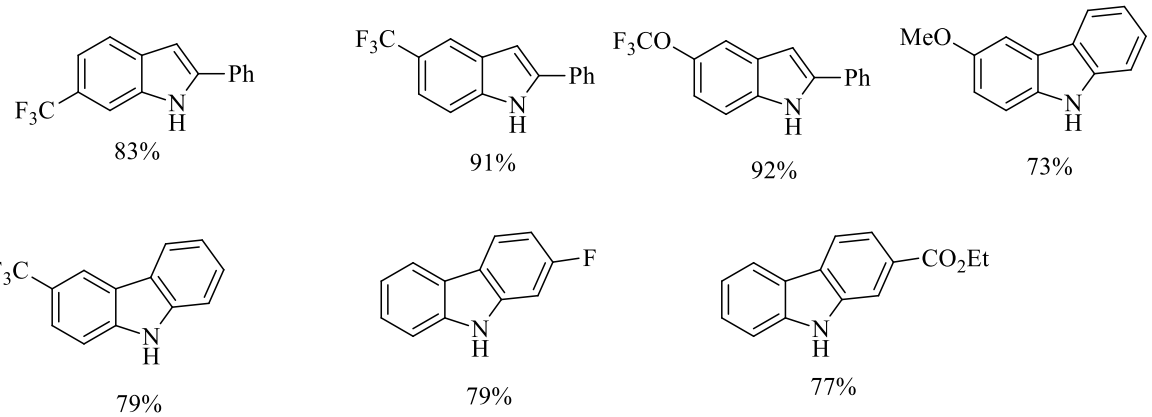
Selected Examples:



Indole and Carbazole Synthesis



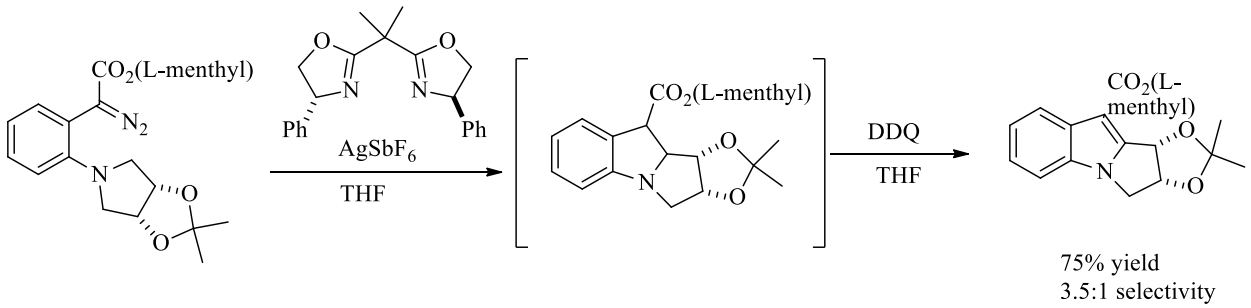
Selected Examples:



Scheme 21

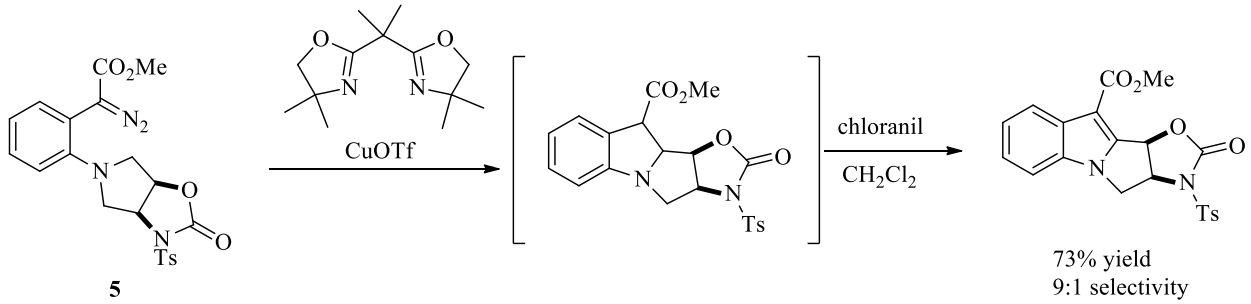
Intramolecular carbene insertion into a C-H bond represents another avenue for indole cyclization. Doyle, Moody, Sulikowski, Padwa and others have employed this strategy to prepare indoles, oxindoles and indolines.[33]

For example, Sulikowski's group has investigated transition metal-catalyzed intramolecular carbene insertion for the construction of indole core in mitomycin antitumor antibiotics (Scheme 22).[34] From high throughput catalyst screen, it was identified that the combination of chiral bisoxazole and $AgSbF_6$ gave the best results in terms of yield and stereoselectivity.



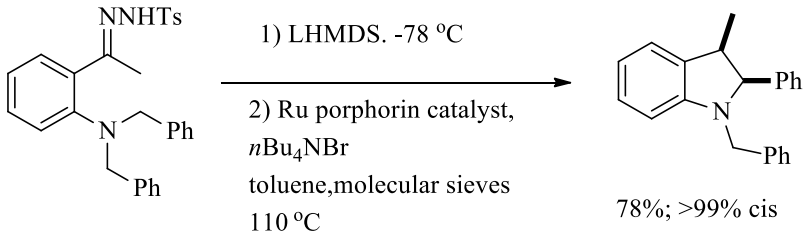
Scheme 22

Using a Cu catalyst derived from bisoxazole ligand and Cu(I) triflate, the selective C-H insertion of compound **5** was achieved for indoline formation with 9:1 selectivity favoring insertion into the C-H bond adjacent to the oxygen substituent. Oxidation with chloranil gave indole products (Scheme 23).



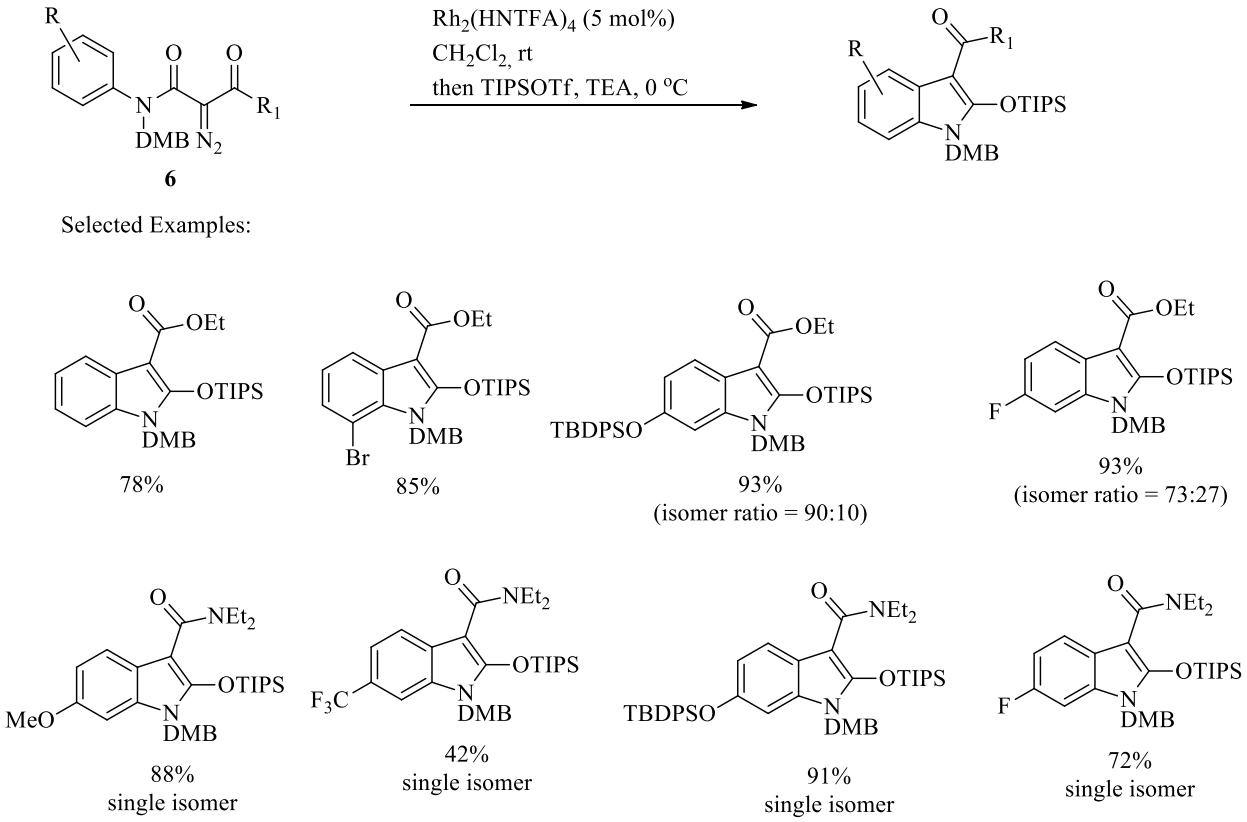
Scheme 23

Che and coworkers developed a Ru porphorin catalyst system for intramolecular carbene insertion reactions and provided one example of indoline formation from an aryl tosylhydrazone (Scheme 24).[35]



Scheme 24

Rhodium-catalyzed carbene C-H insertion was used to access oxindoles. Diazoamides **6** were treated with 5 mol% $Rh_2(HNTFA)_4$ in dichloromethane at rt to give, after TIPS protection, 2-siloxyindoles in moderate to excellent yields (Scheme 25).[36] For *meta*-substituted starting materials, moderate to good regioselectivities were observed when R_1 = OEt while single isomers were isolated when R_1 = NEt_2.

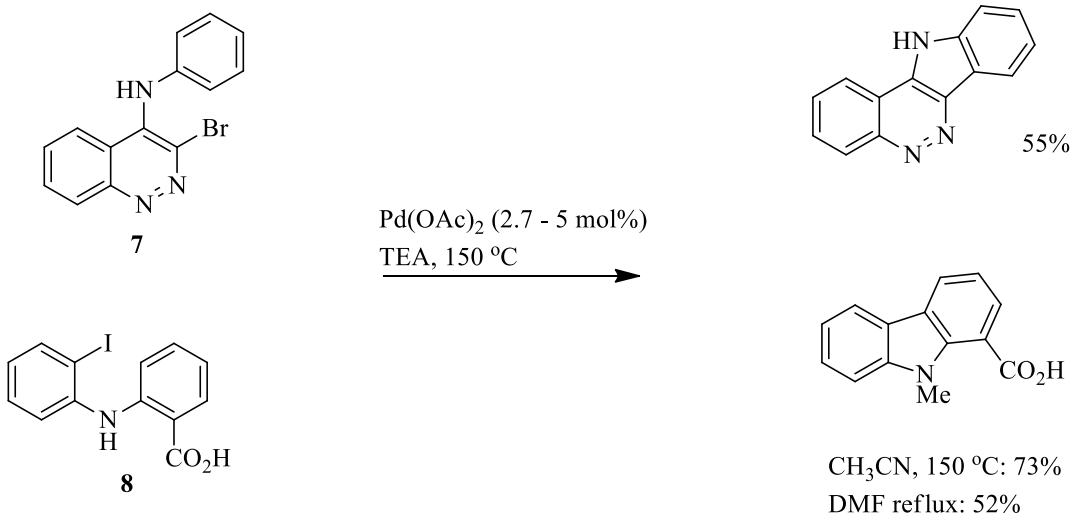


Scheme 25

3. Direct Coupling of Two sp^2 Carbons

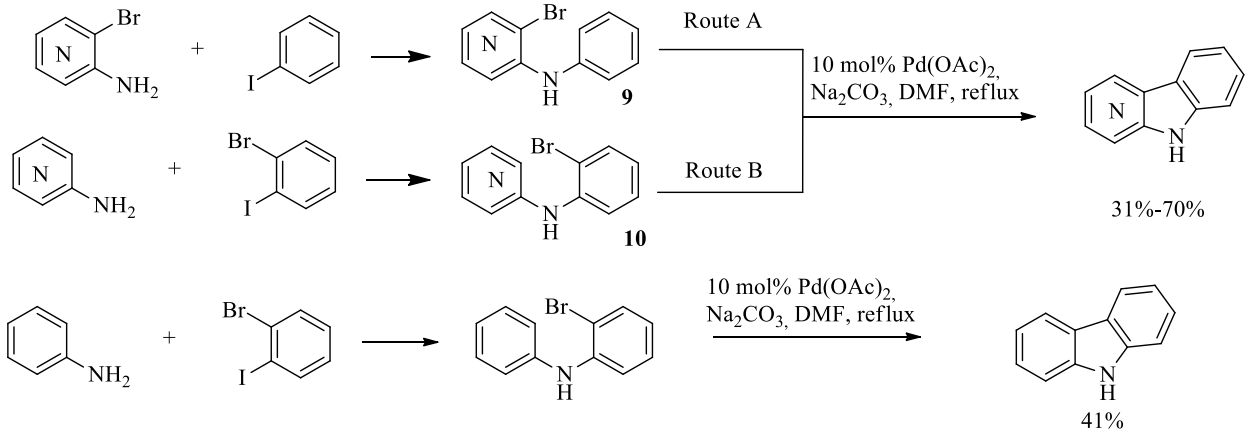
Ames and coworkers[37] provided early examples of carbazole synthesis *via* intramolecular direct Ar-Ar couplings. For example, when compound **7** or **8** (Scheme 26) were treated with a catalytic

amount of $Pd(OAc)_2$ in the presence of TEA, cyclization took place to furnish carbazole products in moderate yields.



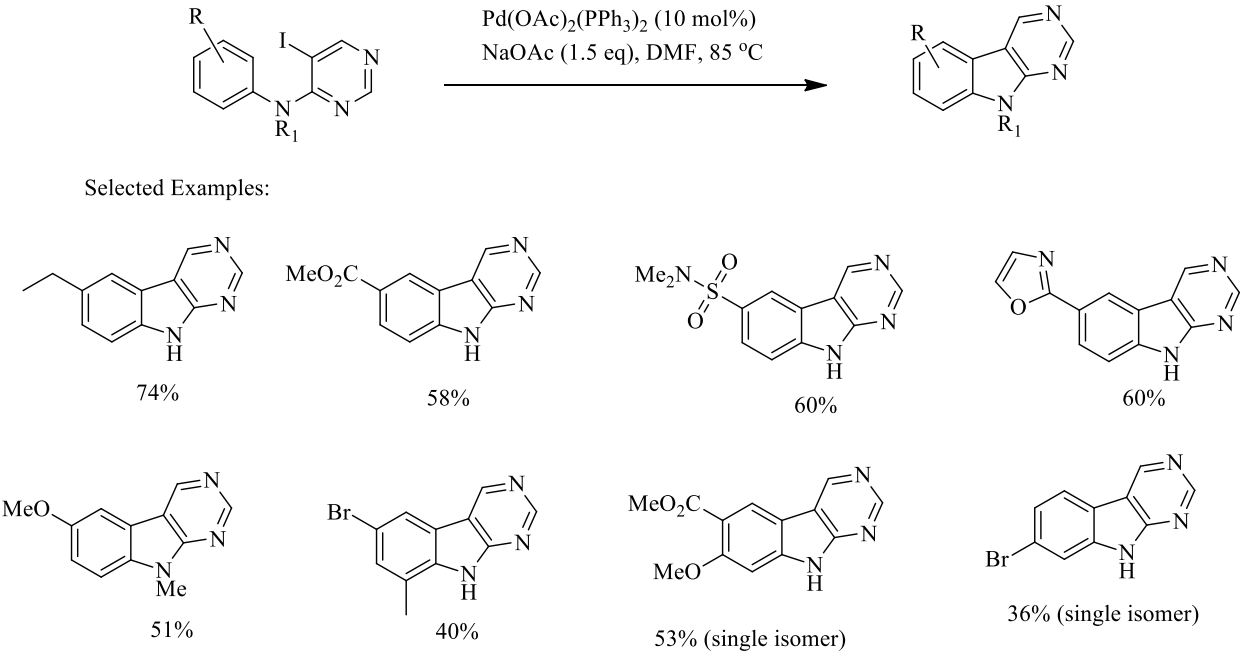
Scheme 26

Application of this strategy to carboline synthesis was reported by Sakamoto et al.[38] Precursors for Ar-Ar coupling were prepared using Buchwald amination *via* coupling of *ortho*-bromoanilines with iodoarenes (Route A, Scheme 27), or from reacting anilines with 1,2-dihaloarenes (Route B). Treatment of compound **9** or **10** with 10 mol% $Pd(OAc)_2$, Na_2CO_3 in refluxing DMF led to the cyclization into carbolines. The intramolecular C-H activation can take place from either aromatic ring of the diarylamine. All four isomers of carbolines were specifically synthesized using either Route A or B. However, it was noted that Route B was preferred due to the better raw material availability. This method was also suitable for carbazole formation as exemplified by the synthesis in the following scheme.



Scheme 27

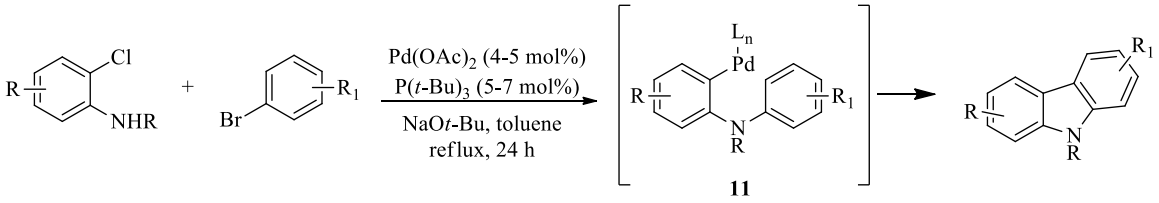
Zhang *et al*. extended this approach to pyrimidine substrates for the preparation of a range of diazacarbazoles (Scheme 28).[39] It was found that the choice of ligand, catalyst and base was critical for the success of this reaction and the combination of $Pd(OAc)_2(PPh_3)_2$, NaOAc and DMF gave the best results. When there are more than one reaction site on the phenyl ring for potential C-H activation, the reaction occurred at the less hindered position.



Scheme 28

Bedford group developed a one-pot carbazole synthesis from chloroarenes involving sequential amination and C-H activation (Scheme 29).[40] The first step of the process was a palladium/P(*t*-Bu)$_3$ catalyzed *N*-arylation of *N*-alkyl-2-chloroanilines with bromoarenes. Oxidative insertion onto the aryl chloride gave the reactive intermediate **11** which underwent a palladium catalyzed C-H activation to furnish carbazole products in 27-61% yields. Notably, under these reaction conditions, the C-H activation step did not occur if the free 2-chloroaniline was employed (R = H).

Subsequently, Bedford's group reported the successful extension of this methodology to the synthesis of *N*-unsubstituted carbazoles, also in a one-pot, two-transformation sequence (Scheme 30).[41] The key modification which promoted the C-H activation step was to use microwave heating (160 ˚C, 3 h). It was shown that the less air-sensitive $[HP(tBu)_3][BF_4]$ was also suitable as a ligand. The methodology was applied to the total synthesis of a natural product (Clausine P). By using vinyl bromides as the starting material instead of aryl bromides, indoles could be produced in good yields. This procedure was used to prepare *N*-H indoles as well as *N*-benzyl indoles.



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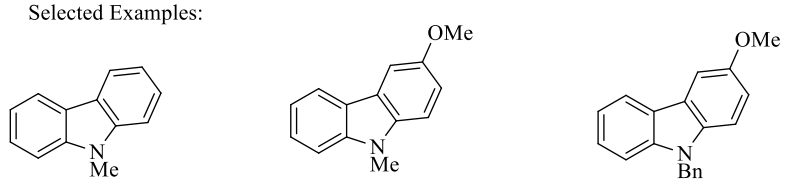
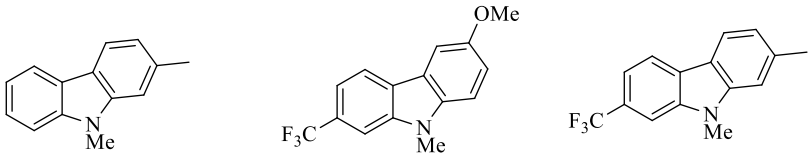
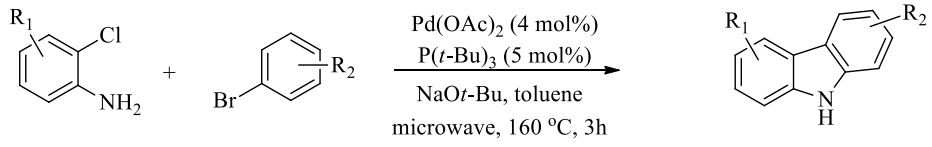


61% 47% 40%



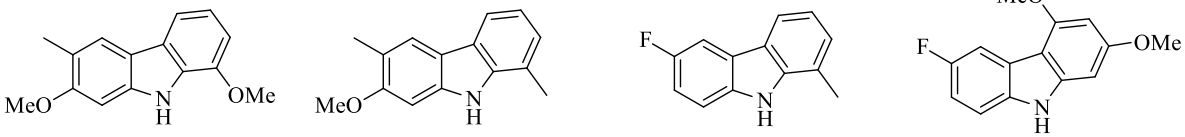
57% 27% 51%

Scheme 29

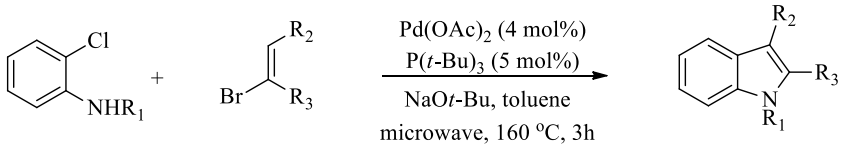


80%

Selected Examples: (with the ring on the left coming from aniline)

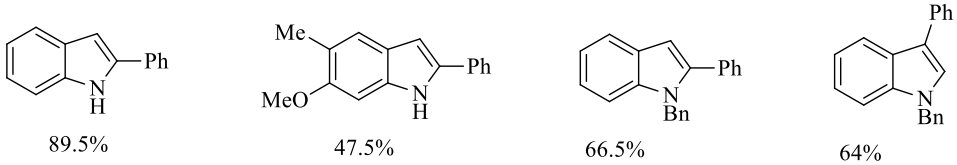


Clausine P, 80% 90% 70% with $[HP(tBu)_3][BF_4]$ 53% with $[HP(tBu)_3][BF_4]$



89.5%

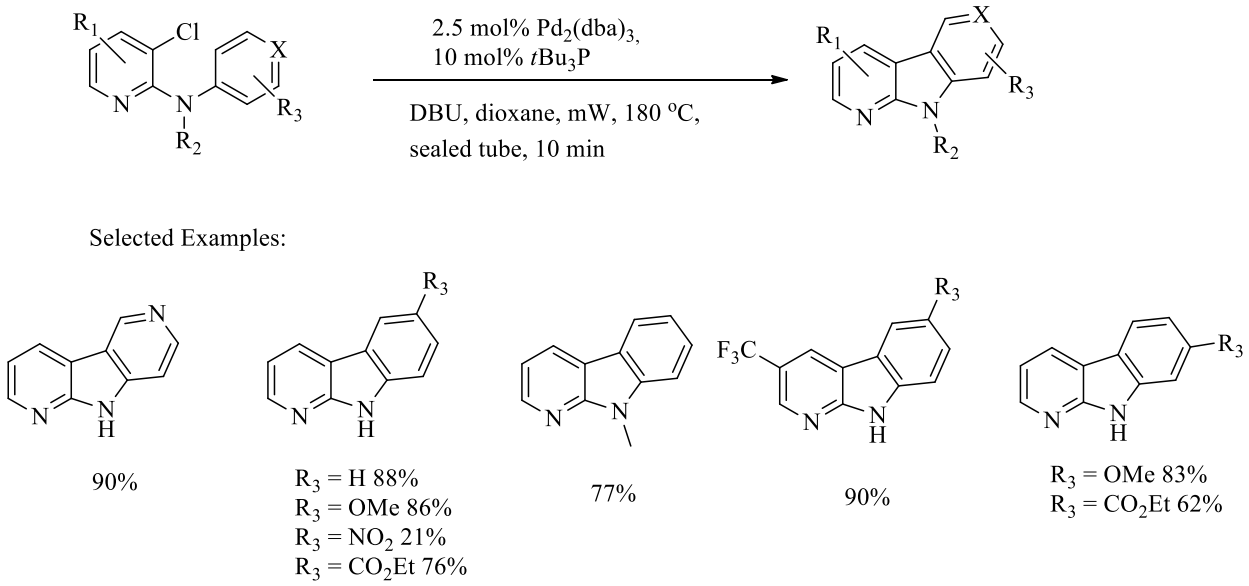
Selected Examples:



89.5% 47.5% 66.5% 64%

Scheme 30

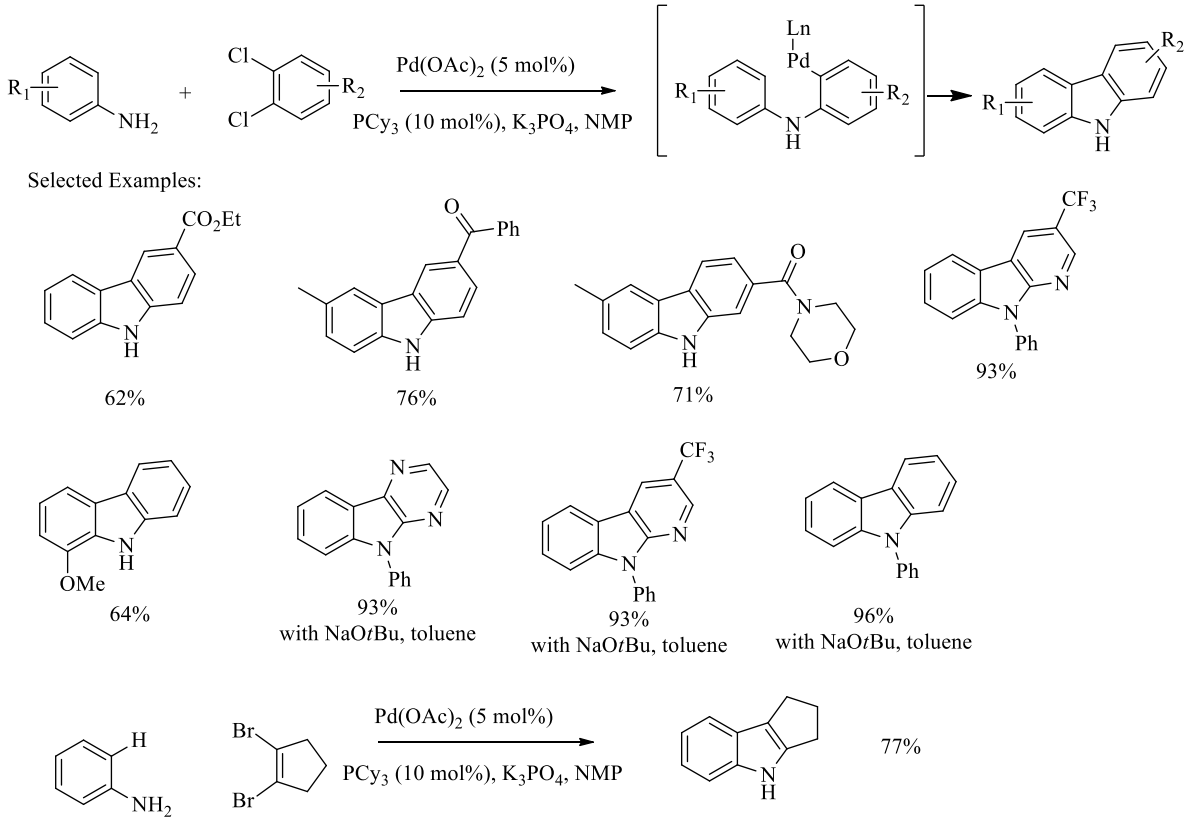
During their study on the total synthesis of alkaloid natural products, Maes *et al*. independently developed conditions to cyclize *N*-pyridyl *ortho*-chloroanilines by using the electron-rich tBu$_3$P as the ligand to facilitate the oxidative addition to aryl chlorides (Scheme 31).[42] It was later reported[43] that normal heating methods (i.e. oil bath heating) were not sufficient for certain substrates to react. Microwave was then tested for this transformation and significantly facilitated the C-H activation/cyclization with relatively low catalyst/ligand loadings at 2.5 mol% $Pd_2(dba)_3$ and 10 mol% tBu$_3$P to provide carbazole derivatives in good yields.



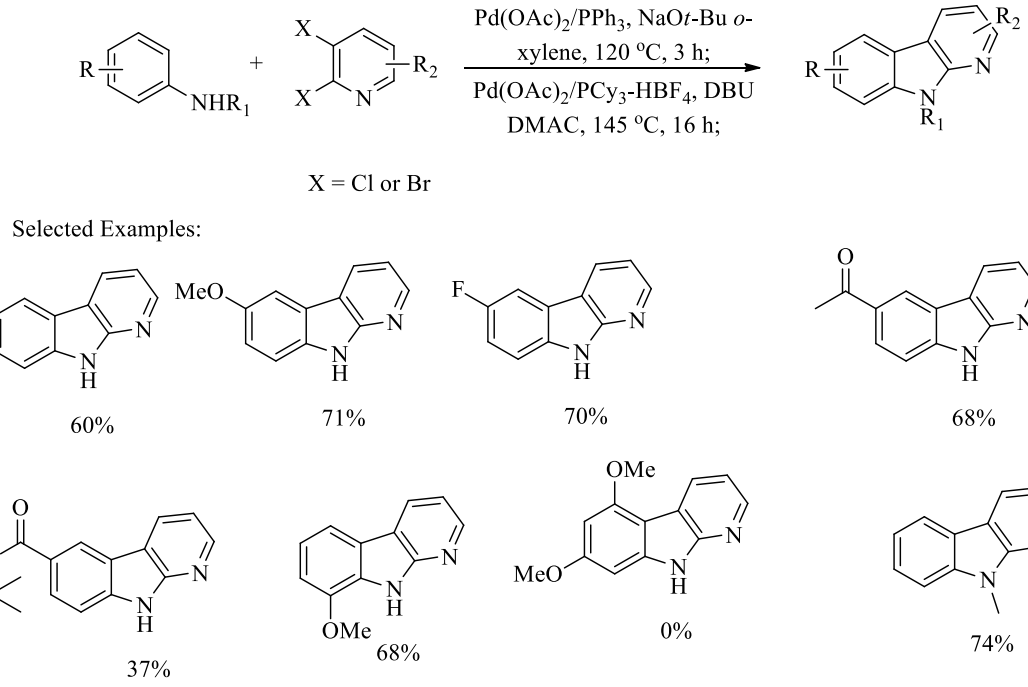
Scheme 31

Ackermann group[44] reported that *N*-unprotected anilines reacted with 1,2-dichlorobenzene derivatives to form *N*-unsubstituted carbazoles in good to excellent yields (Scheme 32). The first step was a palladium catalyzed *N*-arylation followed by an intramolecular direct Ar-Ar coupling *via* C-H activation. It is noteworthy that 1,2-dibromocyclopentene was also successfully employed in this reaction to give an indole product in 77% yield. This method was further illustrated with a large number of examples in a full paper.[45]

Cuny and co-workers reported a one-pot version of Sakamoto's method for the synthesis of both *N*-substituted and *N*-unsubstituted-α-carbolines (Scheme 33).[46] It was found that specific ligands were required for *N*-arylation and the cyclization step. The optimized protocol involves the use of triphenyl phosphine for the initial amination followed by the addition of a second ligand PCy_3-HBF_4 to effect the subsequent C-H activation reaction.

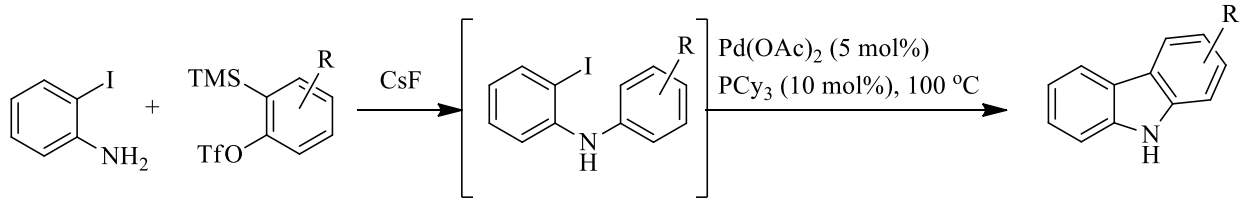


Scheme 32



Scheme 33

Larock group discovered that *N*-arylated *o*-iodoanilines could be accessed through coupling of *o*-iodoanilines with *in situ* generated benzynes (Scheme 34). Subsequent Pd-catalyzed cyclization *via* C-H activation gave carbazoles.[47] The reaction with an unsymmetrical benzyne was also examined and good regioselectivity was observed.



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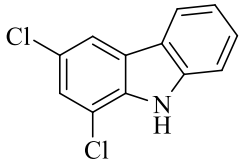
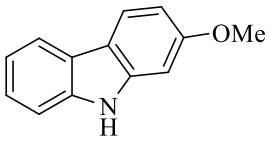
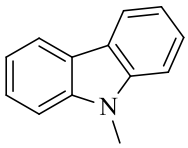


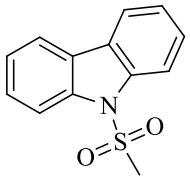
87%



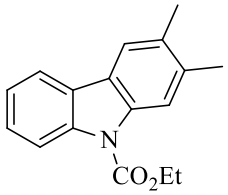
61% (5:1 regioselectivity)



82%



85%



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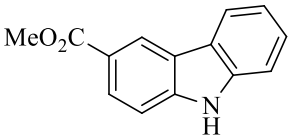
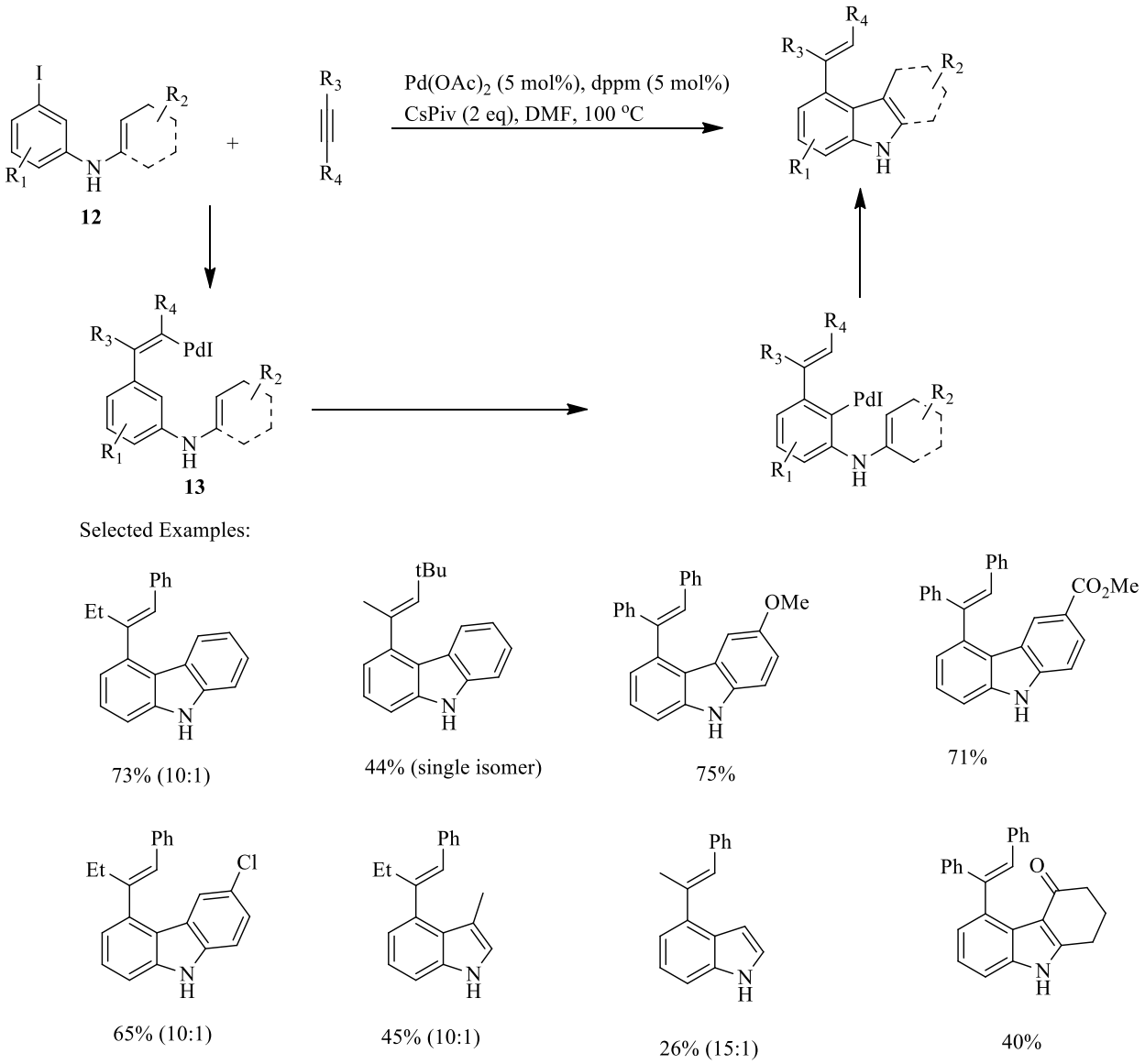


68%

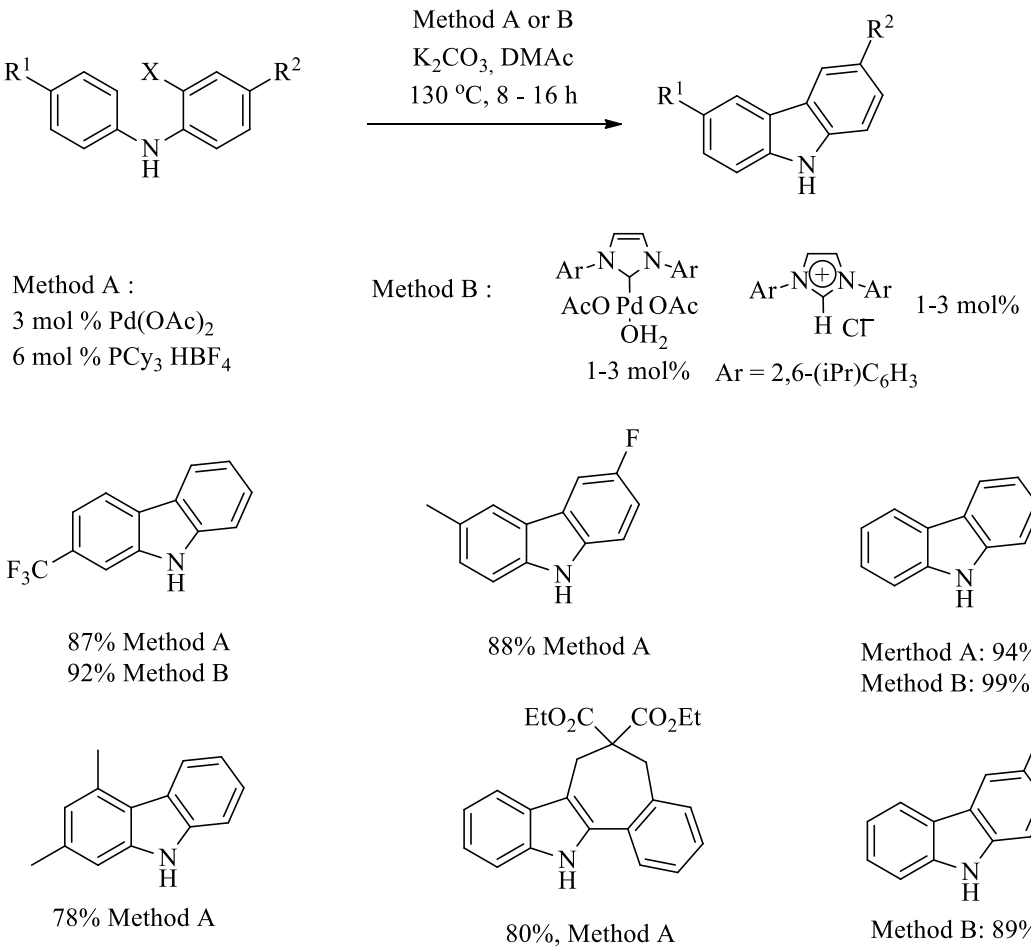
Scheme 34

The same group also engineered a carbazole synthesis involving a novel vinyl to aryl Pd migration mechanism (Scheme 35).[48] When compound **12** was reacted with alkynes under Pd(0) catalysis, *syn*-carbopalladation occurred to provide intermediate **13** which underwent a nitrogen-directed Pd migration to form an aryl-Pd intermediate. Subsequent intramolecular C-H activation and cyclization completed the carbazole synthesis. When an unsymmetrical alkyne was used, good to excellent regioselectivities could often be obtained for the initial carbopalladation: the smaller group preferentially ended up at the vinyl carbon connected to the phenyl ring. Starting with *N*-allyl substituted iodoanilines, indoles were also formed in modest yields.



Scheme 35

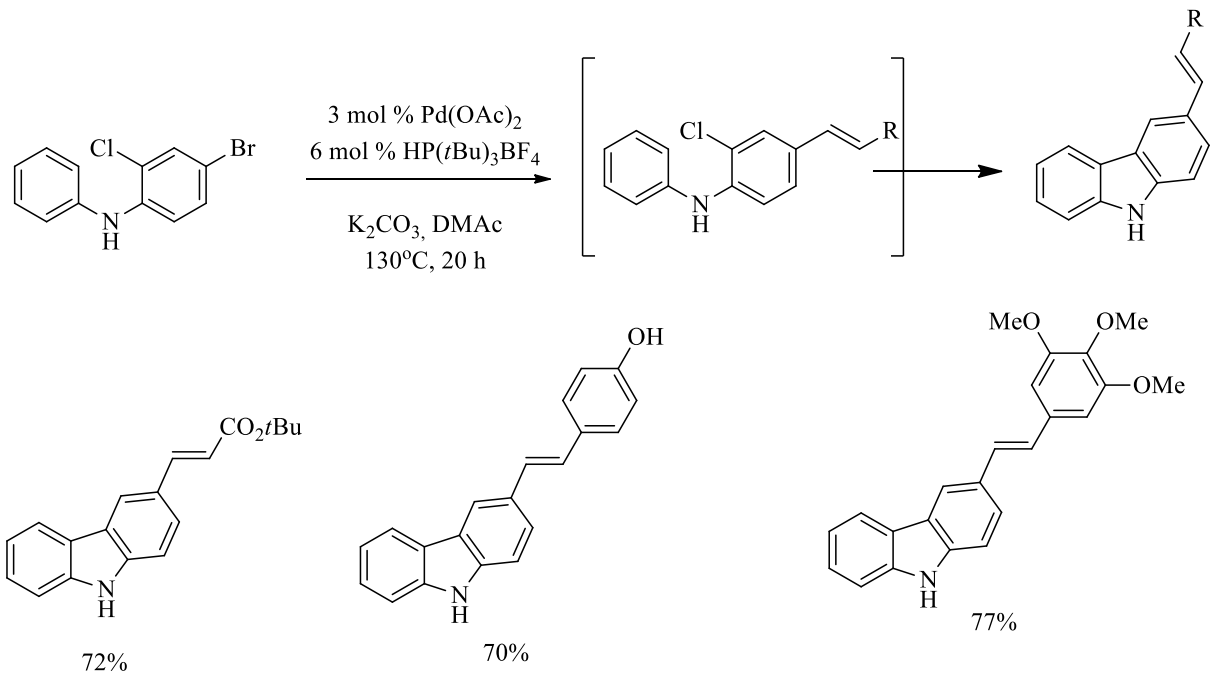
Fagnou and coworkers efficiently constructed the carbazole framework by using their palladium catalyzed intramolecular direct arylation method (Scheme 36).[49,50] The reaction was catalyzed by either $Pd(OAc)_2$/ PCy_3-HBF_4 (Method A) or an NHC-based ligand (Method B). Method B generally gave higher yields. Aryl chloride, bromide and iodide substrates all gave good yields of products, though iodides required the inclusion of 0.5 equiv of Ag_2CO_3. Mechanistic studies with related systems showed only a small preference for C-H activation of electron rich arenes over electron deficient systems. Furthermore, a strong primary kinetic isotope effect for the C-H bond was demonstrated. These observations support a σ-bond metathesis pathway for the C-H activation, but a mechanism through a S_E3 C-H functionalization step cannot be completely ruled out.



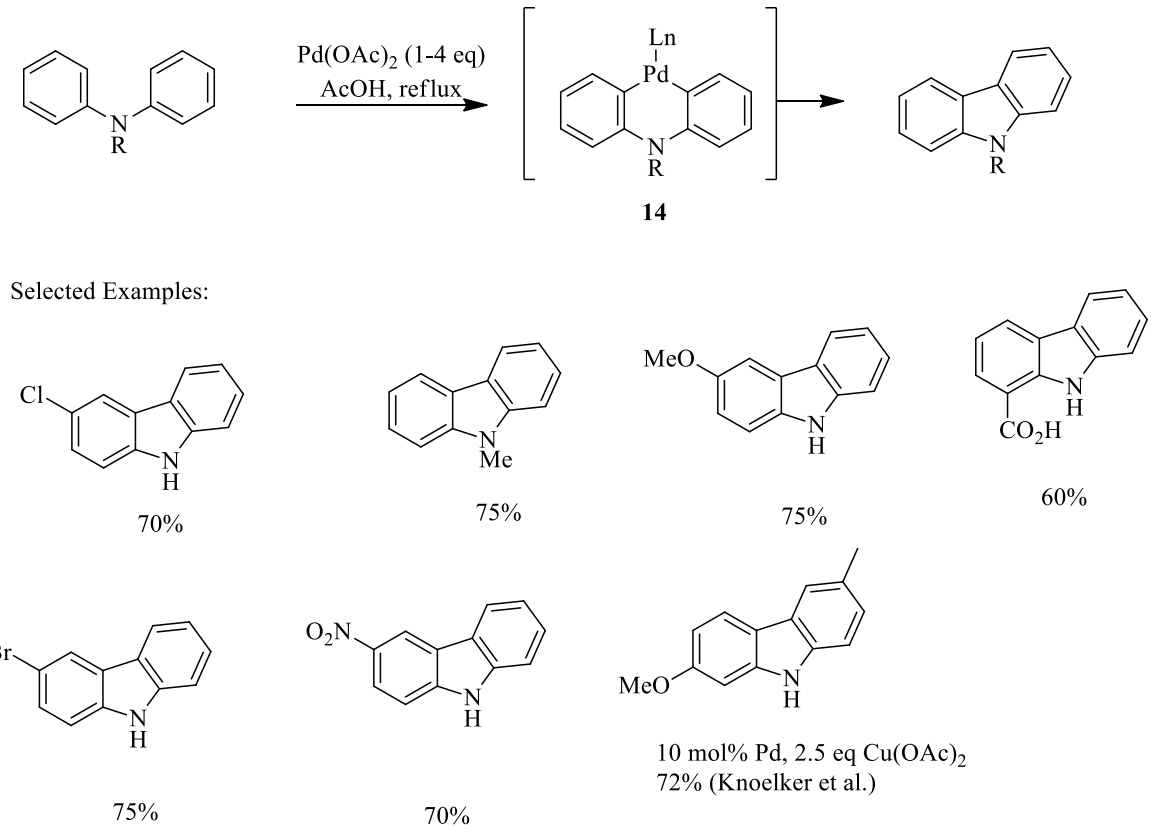
Scheme 36

Fagnou's group[51] further extended the usefulness of this methodology by identifying an optimized catalyst system for a tandem Heck/"direct arylation" sequence (Scheme 37). Several substituted carbazoles were synthesized using this protocol as shown below.

Direct coupling of two sp^2 carbon centers can also be achieved without the aid of any arene preactivation (e.g. *via* aryl halides). Intramolecular oxidative coupling of two aryl groups has been known for many years and applied to indole and carbazole synthesis. As early as in the 1970s, the Yashimoto and Åkermark groups[52] have shown that diphenyl ethers and diphenyl amines underwent intramolecular direct Ar-Ar coupling when treated with a stoichiometric amount of $Pd(OAc)_2$ in refluxing acetic acid (Scheme 38). A variety of carbazoles and dibenzofurans were prepared in good yields. Examples using a catalytic amount of Pd and stoichiometric $Cu(OAc)_2$ or oxygen were also reported.[53] The key step involves a double C-H activation to generate a palladacycle **14** which undergoes reductive elimination to furnish carbazoles.

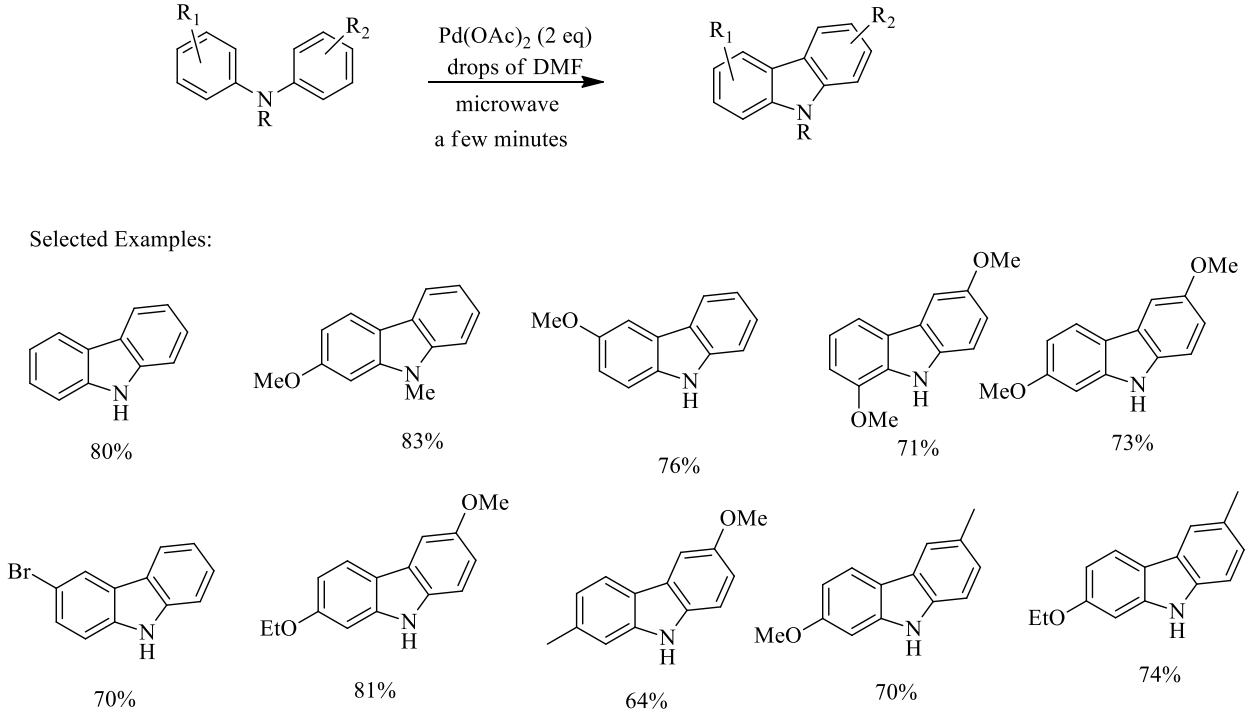


Scheme 37



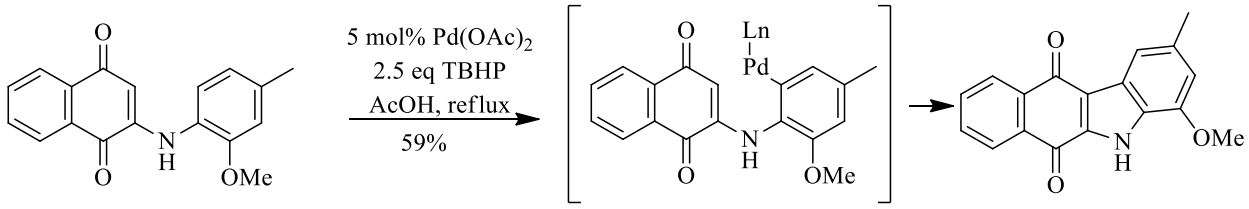
Scheme 38

Recently, microwave was shown to accelerate this reaction and allowed more efficient synthesis of oxygenated carbazoles (Scheme 39).[54] The reactions were conducted without added solvents, but it was discovered that the use of a small of amount of DMF did facilitate the reaction and avoided sparking during the microwave heating.



Scheme 39

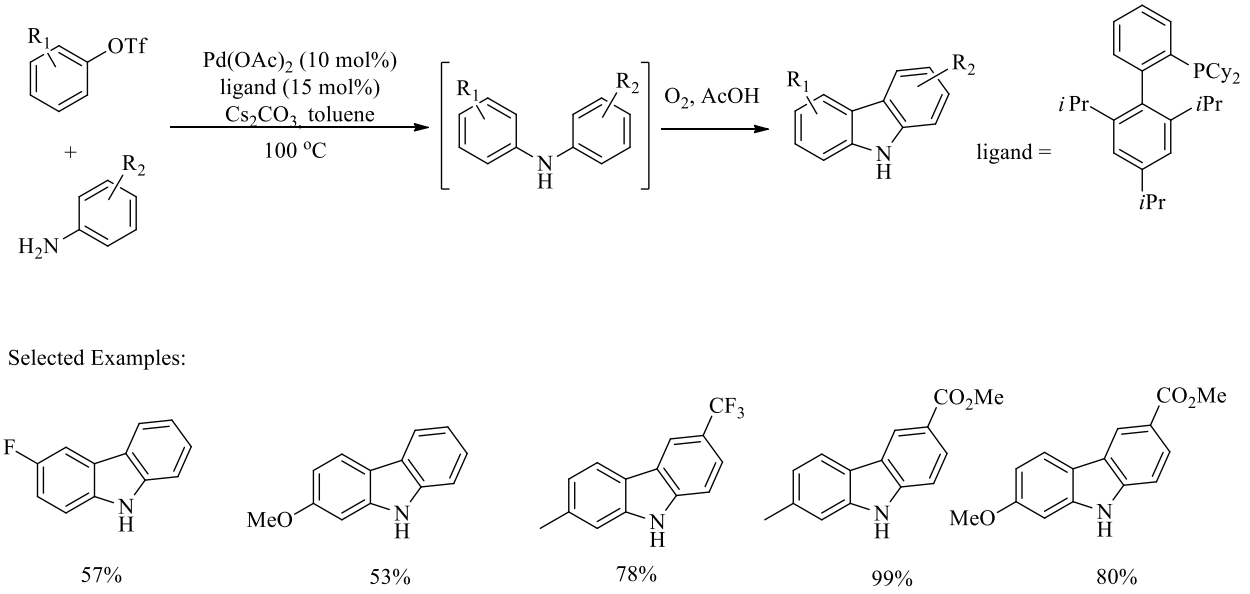
Similar reactions were used for synthesis of indolequinones with a catalytic amount of Pd with TBHP as the stoichiometric oxidant (Scheme 40).[55] The reaction most likely initiated with C-H activation on the aryl ring followed by a Heck cyclization onto the quinone.



Scheme 40

Ohno *et al*. developed a one-pot synthesis of carbazoles from aryl triflates and anilines involving the initial *N*-arylation and the subsequent oxidative Ar-Ar coupling (Scheme 41).[56] Air was conveniently used as the terminal oxidant for the Ar-Ar coupling reaction.[41] Aryl halides

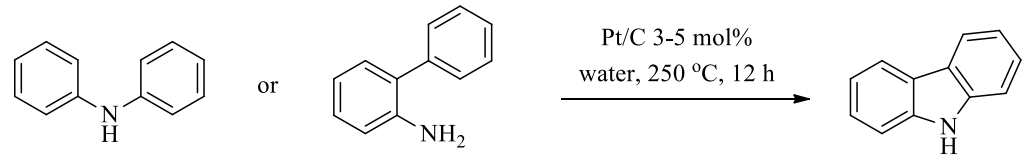
were found to be suitable for this one-pot protocol because the Ar-Ar coupling was known to be inhibited by halide ions generated in the *N*-arylation step.[57]



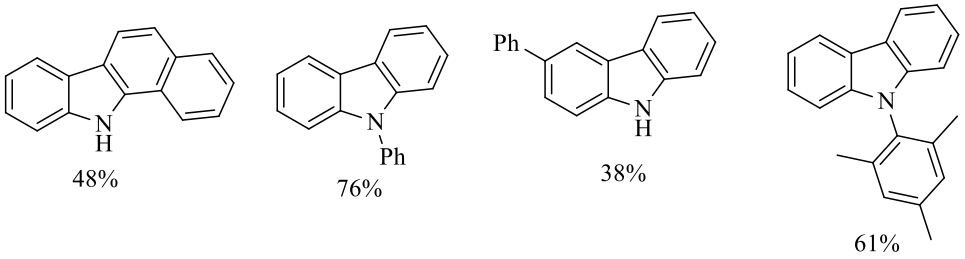
Scheme 41

The direct Ar-Ar coupling can also take place on the metal surface in a catalytic fashion. Matsubara and coworkers found that treatment of diphenylamines or 2-amino biphenyls with 3-5 mol% Pt/C in water at 250 °C, C-H activation occurred to give the carbazole products (Scheme 42).[58] Pd/C was less effective. The authors proposed that water served as an oxidant in the catalytic cycle to bring Pt (0) to Pt (II) which is the active species that breaks the C-H bond.

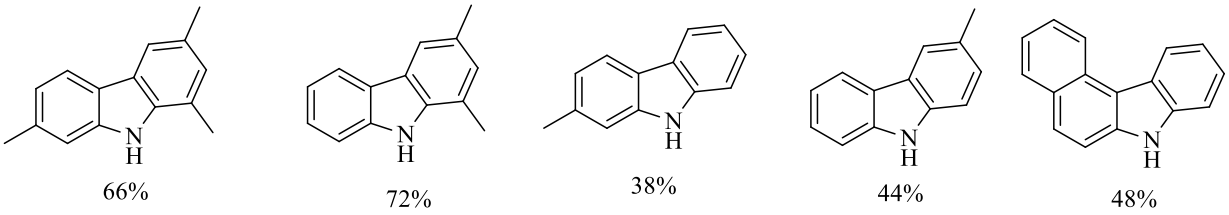
Fagnou's group conducted detailed study on the $Pd(OAc)_2$-catalyzed Ar-Ar coupling reactions and developed optimized conditions[59] that afforded better reproducibility, less side reactions, higher yields and wider scope, particularly for cyclization of electron-rich diaryl amines which proved to be challenging substrates (Scheme 43). The new conditions involve the use of 3-10 mol% $Pd(OAc)_2$, 10 mol% K_2CO_3, PivOH as the solvent and air as the oxidant.



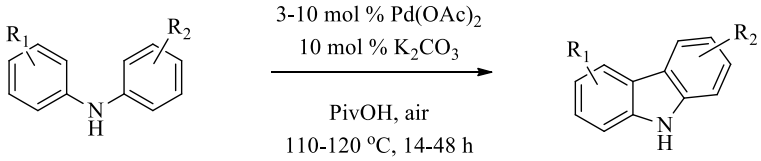
Selected Examples: (from diarylamines)



Selected Examples: (from 2-amino biphenyls)



Scheme 42



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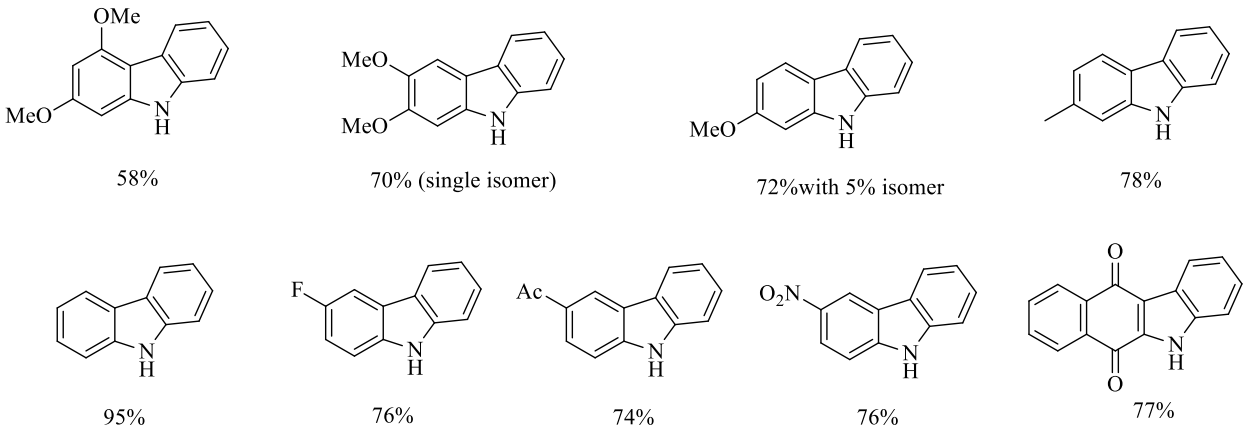
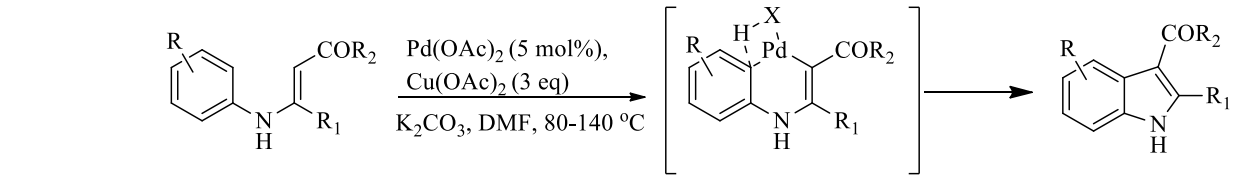
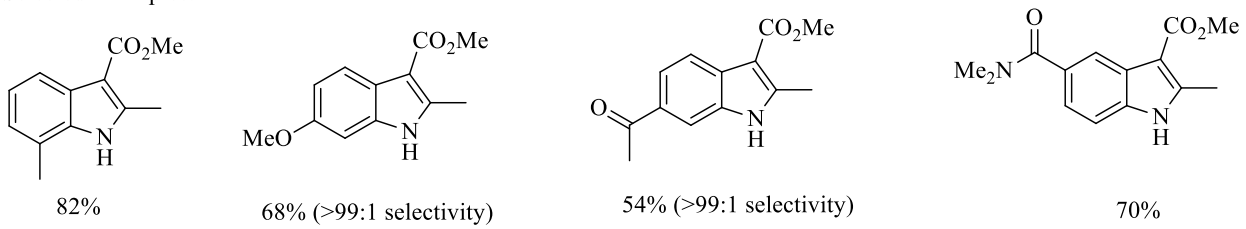


Scheme 43

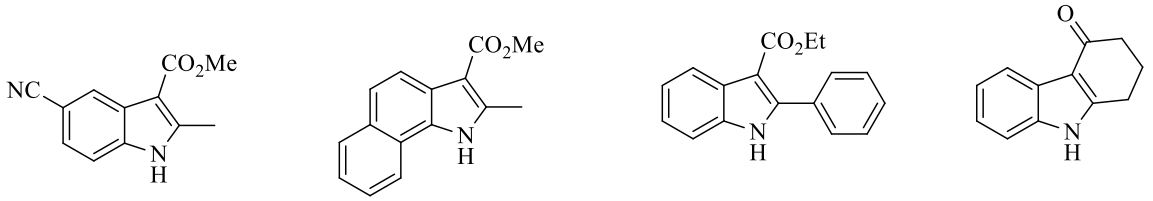
Recently, Glorius and coworkers developed a palladium-catalyzed oxidative cyclization of *N*-aryl enamines for preparation of indoles through intramolecular C-H activation (Scheme 44).[60] The one-pot version of the reaction starting from commercially available anilines was also demonstrated. For *meta*-substituted anilines, the less hindered position was alkylated with excellent selectivities. The proposed mechanism suggested that the reaction initiated with an electrophillic palladation of the nucleophilic enamine followed by deprotonation to form a palladium complex that participated in a C-H bond activation on the aniline moiety. Then reductive elimination afforded the indole product. Pd(0) was re-oxidized to Pd(II) by $Cu(OAc)_2$ to complete the catalytic cycle.



Selected Examples:

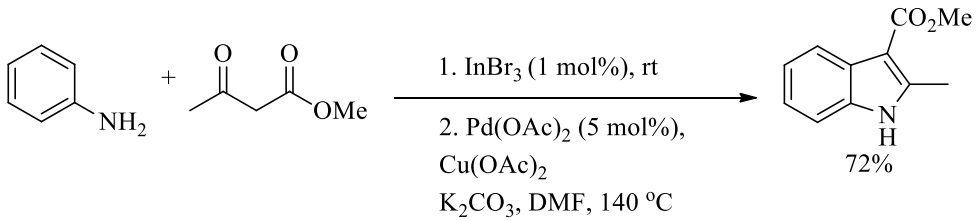


82% 68% (>99:1 selectivity) 54% (>99:1 selectivity) 70%



65% 85% (>99:1 selectivity) 68% 85%

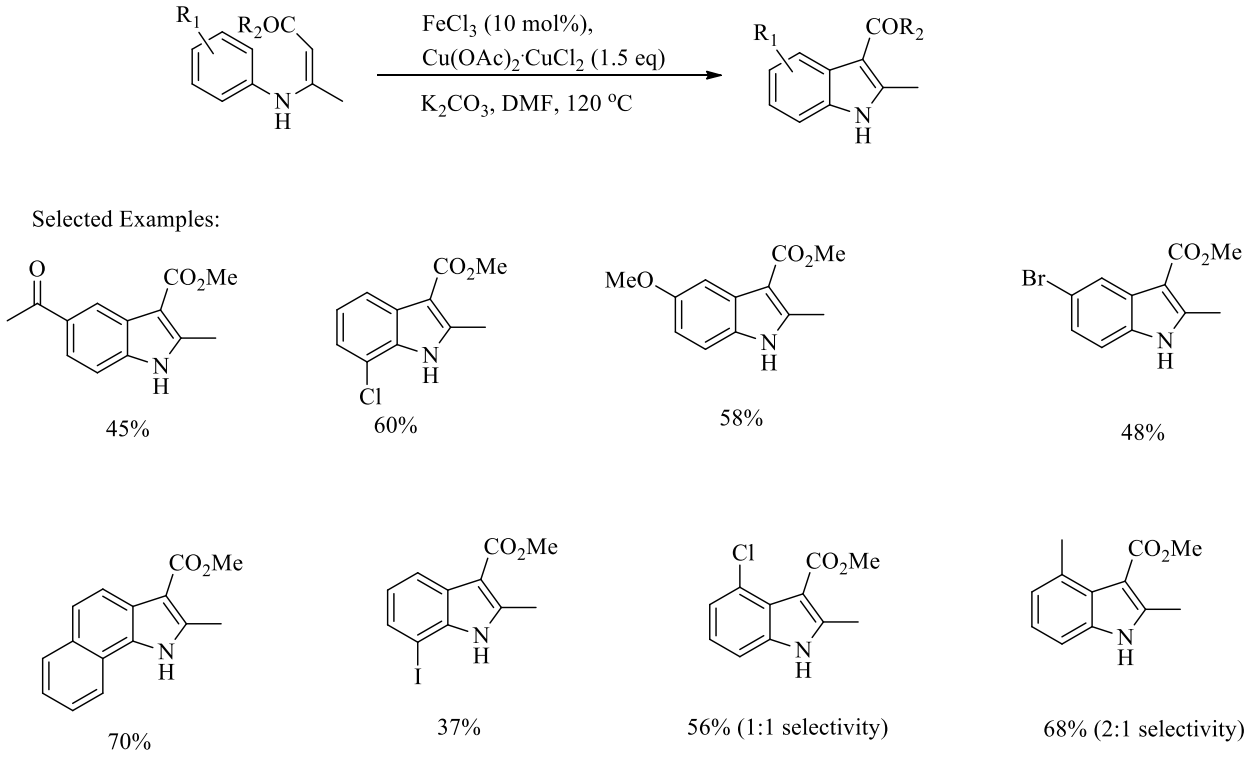
One-pot Version:



72%

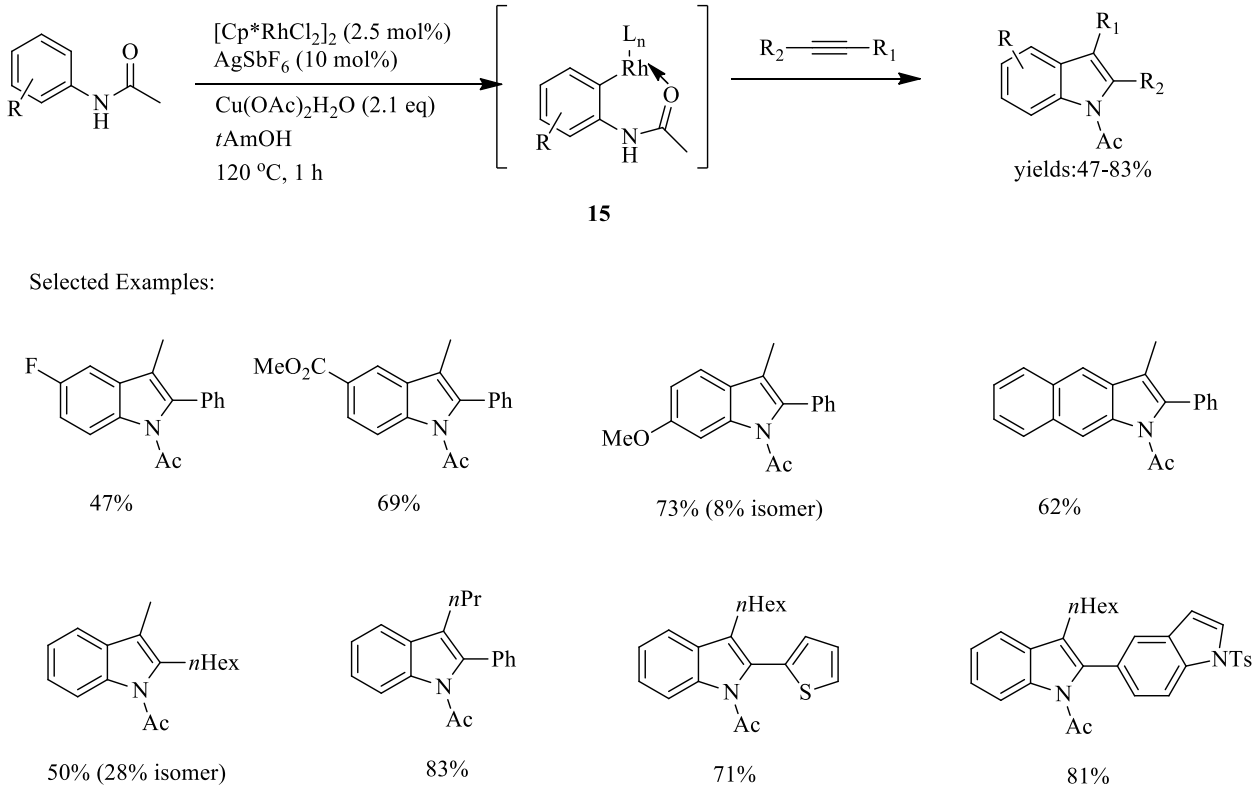
Scheme 44

Liang *et al.* demonstrated that oxidative cyclization of *N*-aryl enamines into indoles could also be achieved with iron catalysis (Scheme 45).[61] After an extensive screen of iron salts and copper oxidants, it was found that with a combination of $FeCl_3$ (10 mol%), $Cu(OAc)_2{\cdot}CuCl_2$ (1.5 eq), K_2CO_3 (3 eq) in DMF at 120 ºC, the direct coupling of two sp2 carbons took place to furnish indole products in moderate to good yields. Unlike the Pd-catalyzed reaction, for *meta*-substituted substrates, little regioselectivities were obtained.



Scheme 45

Fagnou and co-workers[62] reported an interesting rhodium-catalyzed intermolecular cyclization between alkynes and *N*-acetyl anilines (Scheme 46). The key step is an acetamide directed C-H insertion reaction to give reactive intermediate **15**. Isotope study using a *meta*-substituted anilide suggested that the rhodation occurred initially at the sterically more hindered position and was reversible, but the alkyne eventually reacted with the less hindered aryl rhodium intermediate. As a result, *meta*-substituted substrates gave good selectivity for the sterically more accessible position. When an unsymmetrical alkyne was used, the larger group ended up at the C2 position of indole.

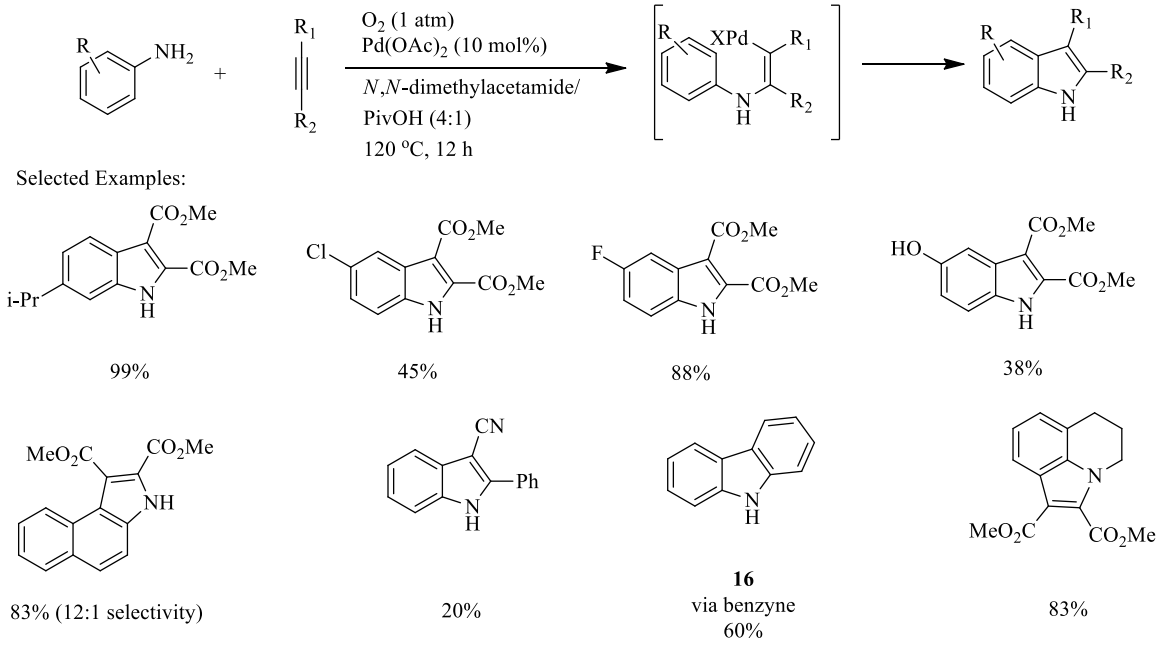


Scheme 46

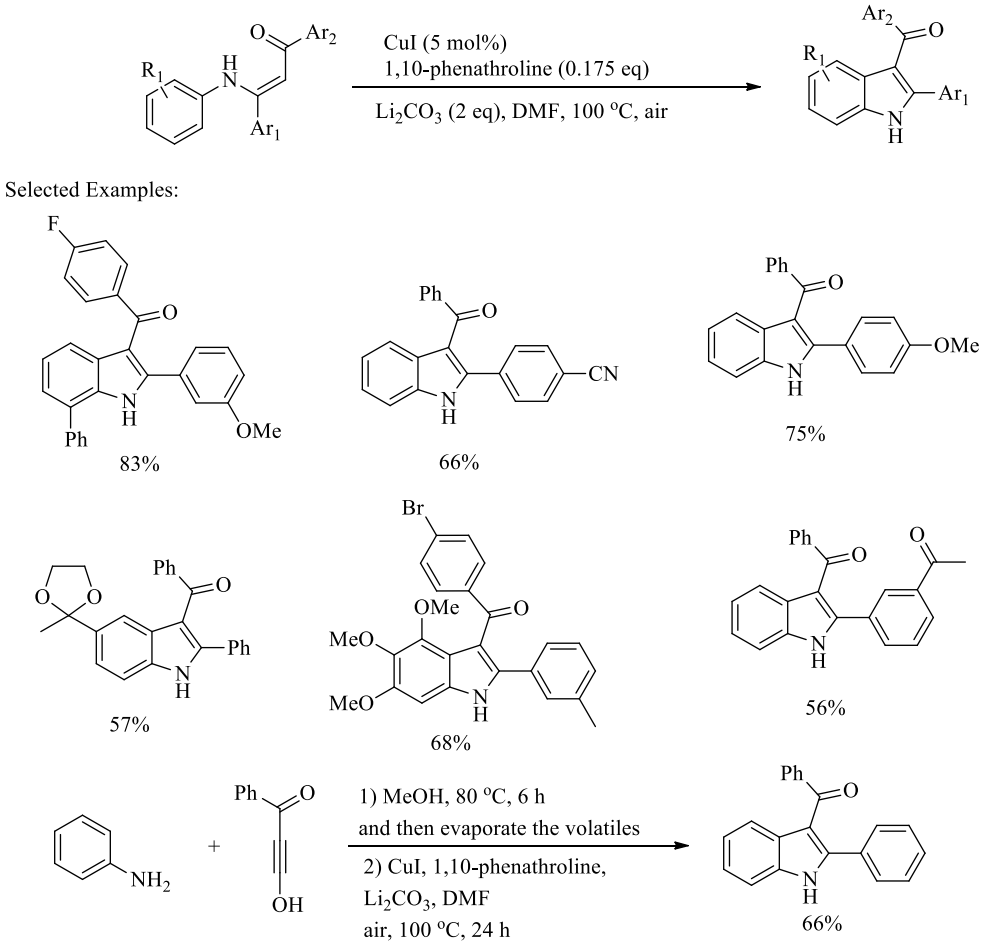
Recently, Jiao and coworkers[63] reported an indole synthesis from simple anilines and alkynes through a catalytic C-H activation reaction without the need for an *ortho* directing group (Scheme 47). It was found that aniline can be activated by treatment of 10 mol% $Pd(OAc)_2$ and using O_2 as the oxidant. The best solvent system for this transformation was a 4:1 mixture of DMF and PivOH.

A wide range of electron-withdrawing or electron-donating groups were tolerated on the aniline. For *meta*-substituted anilines, the C-H functionalization occurred at the sterically less congested position with good selectivities. On the alkyne side, a variety of internal alkynes were successfully employed to give the corresponding indoles. It is interesting to note that even benzyne was suitable for this reaction to give carbazole **16** in 60% yield. The utility of this method was further illustrated by the total synthesis of two biologically active compounds.

Cyclization of enamines onto unactivated arenes was also amenable to copper catalysis as nicely demonstrated by Cacchi and coworkers (Scheme 48).[64] A variety of 2,3-disubstituted indoles were constructed from enaminones by using catalytic amounts of CuI and 1,10-phenathroline in DMF at 100 °C under an atmosphere of air. A wide range of functional groups were compatible with the reaction conditions. It was further shown that enaminone formation and the cyclization can also be carried in a one-pot fashion (with a necessary solvent switch from methanol to DMF).

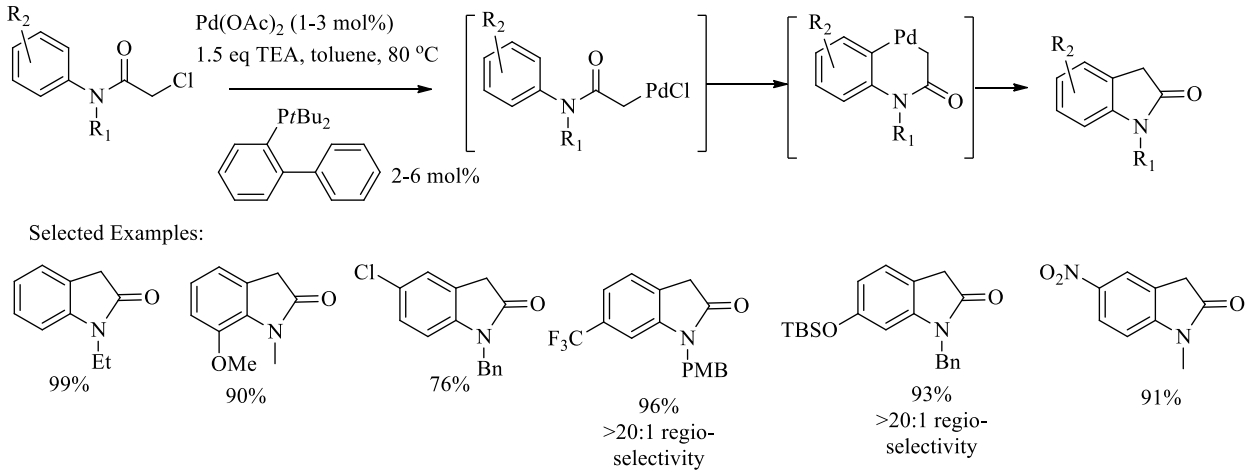


Scheme 47



Scheme 48

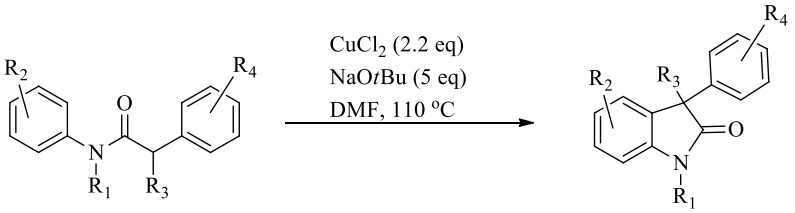
Buchwald group developed a novel oxindole synthesis from α-chloroacetanilides *via* a Pd-catalyzed C-H activation reaction (Scheme 49).[65] When *N*-alkyl-α-chloroacetanilides were treated with catalytic amounts of $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl ligand and 1.5 eq of TEA, oxindoles were obtained in good to excellent yields. Excellent regioselectivities were observed for reactions with *meta*-substituted substrates, favoring the C-H functionalization at the sterically less hindered position of the arene. It was found that *N*-H or *N*-acyl substrates did not participate in this transformation. It was proposed that the first step of the reaction involves the oxidative insertion of Pd(0) into the C-Cl bond to generate a Pd-enolate which subsequently activated the C-H bond ortho to the amide to afford a six-membered palladacycle. Reductive elimination gave the oxindole products.



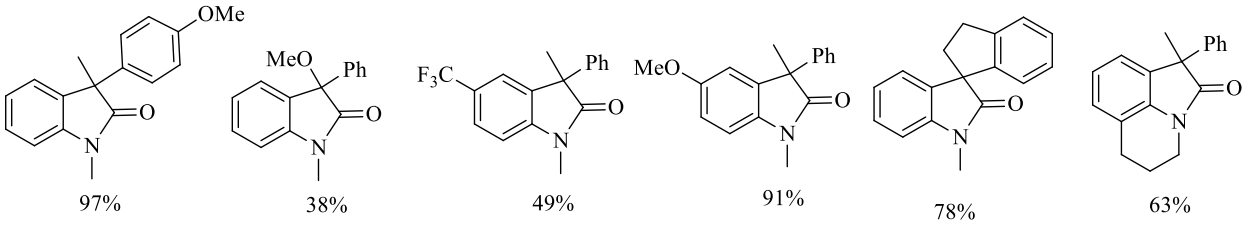
Scheme 49

Kündig group investigated the oxidative cyclization of α-aryl substituted anilide substrates and discovered that with a copper catalyst, the direct C-H/Ar-H coupling could be effected to furnish oxindole products in good to excellent yields (Scheme 50).[66] The transformation was initially achieved using $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as the oxidant. But it was later found that Pd was not necessary for this reaction and the same yields of oxindoles were obtained with a copper salt alone. These observations as well as other experimental data suggested a radical cyclization mechanism rather than the initially hypothesized Pd-catalyzed C-H activation pathway.

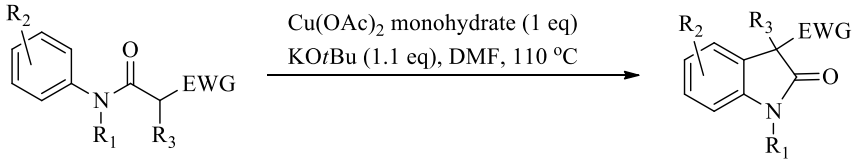
Taylor's group found that when an electron-withdrawing group was present at the α-position of anilides, intramolecular direct C-H/Ar-H coupling could be achieved to form oxindoles under the influence of $Cu(OAc)_2$ (Scheme 51).[67] It was further demonstrated that the α-alkylation of 1,3-dicarbonyl compounds and the subsequent cyclization could be telescoped into a one-pot operation. Additionally, when a *t*-Bu ester was used, the cyclized products were readily hydrolyzed and decarboxylated to give 3-monoalkyl oxindoles as shown in the scheme. Consistent with Kündig's oxindole synthesis, a radical-based mechanism was proposed for this copper-mediated cyclization.



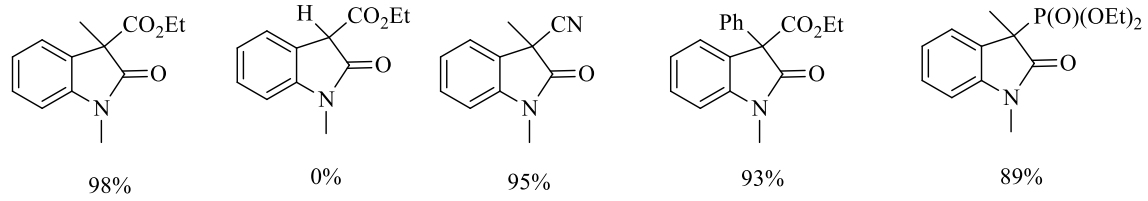
Selected Examples:



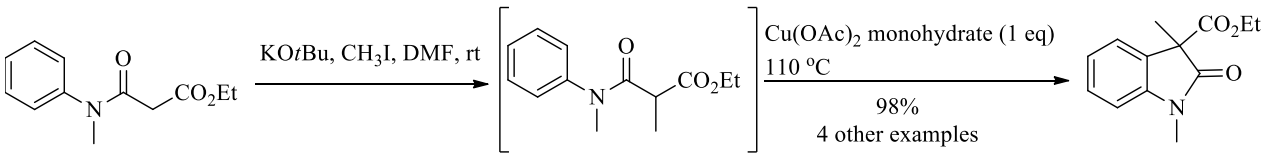
Scheme 50



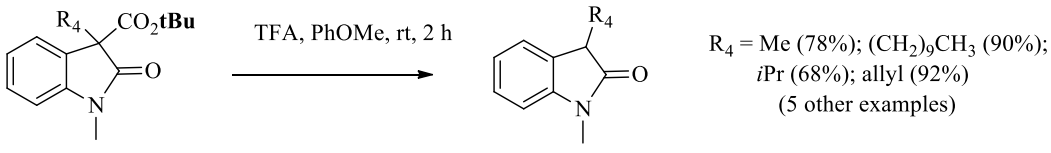
Selected Examples:



Telescoped alkylation-cyclization sequence:

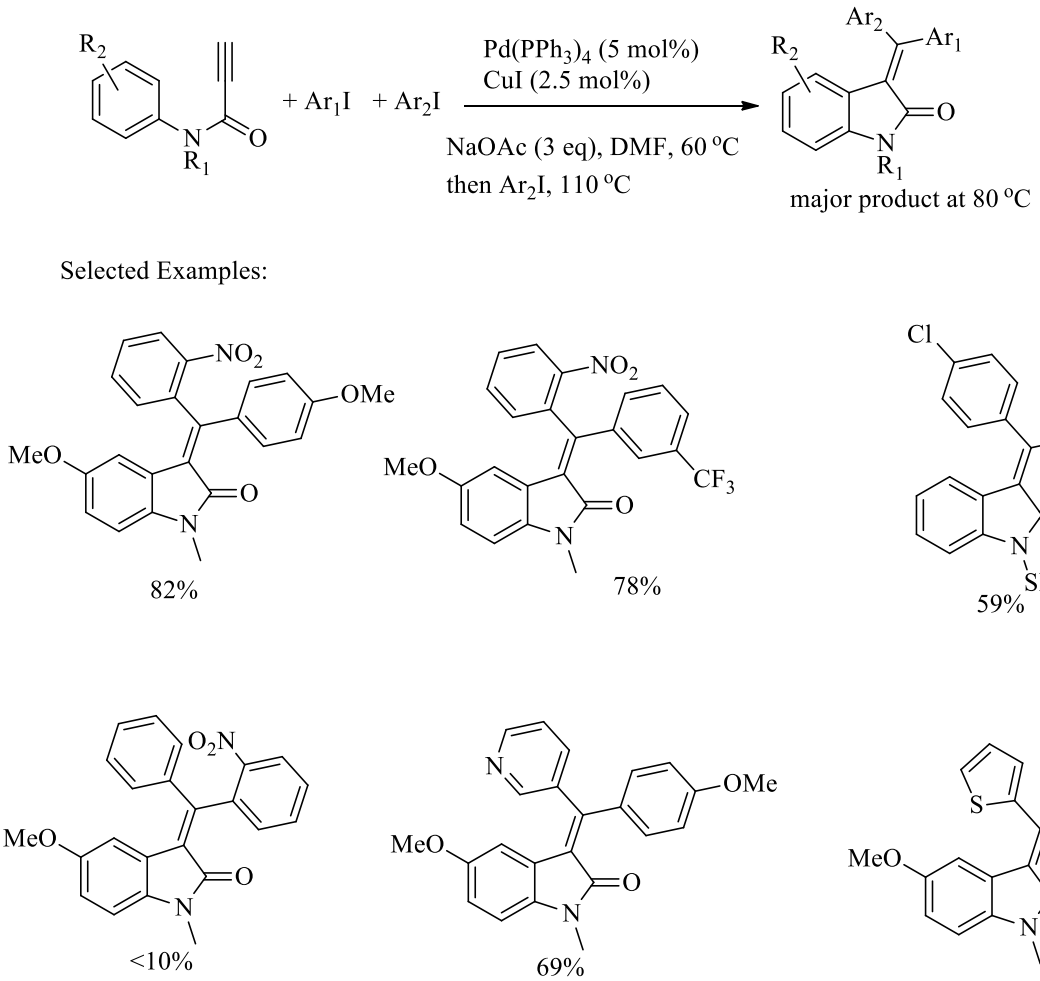


Decarboxylation:



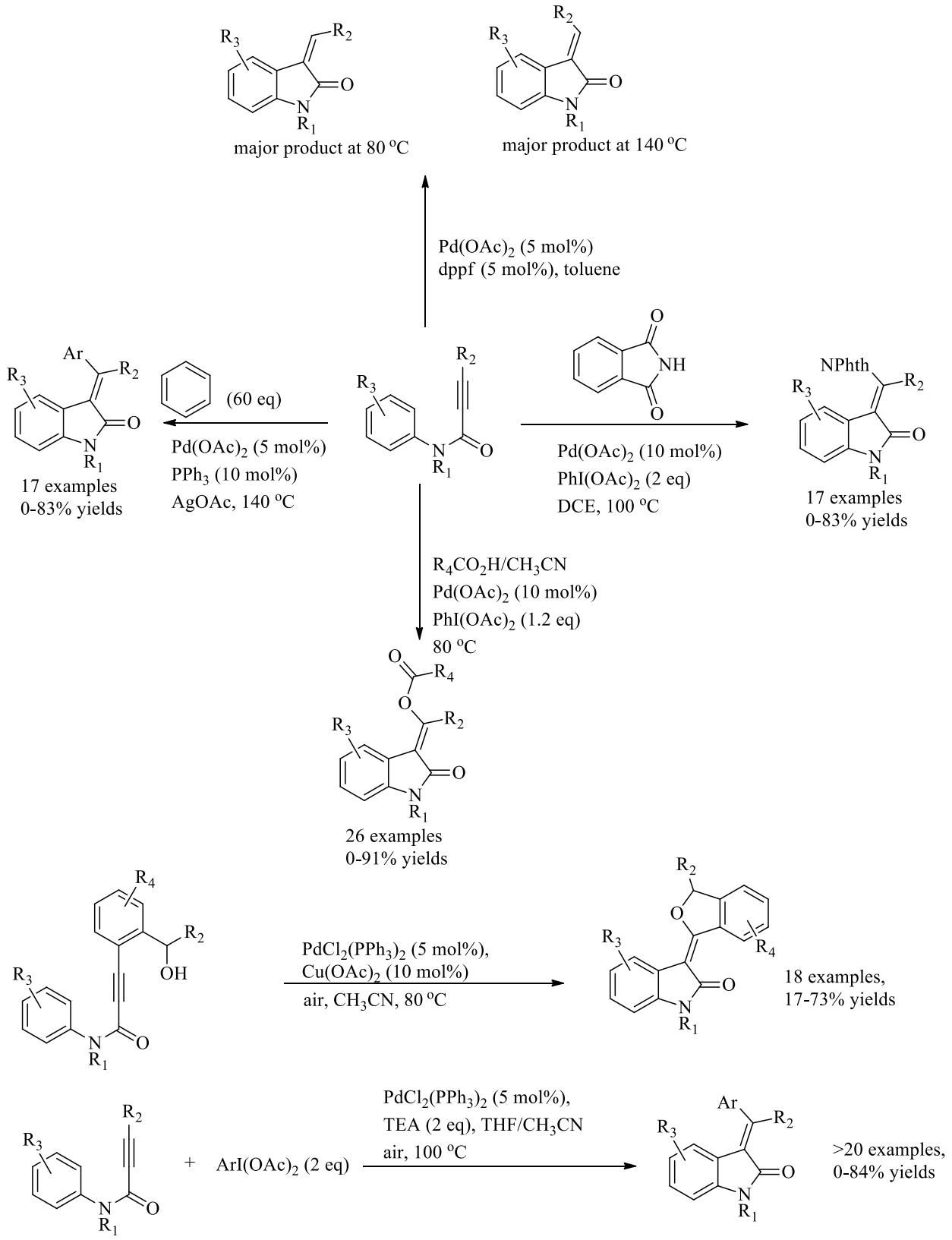
Scheme 51

Zhu's group reported a three-component, one-pot oxindole synthesis *via* a sequence of Sonogashira coupling, carbopalladation, C-H activation and C-C bond formation using a single Pd catalyst (Scheme 52).[68] Using this method, a large number of highly substituted oxindoles were prepared in good to excellent yields in one step. The geometry of the newly formed double bond was defined *via* the *syn* insertion of the Ar_2-Pd-I intermediate onto the Ar_1-substituted triple bond. Another variant of this multi-component oxindole formation was also developed involving *N*-arylation, carbopalladation and C-H functionalization.[68c]



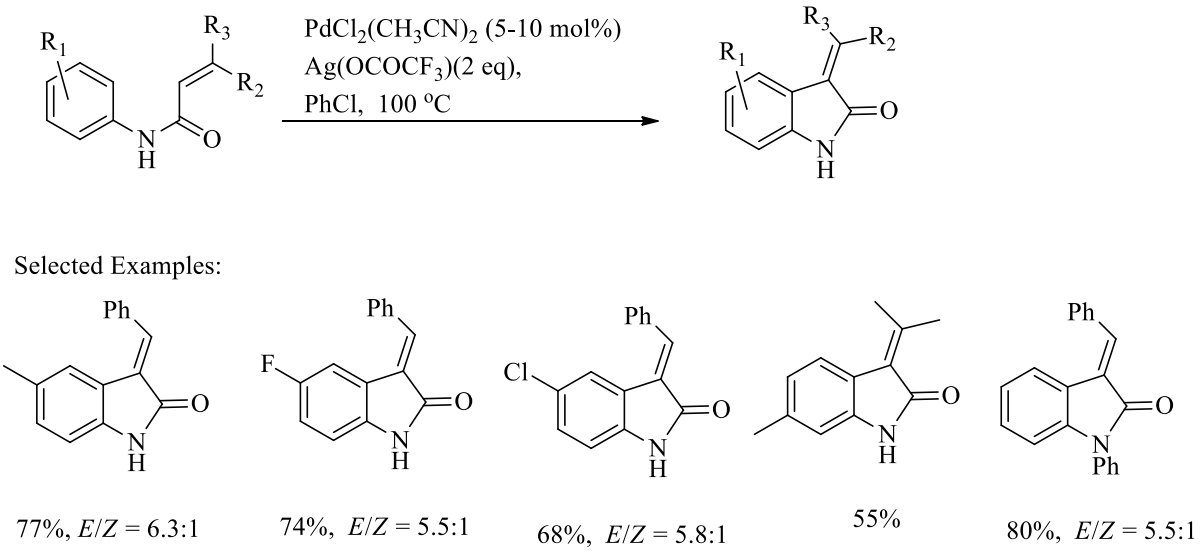
Scheme 52

Several related domino processes were described by Li and coworkers as summarized in Scheme 53. For example, it was shown that the cascade bond-forming event could be initiated by the *syn*-aminopalladation or acetoxypalladation of the triple bond to yield a vinyl Pd intermediate that underwent intramolecular C-H activations for the oxindole ring formation.[69] With an internal oxygen nucleophile tethered with the propiolamide, a cascade process was achieved to form two rings (oxindole and benzofuran) simultaneously in the product.


major product at 80 °C
major product at 140 °C
Pd(OAc)2 (5 mol%)
dppf (5 mol%), toluene
(60 eq)
Pd(OAc)2 (5 mol%)
PPh3 (10 mol%)
AgOAc, 140 °C
17 examples
0-83% yields
Pd(OAc)2 (10 mol%)
PhI(OAc)2 (2 eq)
DCE, 100 °C
17 examples
0-83% yields
R4CO2H/CH3CN
Pd(OAc)2 (10 mol%)
PhI(OAc)2 (1.2 eq)
80 °C
26 examples
0-91% yields
PdCl2(PPh3)2 (5 mol%),
Cu(OAc)2 (10 mol%)
air, CH3CN, 80 °C
18 examples,
17-73% yields
PdCl2(PPh3)2 (5 mol%),
TEA (2 eq), THF/CH3CN
air, 100 °C
ArI(OAc)2 (2 eq)
>20 examples,
0-84% yields

Scheme 53

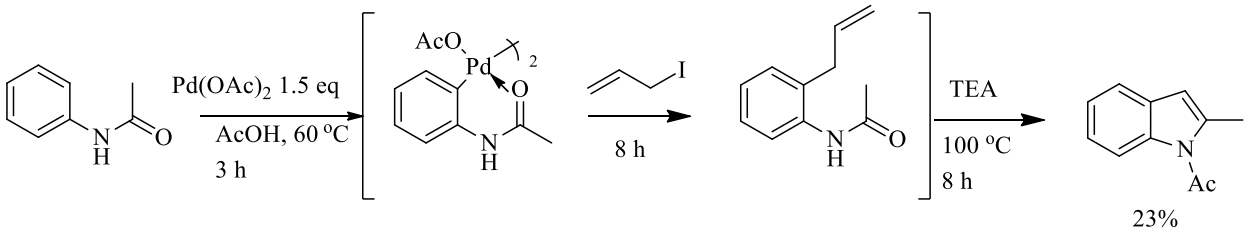
Nagasawa *et al*. reported that oxindoles can be formed *via* a Pd-catalyzed *ortho*-aromatic C-H activation followed by an intramolecular Heck reaction (Scheme 54).[70] When *N*-cinnamoylanilines were treated with $PdCl_2(CH_3CN)_2$ (5-10 mol%) and $Ag(OCOCF_3)$ (2 eq) in chlorobenzene at 110 ºC, aromatic C-H alkenylation took place to give a range of oxindole products in good yields as well as good *E*-selectivities with respect to the olefin driven by the higher thermodynamic stability of the *E*-double bond.



Scheme 54

4. Transition-metal Catalyzed C-H Amination

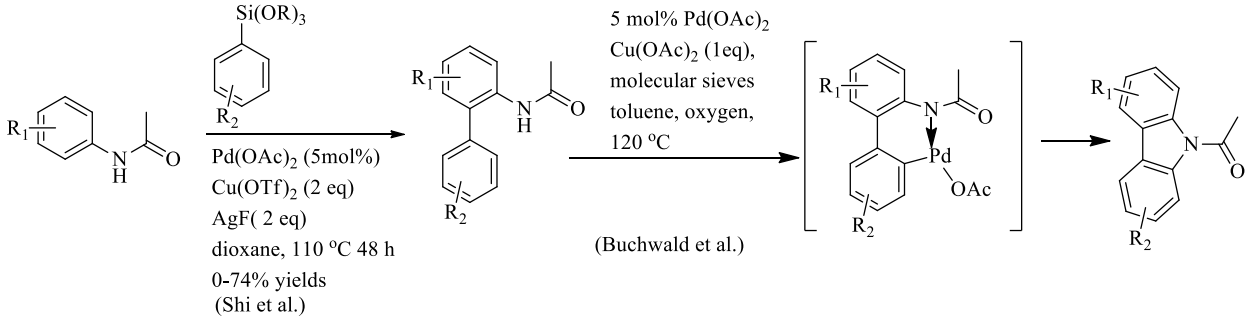
Acetamide is a known directing group for *ortho*-metallation of aromatic rings.[71] Tremont and coworkers demonstrated that with a stoichiometric amount of $Pd(OAc)_2$, the ortho position of acetanilides can be activated to form aryl palladium species which can then be alkylated with alkyl halides such as allyl iodide (Scheme 55). Addition of triethylamine into the same pot promoted the Heck cyclization to form an indole product in 23% yield.



Scheme 55

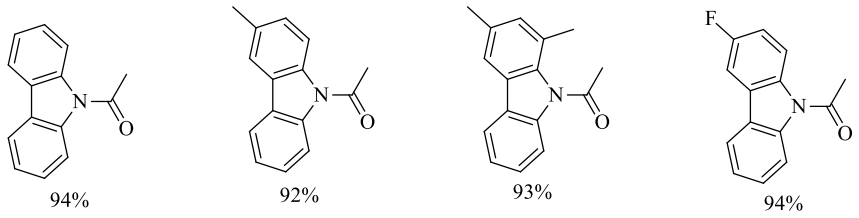
Buchwald et al.[72,73] investigated the synthesis of carbazoles from 2-acetaminobiphenyls *via* a similar *ortho*-palladation reaction (Scheme 56). It was found that heating 2-acetaminobiphenyls in the presence of 5 mol% $Pd(OAc)_2$ and a catalytic amount of $Cu(OAc)_2$ under an atmosphere of oxygen at 120 °C gave high yields of carbazoles (Scheme 30). The requisite 2-acetaminobiphenyls can be synthesized from *o*-halo-*N*-acetyl anilines by using standard cross-coupling reactions or more interestingly, from simple acetanilides by C-H activation as recently described by Shi and coworkers.[74]

The proposed mechanism of the C-N bond formation involves the pre-association of the Pd (II) acetate with acetamide and the subsequent directed palladation. Then reductive elimination leads to the formation of the desired carbazoles and Pd (0), which can be oxidized back to Pd (II) by $Cu(OAc)_2$. This method tolerates electron-rich and electron-deficient substitutions on both rings.

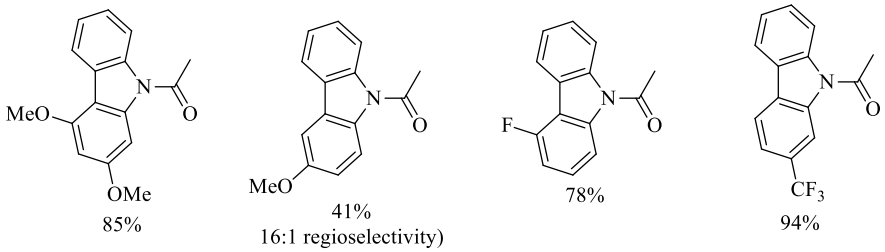


Selected Examples:

With R_1 substitutions:

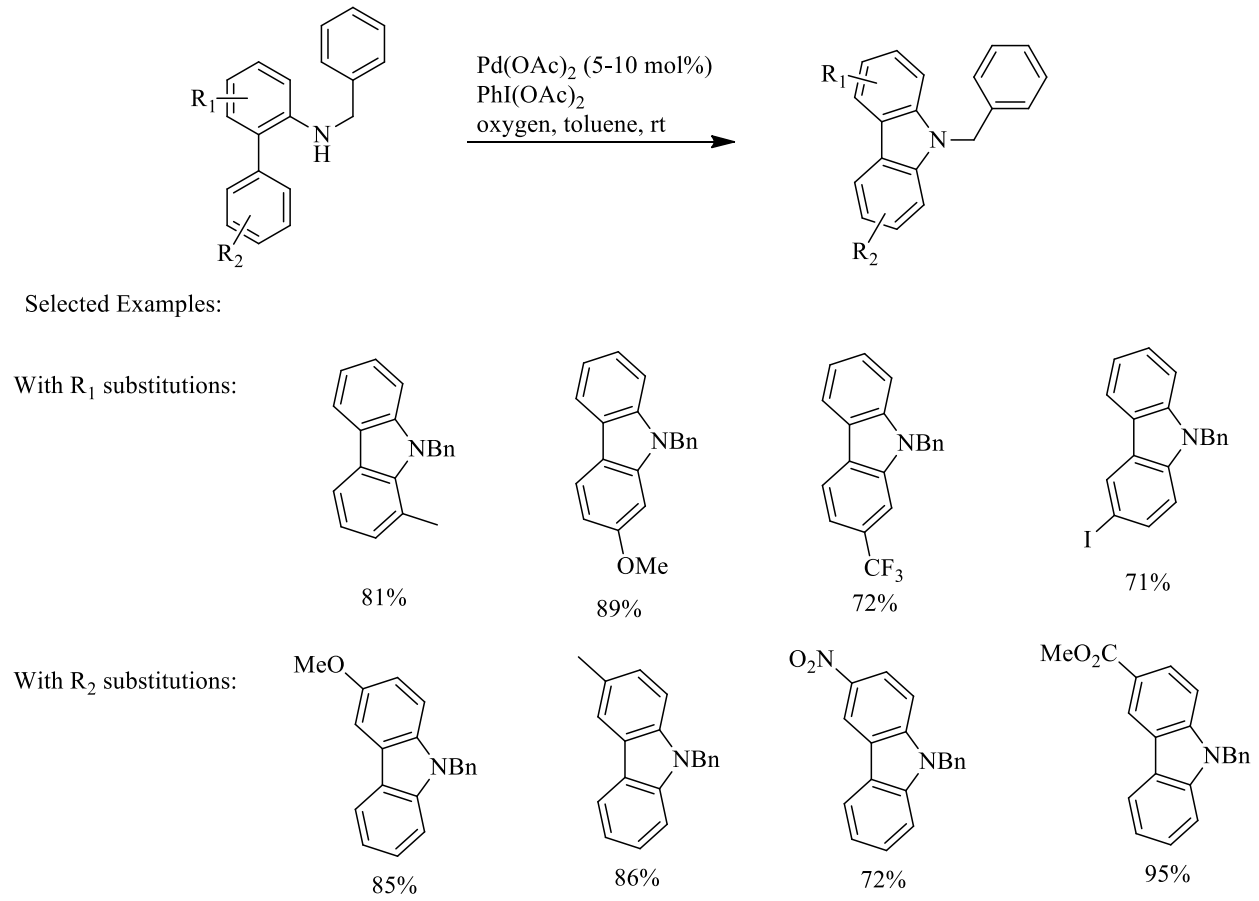


With R_2 substitutions:



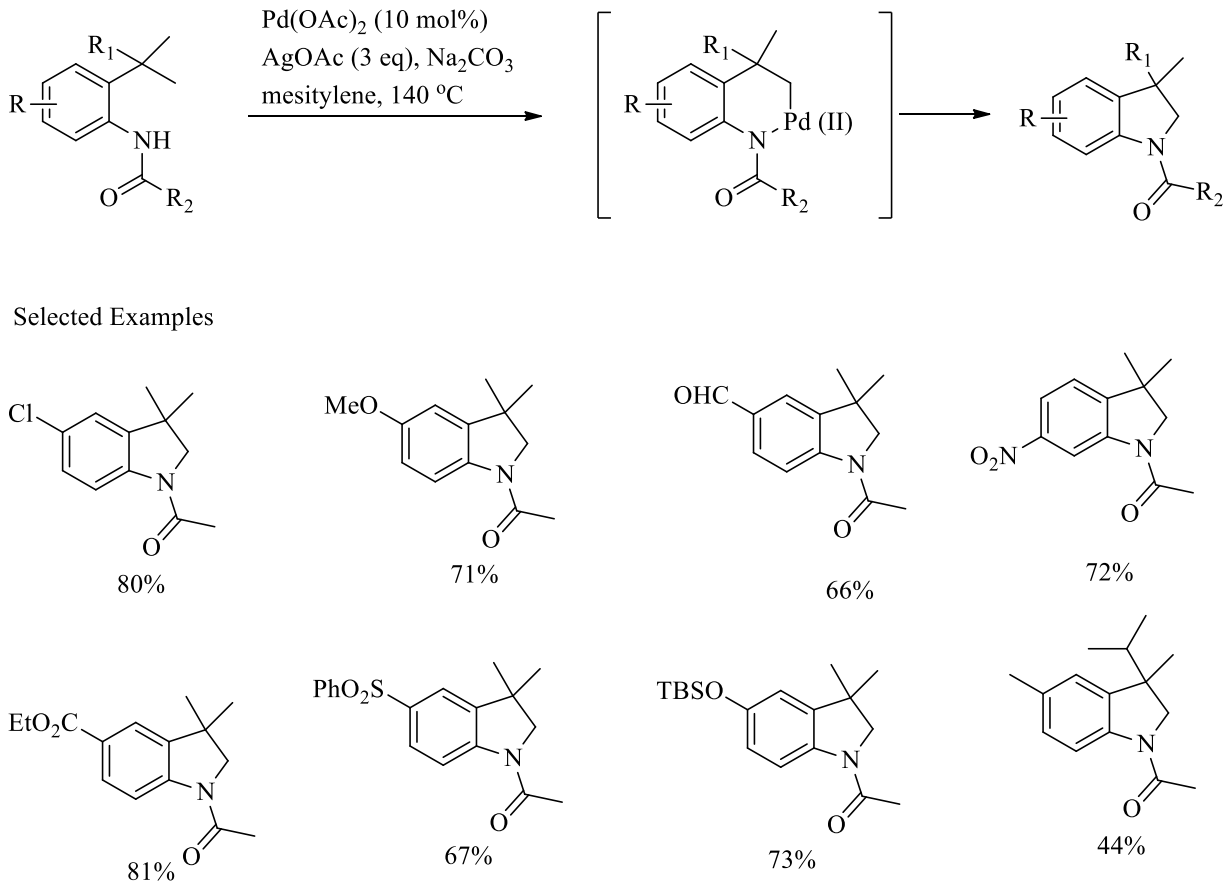
Scheme 56

Gaunt and coworkers[75] engineered a carbazole synthesis by treatment of *N*-benzyl biphenyls with a catalytic amount of $Pd(OAc)_2$ with $PhI(OAc)_2$ as the stoichiometric oxidant (Scheme 57). Amazingly, the reaction can be carried out at room temperature. This reaction is mechanistically distinct from Buchwald's method in that the current method is based on a C-H activation reaction through a Pd (II)/Pd (IV) catalytic cycle. Electron-donating substituents on the nitrogen such as a benzyl group facilitated the reaction. The corresponding acetamide did not give any appreciable amount of carbazole product.



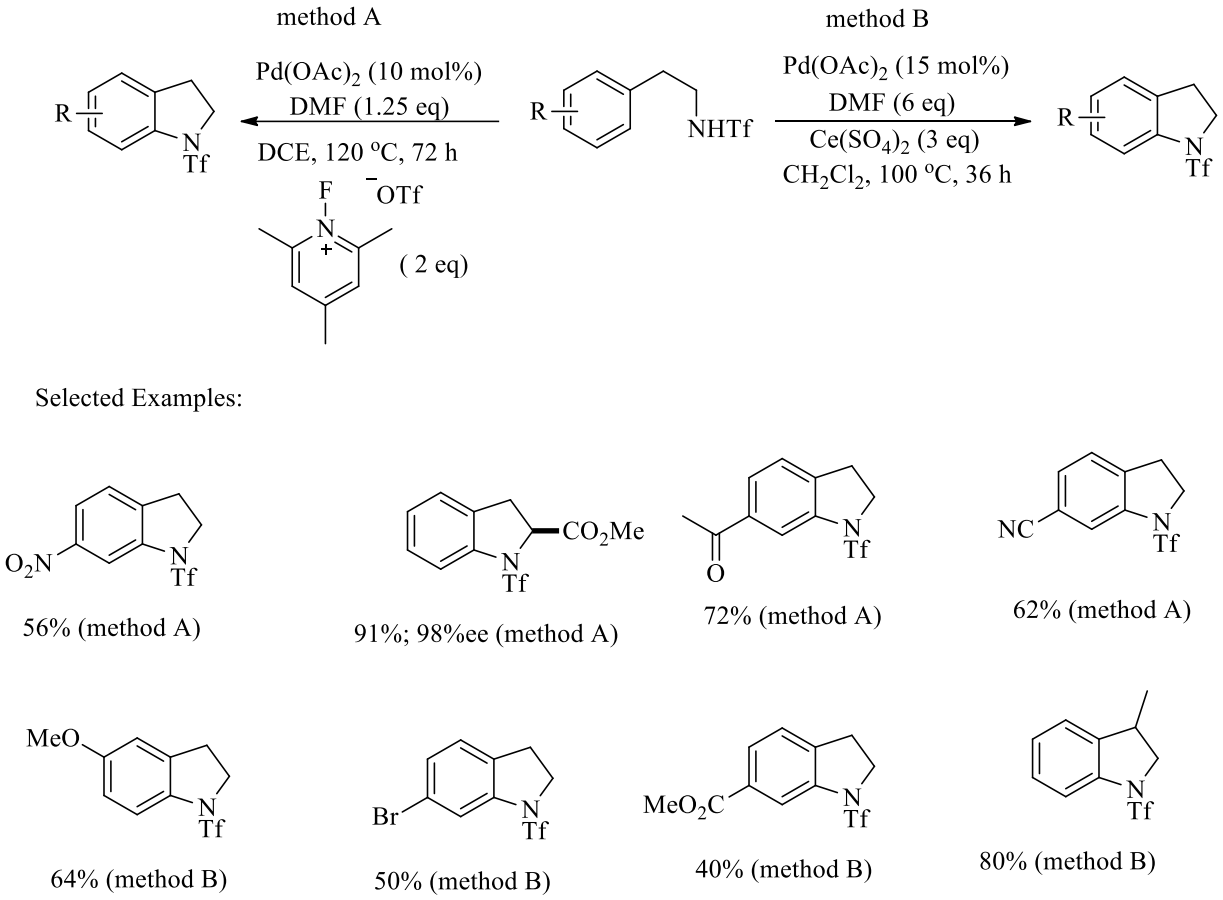
Scheme 57

Glorius *et al.* discovered an indoline synthesis *via* an amide-directed, palladium-catalyzed amination of unactivated C(sp3)-H bonds (Scheme 58).[76] The nature of the capping group on the nitrogen was critical for the reaction. Acetyl group was found to be the most effective, while many other groups such as pivaloyl (Piv) , benzoyl (Bz) , trifluoroacetyl, Boc, CO_2Me, *p*-tolunesulfonyl, methanesulfonyl, 2-nitrophenylsulfonyl (Ns), triflate, Me, benzyl (Bn) or H gave less than 1% of indoline product. A variety of functionalities were tolerated on the aromatic ring.



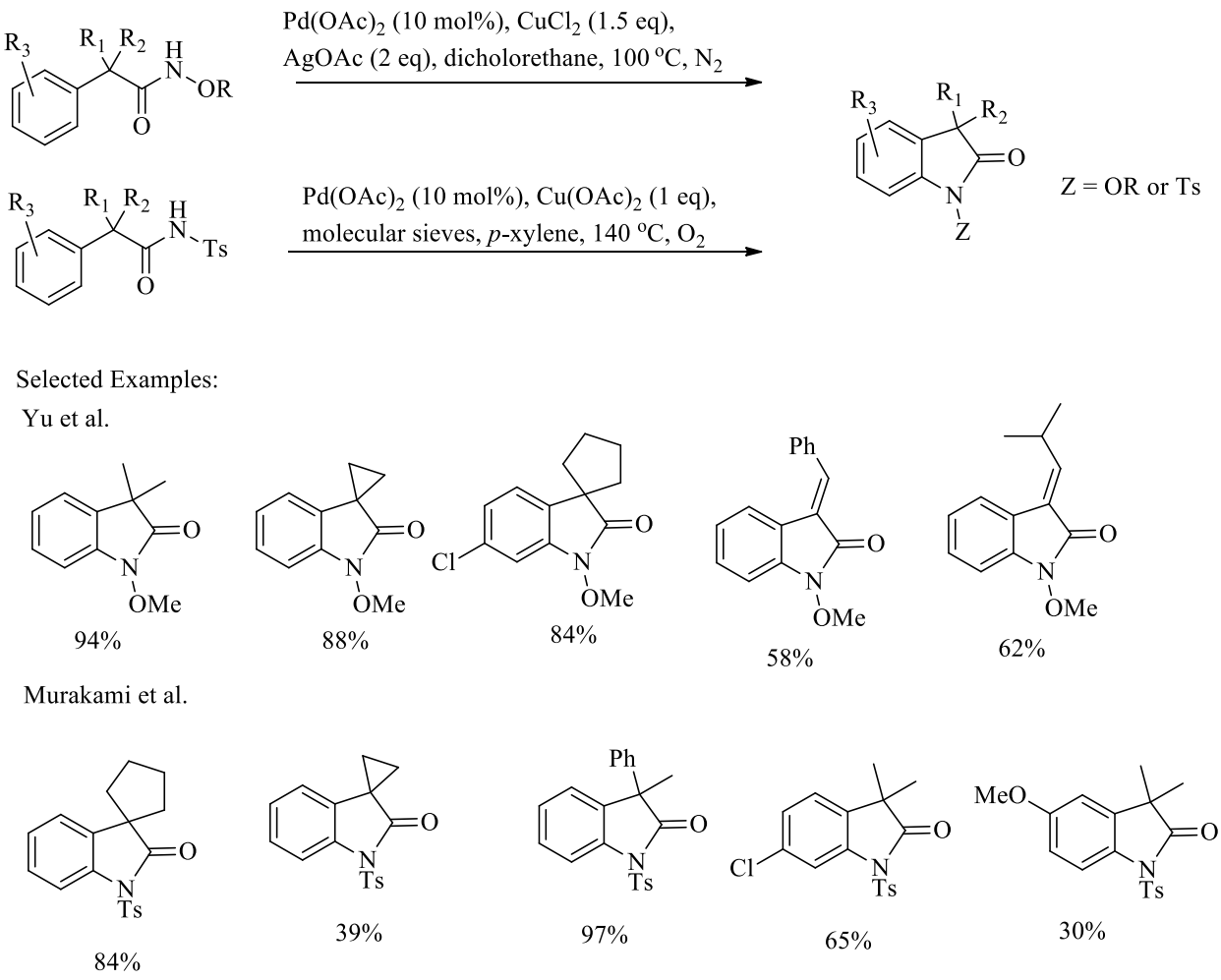
Scheme 58

Yu and co-workers described a palladium catalyzed intramolecular amination *via* C(sp2)-H activation to prepare indolines (Scheme 59).[77] The reaction proceeded in the presence of either a one-electron oxidant [$Ce(SO_4)_2$] or a two-electron oxidant (*N*-fluorocollidinium triflate). The procedure was tolerant of a wide range of functional groups. A chiral amino acid-derived substrate was cyclized into the corresponding indole product without loss of optical purity.



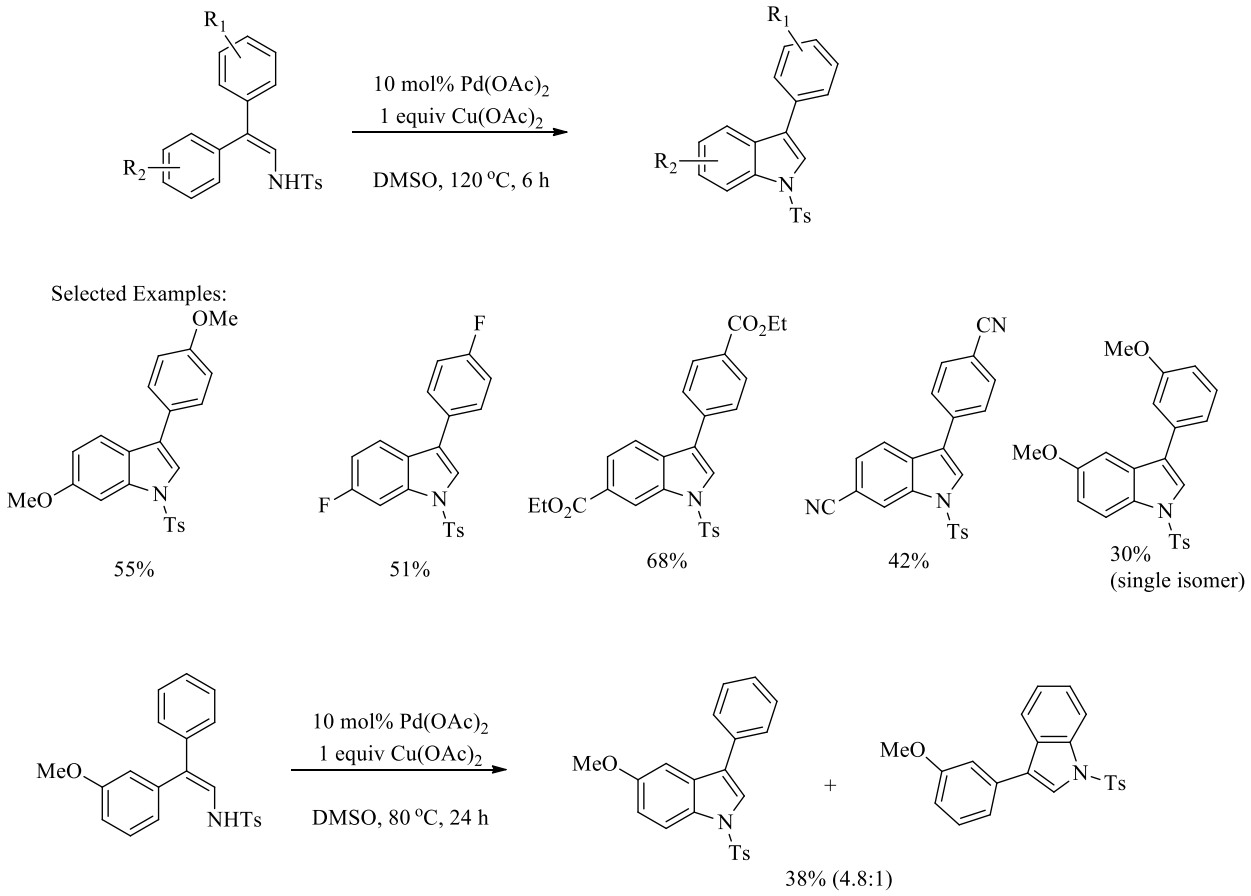
Scheme 59

Yu group showed that *N*-alkoxy 1-aryl-1,1-dialkylacetamides underwent Pd-catalyzed intramolecular C-H bond amination to form oxindoles (Scheme 60).[78a] Soon after, Murakami's group reported that *N*-tosyl 1-aryl-1,1-dialkylacetamides participated in similar transformations, although silver salt was not necessary in this case.[78b] Yu proposed a Pd(II)/Pd(IV) catalytic cycle whereas Murakami proposed a mechanism involving Pd(0)/Pd(II) interconversion. For both methods, a range of functional groups were shown to be compatible with the reaction conditions. Notably, α,β-unsaturated *N*-methoxy amides were successfully employed in Yu's reaction.



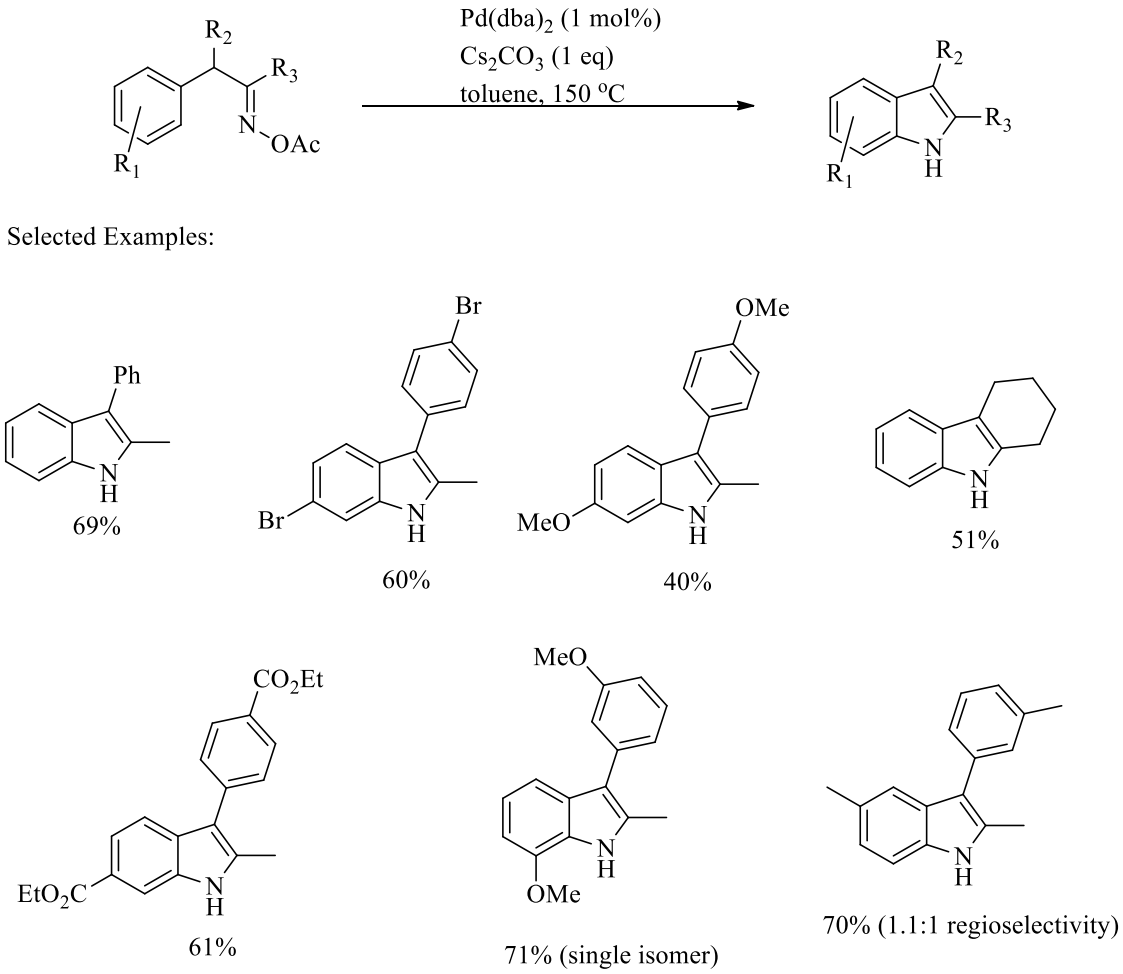
Scheme 60

An alternative approach towards indoles is through the direct intramolecular C-H bond amination of β-aryl enamines. Inamoto, Doi and coworkers reported this type of C-H activation and amination with the use of 10 mol % $Pd(OAc)_2$ and a stoichiometric amount of $Cu(OAc)_2$ as the oxidant (Scheme 61).[79] The methodology provided indoles in low to moderate yields. When there are two possible insertion sites on the phenyl ring, the sterically more accessible position was activated. A substrate with two different aryl groups (R_1 = H, R_2 = OMe) was also subjected to the reaction conditions and the indole product derived from insertion into the more electron-rich, methoxy-containing ring was favored with a ratio of 4.8:1.



Scheme 61

Most recently, Hartwig group developed a novel Pd-catalyzed direct C-H bond amination reaction involving oxime as the nitrogen source (Scheme 62). Notably, the oxidation state of the oxime is conveniently utilized in the catalytic cycle, therefore obviating the need for an external stoichiometric oxidant such as $Cu(OAc)_2$.[80] With only 1 mol% $Pd(dba)_2$, oxime substrates were cyclized into indole products in good yields. For substrates with a *meta* substitution, the regioselectivities for C-H activation seemed to be dependent on the nature of the substitutents: methoxy group containing substrates gave single isomer of the indole while methyl group containing substrates showed little regioselectivity.



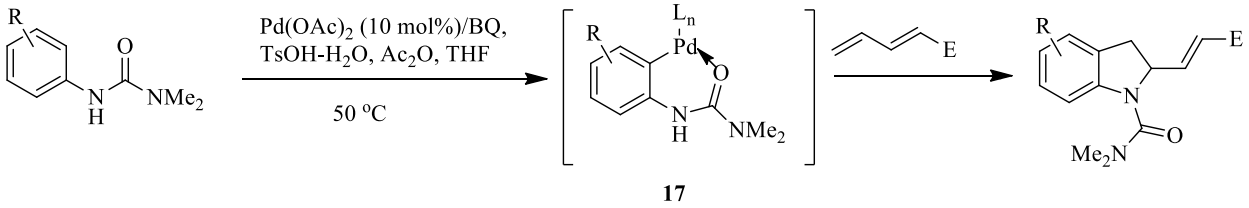
Scheme 62

5. Other Strategies

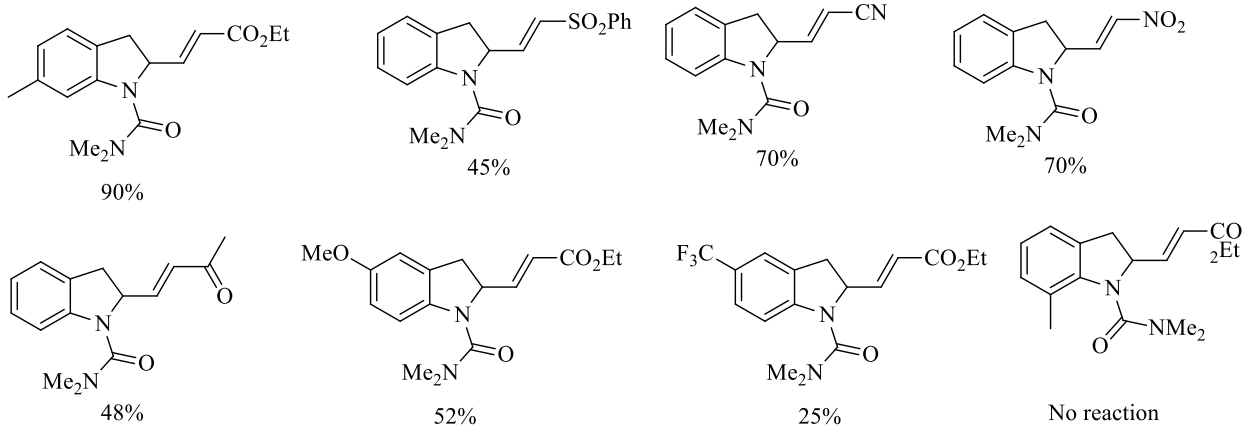
Lloyd-Jones, Booker-Milburn *et al*. observed that when *N*-aryl ureas were treated with 10 mol% $Pd(OAc)_2$, 1 eq of benzoquinone (BQ) and 0.5 eq of tosic acid, the C-H activation took place to give intermediate **17** which participated in an interrupted Heck reaction with electron-deficient dienes to afford various substituted indoline products (Scheme 63). [81] It was also demonstrated that $Pd(OAc)_2$ and tosic acid reacted first to generate $Pd(OTs)_2$ that actually catalyzed the reaction.

In 2000, Jun and coworkers[82] reported an imine-directed intermolecular *ortho*-alkylation of aromatic ketimines with alkenes catalyzed by Wilkinson's catalyst. Subsequently, Bergman and Ellman investigated the intramolecular variant of this methodology for the synthesis of bicyclic ring systems including several indoline derivatives as shown below (Scheme 64).[83] The imine

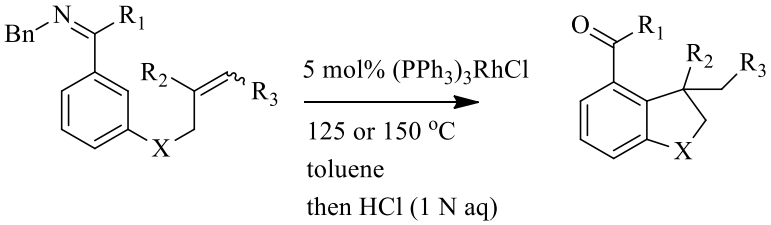
functional group directed the metallation/cyclization to the more hindered position on the aromatic ring. The corresponding ketones did not cyclize under these conditions.



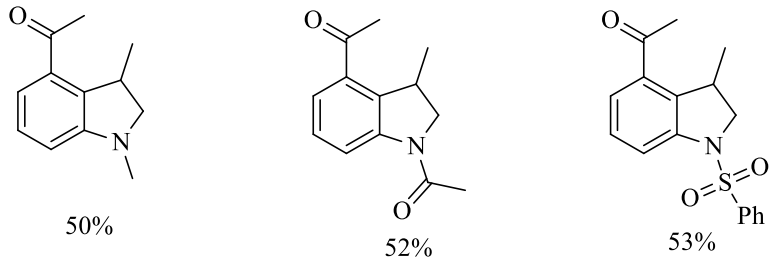
Selected Examples:



Scheme 63

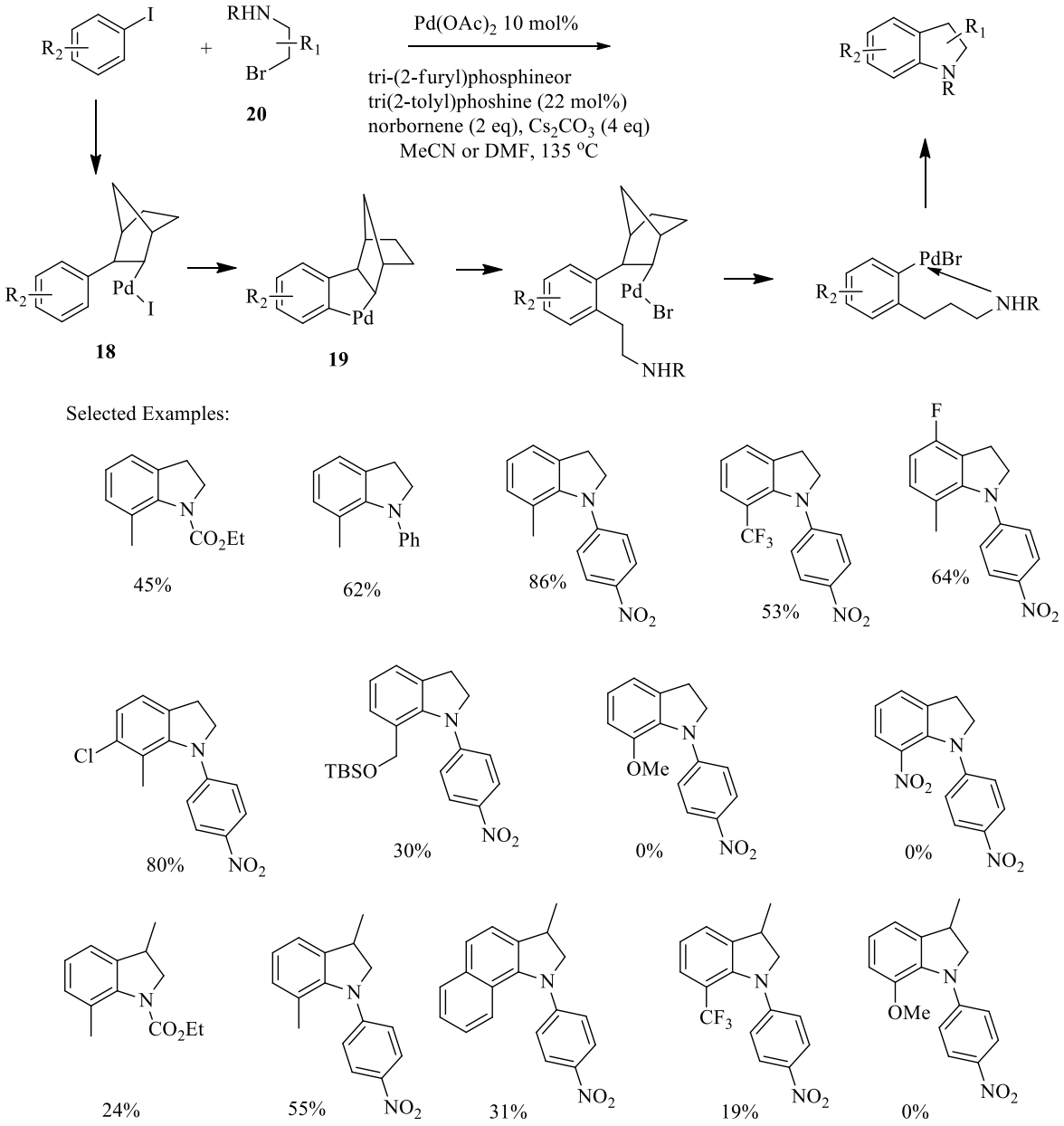


Selected Examples:



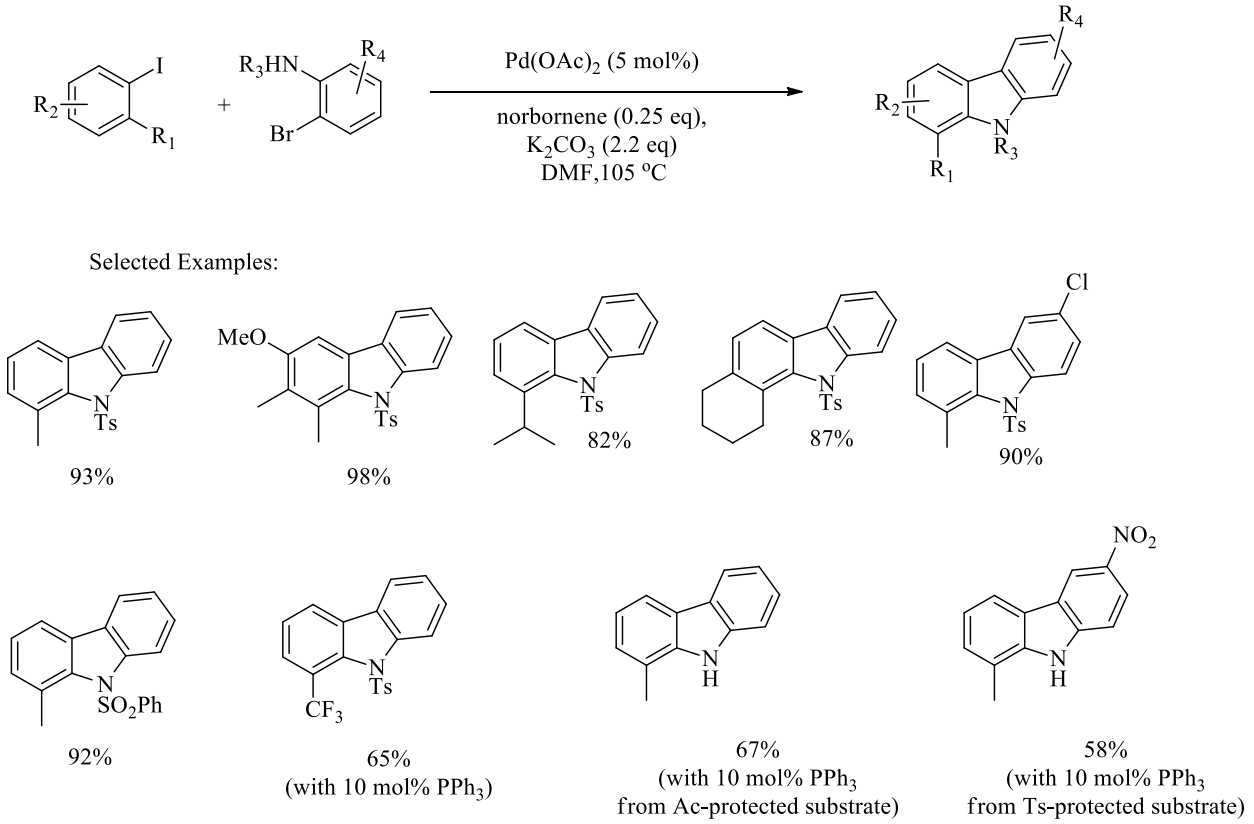
Scheme 64

Lautens group[84] reported a novel indoline synthesis involving sequential C-C and C-N bond formation based on Catellani's norbornene-mediated C-H activation reaction (Scheme 65).[85] Iodoarenes reacted with norbornene under Pd catalysis to give alkyl Pd intermediate **18** which underwent intramolecular C-H activation to give the palladacycle **19**. Alkylation of the arene with bromoethylamine derivative **20** followed by the final intramolecular cyclization of the amine onto the aryl group completed the formation of indoline. For reactions with secondary alkyl bromides, it was found that the use of tri-(2-tolyl)phosphine and DMF gave higher yields. It is interesting to note that when 3-nitro-2-methyliodobenzene was subjected to the standard reaction conditions, the corresponding indole (not indoline) product was obtained.



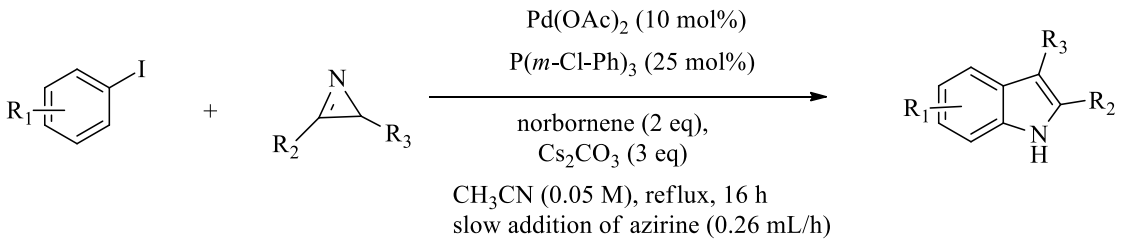
Scheme 65

Catellani's group utilized their C-H activation chemistry for the formation of carbazoles from *ortho*-bromoaniline derivatives (Scheme 66).[86] The use of Ts, bezenesulfonyl, acetyl as the R_3 group on the nitrogen was critical for the success of the reaction. It was observed that the reaction yields actually increased when substoichiometric amounts of norbornene were employed and in most cases, 0.25 eq of norbornene was sufficient for the reaction. For certain difficult substrates, the addition of 10 mol% PPh_3 was required for the cyclization and the reaction gave the *N*-deprotected carbazoles. This method was further showcased with a total synthesis of antibiotic carbazomycin A.

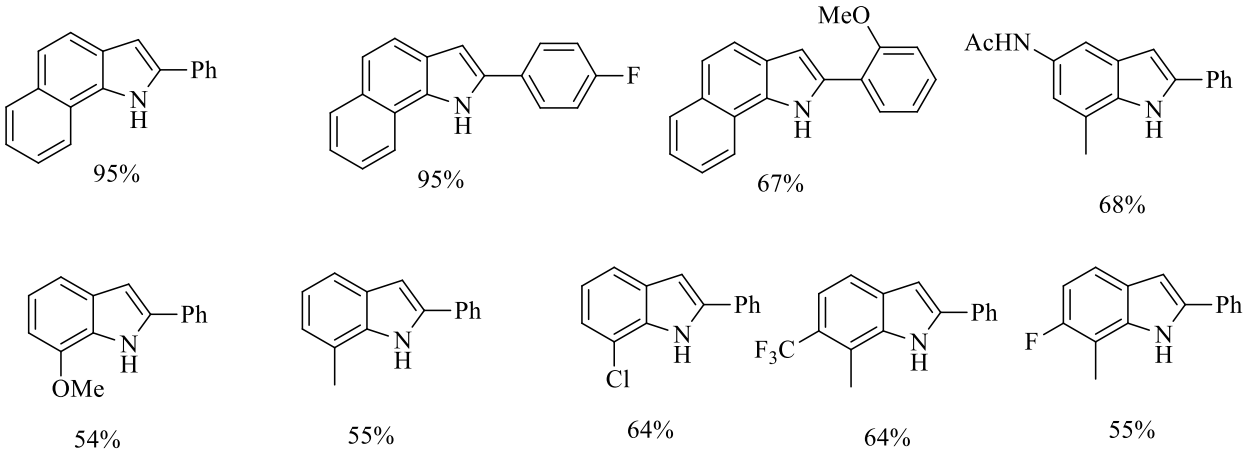


Scheme 66

Most recently, Lautens group engineered an elegant indole synthesis from iodoarenes and 2*H*-azirines through norbornene-mediated C-H functionalization reaction (Scheme 67).[87] The 2*H*-azirine serves as a 1,3-dipole equivalent that condenses with iodoaromatics to furnish indoles. Slow addition of the azirine component was critical for obtaining good yields of indole products, as higher concentrations of azirine led to the formation of dihydroimidazoles. This reaction has shown good functional group tolerance. However, it was indicated that certain substitution patterns were not compatible with the reaction conditions as depicted in Scheme 67.



Selected Examples:

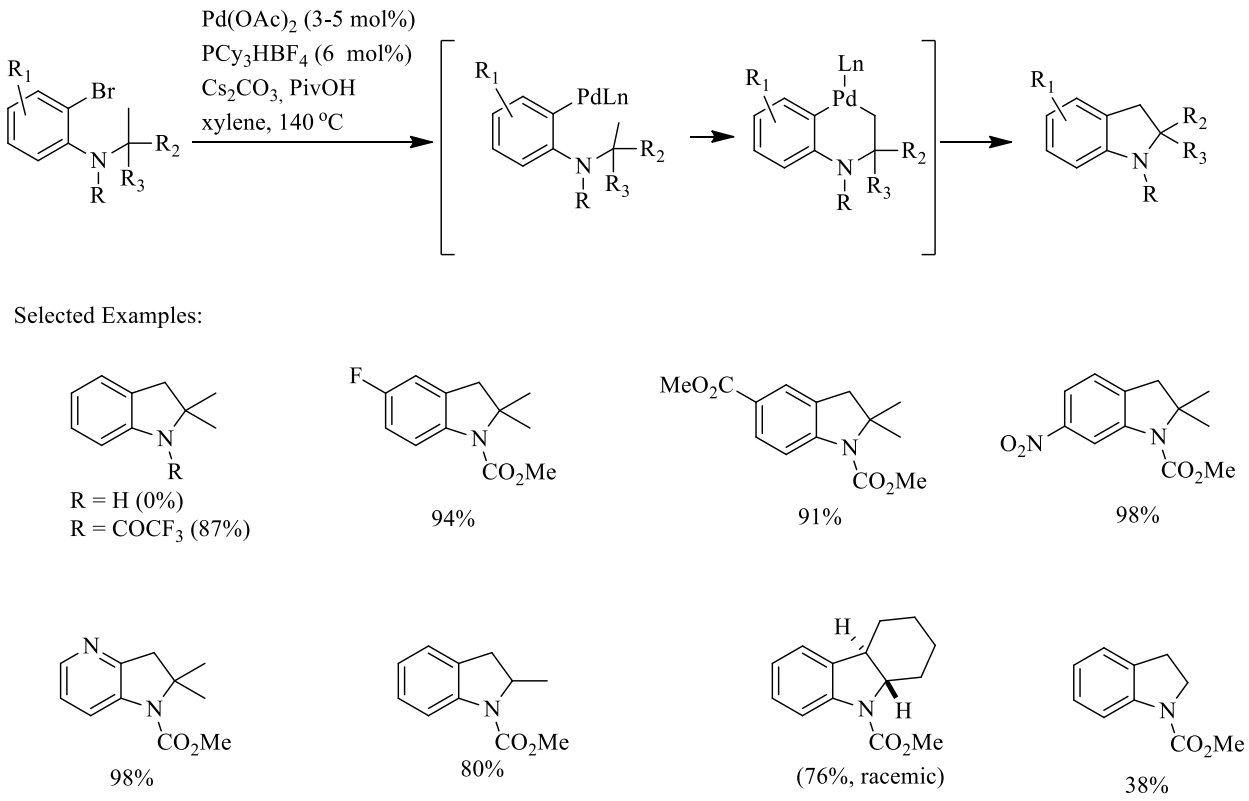


No indole formation between 1-iodonaphthalene and 2*H*-azirine with the following substitutions::

R_2 = Ph, R_3 = Me; R_2 = Ph, R_3 = CO_2Me; R_2 = Bn, R_3 = H; R_2 = CO_2Bn, R_3 = H; R_2 = $CONMe_2$, R_3 = H.

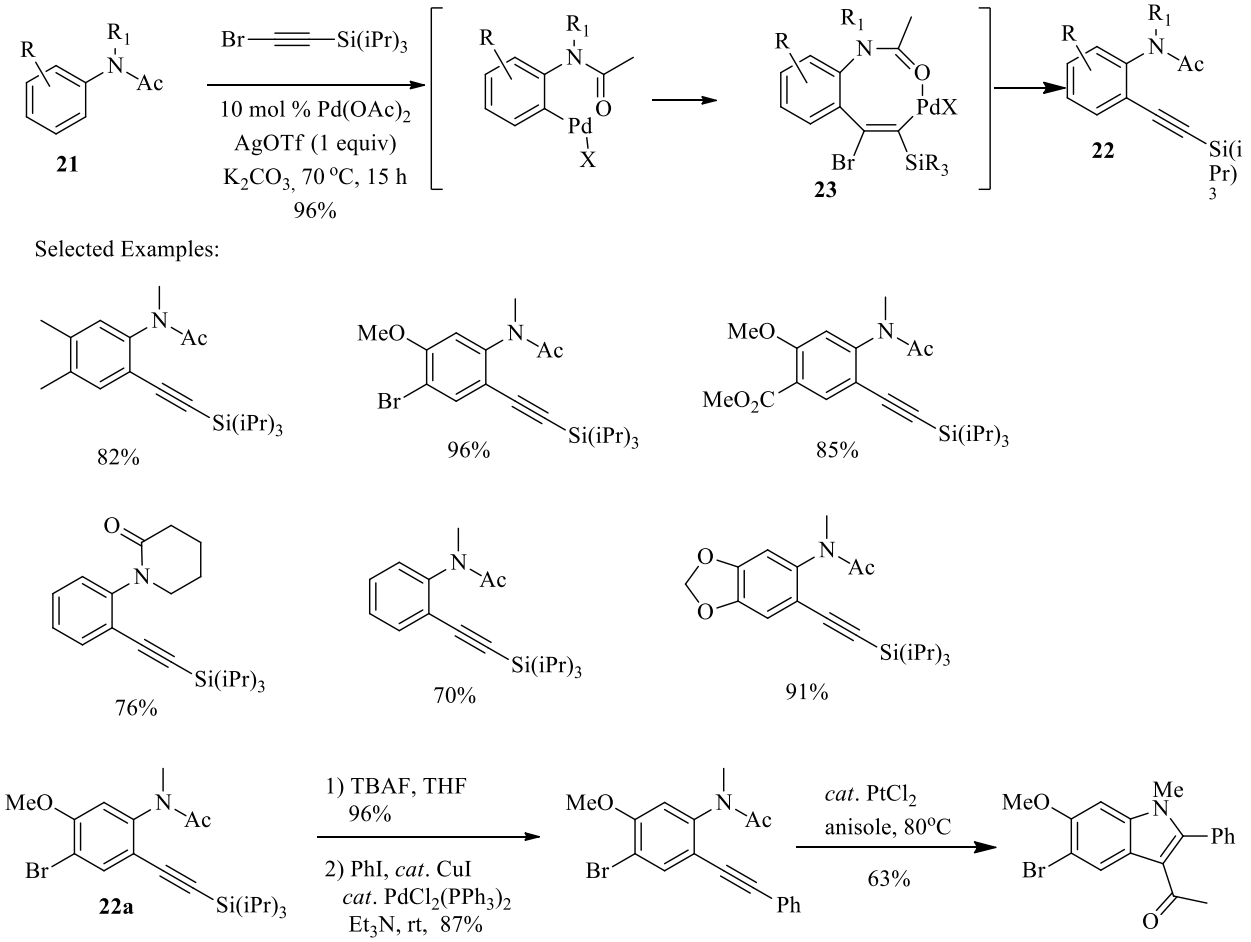
Scheme 67

Ohno and co-workers reported an interesting indoline synthesis *via* Pd-catalyzed activation of an sp3 C-H bond as illustrated in Scheme 68.[88] It was found that the nitrogen needs to be protected as a carbamate or an amide (no product formation when R = H). Aryl bromides worked the best while chloride and iodides were less effective. Importantly this work provided the first examples where a secondary or even a primary sp^3 C-H bond can be activated (R_2 and/or $R_3 \neq$ H).



Scheme 68

o-Alkynyl anilines are versatile substrates for the preparation of indoles.**Error! Bookmark not defined.** They are commonly generated through a Sonogashira coupling from *ortho*-haloanilines. Tobisu and coworkers[89] described the synthesis of these useful indole precursors through the palladium catalyzed direct *o*-alkynylations of anilines with bromo-alkynes (Scheme 69).[90] The $Pd(OAc)_2$-catalyzed, amide-directed C-H activation of anilide **21** followed by cross-coupling with bromo-alkyne gave high yields of compound **22**. Alkyne **22a** was converted into indole through application of an intramolecular platinum-catalyzed aminoacylation reaction.[91] A strong primary kinetic isotope effect was observed for the C-H bond activation. Additionally, the stoichiometric reaction of an acetanilide-derived palladacycle similar to compound **23** with bromoacetylene also generated the *o*-alkynyl aniline **22**. Based on these observations, the authors offered an alkynyl insertion and β-bromo elimination mechanism through the intermediacy of palladacycle **23**.



Scheme 69

6. Summary

The past decade has witnessed a rapid growing of C-H functionalization-based indole, indoline and carbazole synthesis. As a matter of fact, the need for new and more efficient indole synthesis has served as the driving force and platform for C-H activation research. Research efforts are continuing in order to develop catalytic systems that allow C-H activation under milder conditions, with wider substrate scopes and improved selectivities. Undoubtedly, indole synthesis *via* C-H functionalization will gain popularity due to its intrinsic efficiency, and more industrial scale applications of these processes can be anticipated in the near future.

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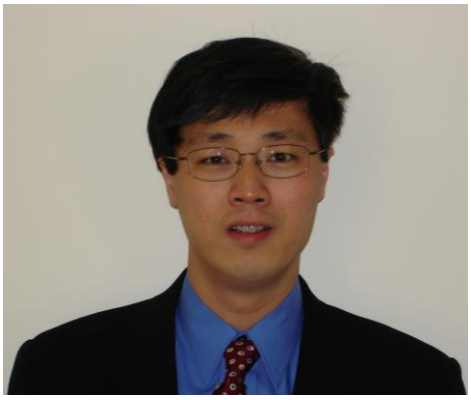
Authors' Biographies

Dr. Jinhua Jeff Song



Dr. Jinhua Jeff Song received his undergraduate education at Nankai University in Tianjin, China (1989 to 1992). After a brief stay at Rice University in Houston, TX, he moved to the Massachusetts Institute of Technology in 1993 and obtained his Ph.D. degree in 1998 under the supervision of Prof. Satoru Masamune. Subsequently, he joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT, where he is currently a Senior Principal Scientist. Dr. Song's research areas encompass natural product synthesis, asymmetric synthesis of chiral biologically active compounds, efficient methodologies for heterocycle synthesis, and novel *N*-heterocyclic carbene catalyzed reactions. He has published ~40 research papers and review articles including some "Most-Cited" and "Most-Accessed" papers. Over the years, Dr. Song has delivered invited lectures at international conferences as well as academic institutions. Some of his work also received media attention and has been highlighted in the *Chemical and Engineering News*. Additionally, Dr. Song holds >15 patents on efficient synthesis of pharmaceutical agents.

Dr. Jonathan T. Reeves

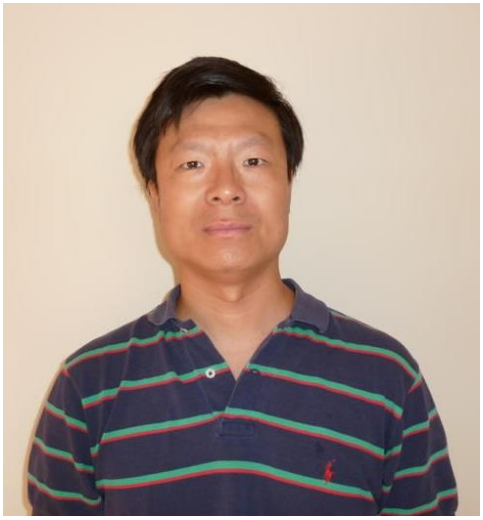
Dr. Jonathan T. Reeves was born in 1975 in Michigan, USA. He received a B.S. degree in chemistry from Hope College, Holland, MI in 1997. He then received a Ph.D. in organic chemistry under the guidance of Professor Peter Wipf at the University of Pittsburgh in 2002. After two years as an NIH postdoctoral fellow at Indiana University with Professor David R. Williams, he joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT, where he is currently a Principal Scientist. His research interests include organometallic, heterocyclic and asymmetric methodology development.

Dr. Daniel R. Fandrick

Dr. Daniel R. Fandrick received his B.S. degree with a major in chemistry from the University of California, San Diego where he synthesized strained organometallic complexes under the guidance of Professor Joseph M. O'Conner. In 2006, he received his Ph.D. degree in organic chemistry at Stanford University under the mentorship of Professor Barry M. Trost. His graduate studies focused on the development of the dynamic kinetic asymmetric transformations of vinyl aziridines and allenes and their applications to total synthesis. After graduation, he joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield,

Connecticut. His main interests are in the development of transition metal catalyzed and sustainable methodologies to address unmet needs in the organic synthesis.

Zhulin Tan



Zhulin Tan received a B.S. degree in chemistry from Sichuan University in Chengdu, China (1988). He then joined Sichuan Chemical Engineering Institute as a research associate in Chengdu, China. After a brief stay at the University of Delaware, he moved to Worcester Polytechnic Institute in 1996 and obtained his M.S. in organic chemistry in 1999 under the guidance of Professor Stephen Weininger. He then joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT, where he is currently a Senior Research Associate. His research interests include heterocyle synthesis and organocatalysis using *N*-heterocyclic carbenes.

Dr. Nathan Yee

Dr. Nathan Yee received his B.S. degree in Chemistry from the University of New York at Stony Brook in 1985, and then moved to the University of Illinois at Urbana-Champaign and obtained

his Ph.D. degree in 1991 under the supervision of Prof. Robert Coates. He was a postdoctoral fellow at Yale University with Prof. Frederick Ziegler in 1991-1992. In 1992 he joined Boehringer Ingelheim Pharmaceuticals, Inc. as a Senior Scientist in the Department of Chemical Development, and he is currently Director of Chemical Development. He has been leading multi-disciplined teams engaged in Process Research, Analytical Research, and Solid State Physicochemical Characterization. His research interests include the development of new synthetic methodologies and their applications to the chemical processes for drug substance manufacturing.

Dr. Chris H. Senanayake

Dr. Chris H. Senanayake was born in Sri Lanka and received a BS degree (First Class) in Sri Lanka. After coming to the United States, he completed his MS at Bowling Green State University with Professor Thomas Kinstle in synthetic chemistry. He obtained his Ph.D. under the guidance of Professor James H. Rigby at Wayne State University in 1987 where he worked on the total synthesis of complex natural products such as, ophiobolanes, and completed the first total synthesis of grosshemin in the guaianolide family. He then undertook a postdoctoral fellow with Professor Carl R. Johnson and worked on the total synthesis of polyol systems such as amphotericin B and compactin analogous, and the synthesis of C-nucleoside precursors.

In 1989, he joined the Department of Process Development at Dow Chemical Co. In 1990, he joined the Merck Process Research Group. After 6 years at Merck, he accepted a position at Sepracor, Inc. in 1996 where he was promoted to Executive Director of Chemical Process Research. In 2002, he joined Boehringer Ingelheim Pharmaceuticals. Currently, he is the Vice President of Chemical Development and leading a group of highly talented scientists, engineers, and administrative staff located in Ridgefield, CT.

Dr. Senanayake's research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules and heterocycles and on catalytic, enzymatic, and mechanistic studies. He has published and lectured in the area of practical asymmetric synthesis and many disciplines of organic chemistry how to develop drugs on an economical, greener and practical manner in large-scale operation for rapid development of drugs. He is the co-author about 250 papers, patents and applications, book chapters and review articles in many

areas of synthetic organic chemistry, drug development and design of improved chemical entities. Dr. Senanayake is an Editorial Advisory Board member of the Organic Process Research & Development Journal. In 2008, he was the chairperson of Stereochemistry Gordon Conference. In 2010, he received the prestigious Siegfried gold medal award for development of practical processes for APIs and Process Chemistry.