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Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions[†]

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Contents

1. Introduction

The substituted indole nucleus [indole is the acronym from *ind*igo (the natural dye) and *ole*um (used for the isolation)] is a structural component of a vast number of biologically active natural and unnatural compounds. The synthesis and functionalization of indoles has been the object of research for over 100 years, and a variety of well-established classical methods are now available, to name a few of them, the Fisher indole synthesis, the Gassman synthesis of indoles from *N*-halo-anilines, the Madelung cyclization of *N*-acyl-*o*-toluidines, the Bischler indole synthesis, the Batcho-Leimgruber synthesis of indoles from *o*-nitrotoluenes and dimethylformamide acetals, and the reductive cyclization of *o*-nitrobenzyl ketones.[1]

In the last 40 years or so, however, palladium-catalyzed reactions, generally tolerant of a wide range of functionalities and therefore applicable to complex molecules, have achieved an important place in the arsenal of the practicing organic chemist. Since the invention of an industrial process for the palladium-catalyzed production of acetaldehyde from ethylene in the presence of $PdCl_2$ and $CuCl_2$, an ever-increasing number of organic transformations have been based on palladium catalysis. Almost every area of the organic synthesis has been deeply influenced by the profound potential of this versatile transition metal, modifying the way organic chemists design and realize synthetic processes.[2,3] Because of its catalytic nature, palladium-catalyzed synthesis can provide access to fine chemicals, agrochemical and pharmaceutical intermediates, and active ingredients in fewer steps and with less waste than classical

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[†] In memory of Prof. Bianca Rosa Pietroni, a colleague and very close friend.

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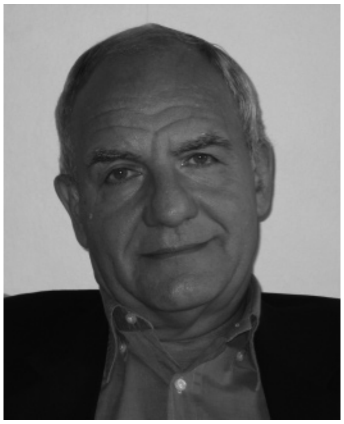


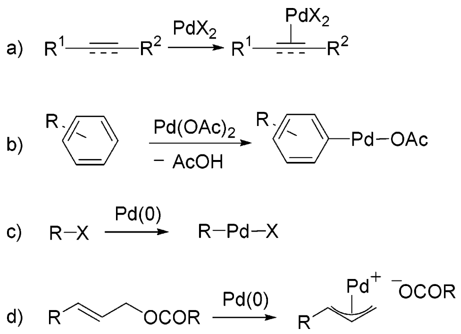
Born in Macerata (Marche) in 1943, Sandro Cacchi began his university training at the University of Camerino where he obtained his laurea degree in Chemistry in 1967. He directly moved to the University of Bologna where he worked under the guidance of Professor Luciano Caglioti. After doing his national service (October 1968 to December 1969), he went back to the University of Bologna and was promoted to Assistant Professor in 1970. In 1972, he joined the University "La Sapienza", Rome, where he became (1983) Associate Professor of Organic Chemistry and subsequently (1986) full Professor of Organic Chemistry. His research interests include various aspects of palladium catalysis applied to the preparation of fine chemicals and pharmaceutical products with the search for new and selective methodologies being a major thrust. The utilization of palladium-catalyzed reactions in the development of environmentally friendly processes is also an area of current extensive interest.

Giancarlo Fabrizi was born in Rome in 1963. He obtained his laurea degree in Medicinal Chemistry and Technology at the University "La Sapienza" of Rome in 1987. He spent four years (1990–1994) at the Science Department of the University of L'Aquila as Inorganic Chemistry Researcher. In 1994, he became Organic Chemistry Researcher at the Dipartimento di Studi Chimica e Tecnologia delle Sostanze Biologicamente Attive of Rome working under the supervision of Professor Sandro Cacchi, and since 2001, he has been Associate Professor in the same Department. His research interests include organic synthesis, organometallic chemistry of palladium, asymmetric synthesis, and NMR techniques.

methods. Heterocyclic chemistry is no exception to this trend, and a great deal of studies have been directed toward the use of palladium catalysis in the synthesis and functionalization of heterocycles,[4,5] including indoles. The impact of palladium chemistry of indoles in academic and medicinal chemistry communities has been extraordinary, as outlined by the number of studies developed in this area.

There are several review articles[6] and books[4,7] covering different or limited aspects of the palladium chemistry of indoles. Our aim is to try to provide a comprehensive and updated overview of recent developments in the palladium-catalyzed approaches to the preparation of indole derivatives with the emphasis on the rationale behind each synthetic procedure and the dependence of the results on a proper selection of reaction conditions. Palladium-catalyzed reactions are in fact strongly dependent on a number of factors such as the nature of stabilizing ligands (as well as their presence or absence), bases, additives, the combination of them, solvents, and temperature. All of these factors combine to afford a toolbox of tunable reaction conditions that make palladium chemistry so flexible and, to some extent, unpredictable, leaving room for an uninterrupted discovery of new, exciting chemistry despite the vast amount of studies developed so far.

Scheme 1



In general, methodologies based on the use of a stoichiometric amount of palladium will not be treated. Even palladium-catalyzed procedures producing indole-related compounds such as indolines, oxindoles, and indazoles or condensed polycyclic compounds such as carbolines and carbazoles, as well as multistep procedures where palladium catalysis is not directly involved in the construction of the indole ring will not be discussed. Only reactions leading to the direct functionalization of the indole core motif will be treated and functionalizations involving intramolecular processes are also beyond the scope of this review.

2. Pd(II)- and Pd(0)-Catalyzed Reactions, Phosphine Ligands, and Additives

Both palladium(II) salts and palladium(0) complexes have been used in indole chemistry. Palladium(II) salts are fairly electrophilic species and tend to react with electron-rich compounds such as alkenes, alkynes, and arenes. The most commonly used palladium(II) salts in general, and particularly in indole chemistry, are commercially available $PdCl_2$ and $Pd(OAc)_2$, very often utilized as complexes of the type PdX_2L_2 (where L stands for a ligand) such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2(PPh_3)_2$, and $PdCl_2(MeCN)_2$. Complexes containing phosphine ligands are frequently formed in situ combining $PdCl_2$ or $Pd(OAc)_2$ with phosphine ligands.

The typical reaction of palladium(II) salts with alkenes or alkynes affords π-complexes (Scheme 1a), which because of the decreased electron density at the carbon−carbon multiple bond can undergo an intermolecular or intramolecular nucleophilic attack across the coordinated olefinic or acetylenic moiety. Intramolecular nucleophilic attack on π-palladium complexes by a heteroatom close to the carbon−carbon multiple bond is particularly useful for the synthesis of heterocycles.[8] With nitrogen nucleophiles, the procedure has been extensively employed in the synthesis of indoles.

With arenes, palladium(II) salts—typically Pd(OAc)$_2$, which may also be prepared in situ from PdCl$_2$ and AcONa—can produce palladation intermediates (compounds containing carbon−palladium σ-bonds), basically through an electrophilic substitution reaction (Scheme 1b). These palladation intermediates can give rise to homocoupling reactions,[9] acetoxylation reactions,[10] or, in the presence of alkenes, vinylic substitution reactions.[11] This C$_{\text{aryl}}$-H activation chemistry has been used to functionalize selectively the pyrrole ring contained in the indole system.

In many Pd(II) salt-catalyzed reactions, Pd(II) species are reduced to Pd(0) species at the end of each cycle. Consequently, to make the reaction catalytic with respect to Pd(II), the presence of oxidants such as CuCl$_2$, Cu(OAc)$_2$, benzoquinone, *tert*-butyl hydroperoxide (TBHP), MnO$_2$, or HNO$_3$ is required to allow for the conversion of Pd(0) into Pd(II) in situ.

Palladium(0) complexes contain a d^{10} palladium and are usually nucleophilic. Most of the catalytic processes based on their utilization involve, in the initial step, their reaction with a variety of covalent polar and nonpolar X−Y bonds (for example, H−H, N−H, O−H, C−H, C−halogen, or C−O). Coordinatively unsaturated Pd(0) complexes react with X−Y bonds via an oxidative addition process producing X−Pd(II)−Y derivatives (containing an electrophilic palladium), which, depending on reaction conditions, can undergo a variety of transformations. In general, oxidative addition is favored by increasing the electron density on palladium. The usually observed rate of oxidative addition with C$_{\text{aryl}}$−halogen bonds increases according to the following order:[12] C−F < C−Cl < C−Br < C−I (with aryl fluorides being almost inert). Vinyl triflates undergo facile oxidative addition, while the reactivity of aryl triflates is more or less between that of aryl iodides and aryl bromides.

In the presence of monodentate ligands, the cis complex is likely to be the initially formed oxidative addition complex that subsequently isomerizes to the thermodynamically stable trans complex. As to the influence of ligands on the oxidative addition reaction, in general, oxidative addition is favored by σ-donor ligands coordinated to the palladium center. With bidentate ligands, the cis complex is the usual intermediate, though Buchwald et al.[13] has recently shown that xantphos [9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene], a rigid bidentate ligand with a wide natural bite angle,[14] can be trans-chelating in palladium complexes. A great deal of indole chemistry is based on the oxidative addition of vinyl, aryl, heteroaryl halides, or triflates to generate addition intermediates containing σ-carbon−palladium(II) bonds (Scheme 1c) in an initial step of their catalytic process, including the reactions involving indolyl halides and triflates.

The reaction of palladium(0) complexes with allylic esters, typically acetates or carbonates, affords π-allylic palladium complexes (Scheme 1d) which can undergo a nucleophilic attack at one of the allylic termini to afford allylation products.[15]

Scheme 2

$$\mathrm{Pd_2(dba)_3 + n\,PR_3 \longrightarrow 2\,Pd(PR_3)_n + 3\,dba}$$

Two of the most commonly used palladium(0) complexes are the commercially available Pd(PPh$_3$)$_4$, unstable in air and light sensitive, and Pd$_2$(dba)$_3$ (dba = dibenzylideneacetone), the storage and manipulation of which is much easier than that for Pd(PPh$_3$)$_4$. When Pd(PPh$_3$)$_4$ is used, the coordinatively unsaturated, catalytically active Pd(PPh$_3$)$_2$ (a 14-electron species) is generated via a two-step equilibrium process involving the initial loss of a phosphine ligand to give Pd(PPh$_3$)$_3$ followed by the loss of a second phosphine ligand. In the Pd$_2$(dba)$_3$ complex, each palladium is coordinated to three olefinic double bonds. In practice, two dba molecules are involved in the coordination of one palladium atom. In some cases, Pd$_2$(dba)$_3$ was utilized without the addition of phosphine ligands. Most frequently, however, it is used as a source of Pd(0) to prepare palladium−phosphine complexes in situ by a ligand exchange reaction with a vast range of monodentate and bidentate phosphines (Scheme 2). This preparation of palladium−phosphine complexes in situ is based on the assumption that dba, being a weaker ligand than phosphine, should be easily and completely removed from the coordination sphere of palladium to give active Pd(0)L$_2$ species. It has been shown that this assumption is at least an oversimplified view.[16] Nevertheless, the preparation of palladium−phosphine complexes via this protocol may represent a ready and convenient entry into the generation of "tailor-made" catalyst systems. For example, it is particularly useful when the reaction requires the use of Pd(0) complexes containing chiral or electron-rich bulky ligands (the latter have been found to be the ligands of choice in the oxidative addition of aryl bromides, chlorides, and, more recently, sulfonates). On the other hand, though there are examples of reactions carried out under "ligand-free" conditions, ligands are frequently required to generate soluble palladium catalysts and to modulate the reactivity of palladium complexes. Phosphine ligands are by far the most commonly used ligands in indole chemistry.

Palladium on charcoal or other supported palladium metal catalysts have also been employed as a source of Pd(0). Reactions are considered to occur under heterogeneous conditions but may involve soluble palladium complexes, which are formed via leaching of palladium into solution (which depends on the catalyst system being used and reaction conditions). The involvement of dissolution/reprecipitation processes during the reaction when supported palladium catalysts are utilized is the object of an ongoing debate.[17] The leaching of palladium into solution may be a major phenomenon when palladium on charcoal is employed in the presence of phosphine ligands. In practice, in the presence of phosphine ligands palladium on charcoal can be used as a catalyst system similar to Pd(PR$_3$)$_n$.[18]

Palladium(0) species are frequently formed in situ via reduction of palladium(II) species by several reagents such as alkenes, terminal alkynes, carbon monoxide, alcohols, amines, formate anions, metal hydrides, and butyllithium. Interestingly, $Pd(OAc)_2$ can be reduced by phosphines.[19]

Additives, mostly halide additives[20] (and often their stoichiometry), also play a significant role in controlling the reaction outcome of palladium-catalyzed reactions and have been widely utilized in indole chemistry.

Particularly, after the pioneering work of Jeffery,[21] who showed that the Heck reaction could be run under mild conditions in the presence of $Pd(OAc)_2$, carbonate or bicarbonate bases, and Bu_4NCl (reported to be much more efficient than other ammonium salts, for example, Bu_4NBr), a great number of papers have described the beneficial effects of Bu_4NCl in palladium(0)-catalyzed transformations, including the synthesis of indole derivatives. Amatore and Jutand have subsequently shown that chloride anions can stabilize palladium species and provide more efficient catalytic cycles.[22] Furthermore, the large ammonium cation can stabilize halide-ligated zero-valent or divalent palladium-centered complexes. Bu_4NCl is superior to LiCl in this respect.[22] In some cases, however, even the presence of LiCl has been found to provide beneficial effects on Pd(0)-catalyzed reactions. For example, LiCl has been shown to play a key role in the Stille reaction,[23] affording better results than other salts, such as LiBr, LiI, NaCl, and KCl, or in preventing homocoupling reactions in some carbonylations of aryl iodides.[24] Chloride anions play a crucial role in the isomerization of π-allyl palladium complexes.[25] The nature of the halide anions influence the stability of five-coordinate palladium complexes[26] and the stability of dimeric palladium complexes in amination reactions.[27] Halide effects are important in asymmetric allylic alkylations[28] and asymmetric Heck reactions.[29]

Halide additives are also crucial for the success of a variety of palladium(II)-catalyzed reactions, such as the 1,4-difunctionalization of 1,3-dienes,[30] the palladium-catalyzed 1,4-oxylactonization,[31] and the heteroatom addition to carbon−carbon multiple bonds,[32] and to control the vinylic substitution/conjugate addition-type ratio in Heck-type reactions with α,β-unsaturated carbonyl compounds[33] and the competition between β-heteroatom elimination and β-hydride elimination of intermediates containing a σ-carbon−palladium bond.[34] Halide additives have been extensively used in several synthetic approaches to indole derivatives.

Apart from some important rationalizations, however, the general behavior of phosphine ligands and additives is not always clearly understood. It may also vary from one type of reaction to another. For example, it is not unusual that a given set of conditions gives satisfactory results with electron-rich aryl halides whereas electron-poor aryl halides require a different set of conditions.[35] One of the reasons for this lack of general theories is that catalytic cycles usually consist of several consecutive steps and the chemical nature as well as the reactivity of each intermediate can differ widely depending on reaction conditions. Some reaction parameters can also exhibit opposing effects on different steps of a catalytic cycle. Therefore, it is advisable that in the initial search for optimal conditions a variety of phosphines (with different electronic and steric properties) and additives, as well their presence or absence, be investigated.

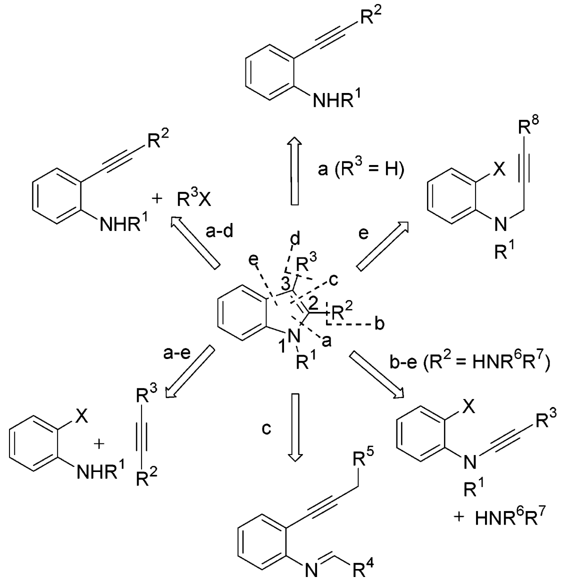


Figure 1. Retrosynthetic representation of the alkyne-based palladium-catalyzed assembly of the pyrrole ring.

3. Strategies in the Palladium-Catalyzed Synthesis of Indole Derivatives

There are many approaches to the palladium-catalyzed synthesis of indole derivatives which, in this review, have been categorized into two main types, corresponding to two main sections: the de novo indole system construction from benzenoid precursors through cyclization reactions and the functionalization of preformed indole rings. The two main sections are further subclassified by the nature of precursors and, furthermore, by the reaction mechanisms.

Cyclization reactions usually involve the assembly of the functionalized pyrrole nucleus on a benzenoid scaffold. This has been a very successful synthetic approach, as evidenced by the vast number of published material available. Construction of the pyrrole nucleus on heteroaromatic scaffolds has also been described.

A considerable part of the studies dedicated to the development of new sequences in the bond-making process leading to the construction of the pyrrole ring is based on the utilization, as precursors, of compounds containing nitrogen nucleophiles and carbon−carbon triple bonds. Nitrogen nucleophiles and alkyne moieties can be part of the same molecule or belong to two different molecules. Most of the alkyne-based palladium-catalyzed approaches to the assembly of the pyrrole ring are represented in Figure 1. The pyrrole nucleus can also be assembled by using precursors containing nitrogen nucleophiles and carbon−carbon double bonds (Figure 2). The chemical structure of olefin precursors can vary widely, but

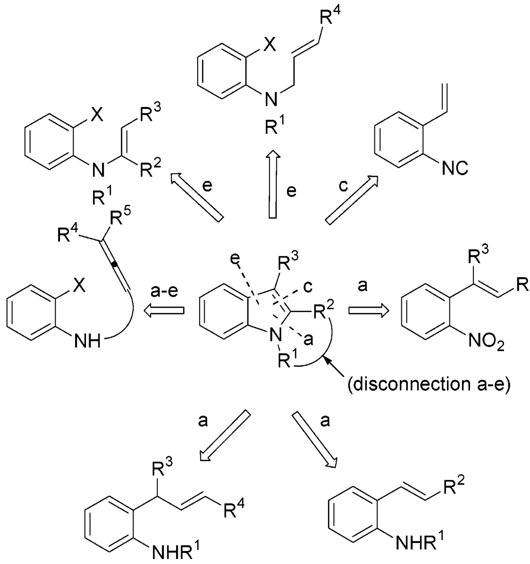


Figure 2. Retrosynthetic representation of the alkene-based palladium-catalyzed assembly of the pyrrole ring.

in terms of the bonds that can be created in the construction of the pyrrole rings, the alkene-based approach appears to be less versatile than the alkyne-based approach.

In addition to alkyne- and alkene-based procedures, other less frequently applied strategies for the construction of the functionalized pyrrole nucleus have been described that are based on the intramolecular vinylation and the Buchwald/Hartwig *N*-arylation process.[36]

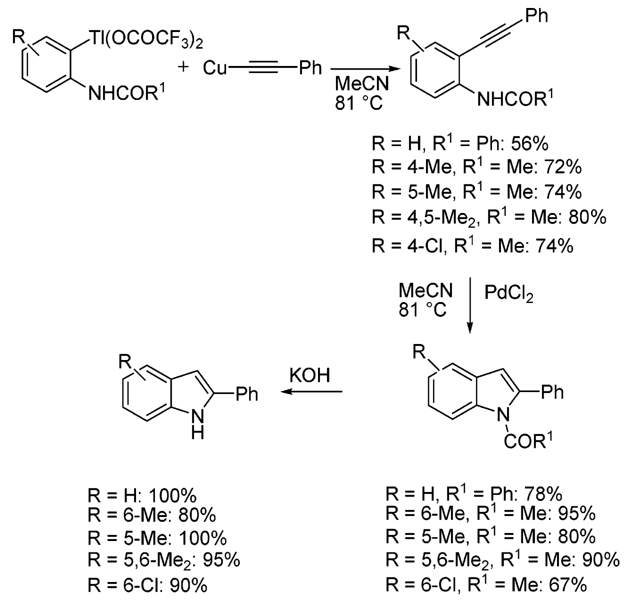
As to the functionalization of the preformed indole system, two main trends can be recognized: (a) functionalization via the intermediacy of indolylpalladium complexes and (b) functionalization via organometallic derivatives of indoles such as indolylstannanes, indolylboronic acids, and indolylzinc compounds. In the former case, indolyl halides and triflates have been widely used to generate indolylpalladium complexes in situ via oxidative addition to Pd(0)-complexes. Examples of indolylpalladium complexes formed via direct activation of C$-$H bonds with $Pd(OAc)_2$ have also been reported. In the second case, indole derivatives have been prepared via palladium-catalyzed cross-coupling reactions of indolylstannanes, indolylboronic acids, and indolylzinc compounds with a number of organic halides and triflates.

4. Assembly of the Pyrrole Nucleus Contained in the Indole System

4.1. Cyclization of Alkynes

As shown in the retrosynthetic representation shown in Figure 1, alkyne-based procedures have been found to provide a wide range of possibilities for the construction of the pyrrole ring. Both Pd(II)- and Pd(0)-catalyzed cyclizations have been described, and as can be seen in the following five subsections, a variety of structurally diverse substrates function well in these transformations.

Scheme 3



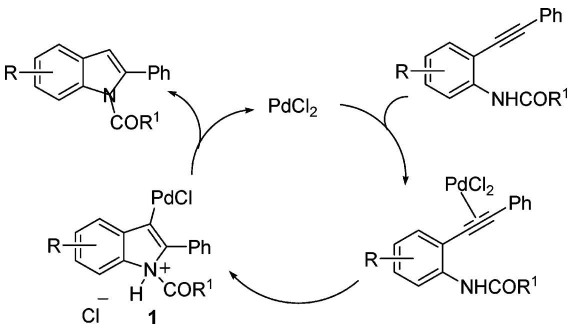
4.1.1. Cyclization of o-Alkynylanilines and o-Alkynylanilides Catalyzed by Pd(II) Salts

Disconnection a, Figure 1. The first example of palladium-catalyzed cyclization of *o*-alkynylanilides to indoles was by Taylor and McKillop.[37] Their synthesis, which dates back to the mid-1980s, features the coupling of the preformed copper(I) salt of phenylacetylene with *o*-thallated anilides in acetonitrile to give *o*-(phenylethynyl)acetanilides. Treatment of *o*-(phenylethynyl)acetanilides with $PdCl_2$ in acetonitrile results in smooth cyclization to *N*-acyl-2-phenylindoles, from which free NH indoles are obtained by deacylation with alcoholic potassium hydroxide (Scheme 3). The process occurs under conditions consistently milder than those described by Castro et al.[38] in the early 1960s for the synthesis of indoles from *o*-iodoanilines and cuprous acetylides. For example, under Castro conditions, 2-phenylindole was isolated in 89% yield upon warming *o*-iodoaniline and cuprous phenylacetylide in DMF at 175 °C (a two-step sequence, involving the isolation of the coupling intermediate followed by cyclization in the presence of CuI, was suggested for the preparation of 2-alkylindoles).

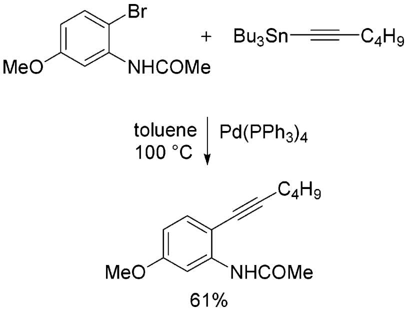
The proposed reaction mechanism for the palladium-catalyzed cyclization, in analogy with the mechanism proposed in a seminal work by Utimoto et al. for the palladium(II)-catalyzed intramolecular cyclization of alkynylamines,[39] comprises the following basic steps: (a) initial formation of a π-alkyne-palladium complex, (b) intramolecular nucleophilic attack of the nitrogen nucleophile across the activated carbon$-$carbon triple bond to give the σ-indolylpalladium complex **1**, (c) proton transfer with loss of Pd(II), which enters a new catalytic cycle, and formation of the *N*-acyl-2-phenylindole (Scheme 4).

This procedure, however, has rarely found applications in indole synthesis, most probably because of the toxicity of the metal used. Subsequently, Stille et al. reported that *o*-bromoacetanilides could be more conveniently used as the aniline partner for the coupling reaction instead of *o*-thallated anilides.[40]

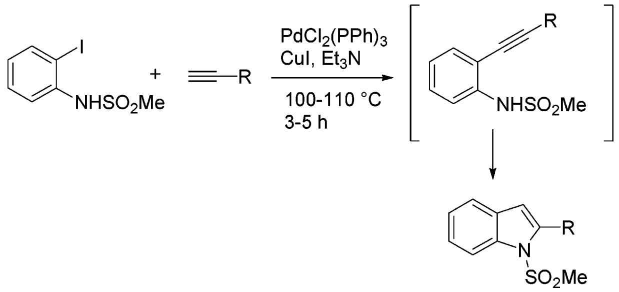
Scheme 4



Scheme 5



Scheme 6

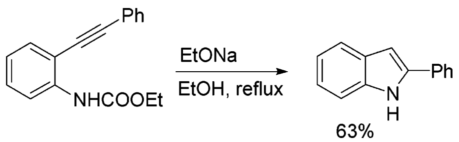


o-(Alkynyl)acetanilides could be prepared through palladium(0)-catalyzed reaction of alkynylstannanes with *o*-bromoacetanilides. The reaction tolerates various substituents on the anilides, including esters, ether, and chloro and trifluoromethoxy groups. However, it still uses toxic reagents such as organostannanes. The prototypical reaction is shown in Scheme 5.

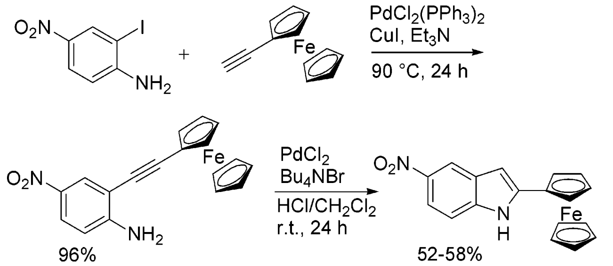
A significant improvement is due to Yamanaka et al.,[41] who observed that treatment of 1-alkynes with *o*-iodo-*N*-mesylanilides under Sonogashira conditions[42a−c] could directly afford indole products in a single operative step through a domino coupling−cyclization process with palladium and copper catalysts involved both in the coupling and in the cyclization reaction (Scheme 6). Control experiments revealed that formation of the indole product was observed by heating *o*-trimethylsilylethynyl-*N*-mesylanilide, prepared by an alternative procedure, in the presence of both cuprous iodide[43] and dichlorobis(triphenylphosphine)palladium, whereas no indole derivative was obtained in triethylamine and DMF for 10 h.

Interestingly, treatment of the crude *o*-(phenylethynyl)-*N*-ethoxycarbonylanilide, prepared through a Sonogashira coupling, with a strong base such as sodium ethoxide was found to give 2-phenylindole in good overall yield,[41] showing that the cyclization of *o*-alkynylanilides can be performed through base-mediated reactions as well (Scheme 7).

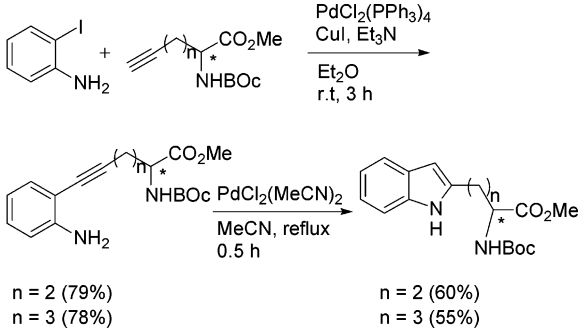
Scheme 7



Scheme 8

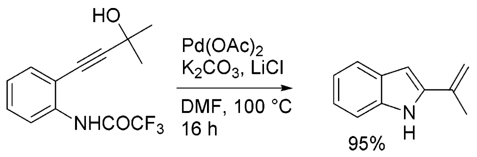


Scheme 9

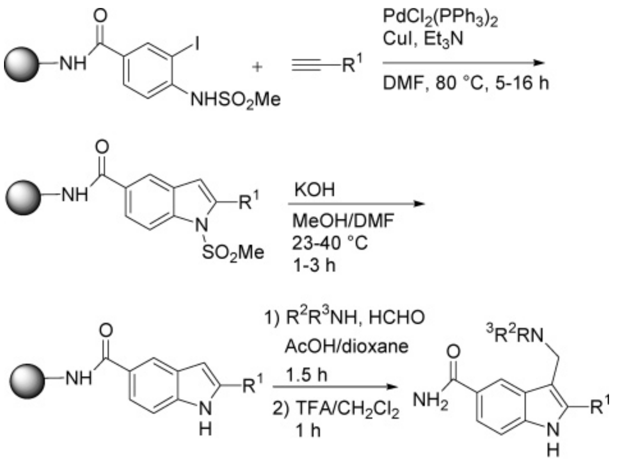


The palladium-catalyzed coupling (with[42a−c] or without[42d,e] copper cocatalysts) of terminal alkynes with *o*-haloanilines or *o*-haloanilides followed by a cyclization step revealed a particularly useful approach to the synthesis of 2-substituted indoles, and a large number of applications were developed based on this synthetic protocol. Both base-mediated[44] and palladium-catalyzed protocols were developed to perform the cyclization of coupling intermediates. In some cases, particularly when 2-substituted indoles are directly obtained through domino processes and the authors have not investigated the mechanism of the cyclization step,[44l,45] the specific role of palladium and the base in the formation of the pyrrole ring cannot be clearly established. The versatility of the palladium-catalyzed cyclization of *o*-alkynylanilines and *o*-alkynylanilides was demonstrated in the synthesis of pyrrolo[2,3-*b*]pyrimidine derivatives,[46] 5-azaindoles,[47a] and 6-substituted 5*H*-pyrrolo[2,3-*b*]pyrazines,[47b] in the preparation of 2-ferrocenyl indoles[48a] (Scheme 8) and bisindoles,[48b] and in the synthesis of novel optically active tryptophan analogues from aniline-containing acetylenic amino acids[49] (Scheme 9). *o*-[(3-Hydroxy-3,3-dimethyl)prop-1-yl)trifluoroacetanilide was converted into *o*-(1-methylethenyl)indole.[50] In this case, the palladium-catalyzed cyclization was followed by the hydrolysis of the amide bond and a dehydration process leading to the formation of the olefinic double bond (Scheme 10). Cacchi et al. showed that the cyclization of *o*-alkynylanilines can be performed in an acidic CH$_2$-

Scheme 10



Scheme 11



R^1 = Ph; $R^2 = R^3$ = -$(CH_2)_4$-: 90% (purity 80%)
R^1 = Ph; $R^2 = R^3$ = -$(CH_2)_5$-: 85% (purity 86%)
R^1 = Ph; $R^2 = R^3$ = Et: 86% (purity 93%)
R^1 = C_5H_1; $R^2 = R^3$ = -$(CH_2)_4$-: 91% (purity 94%)
R^1 = C_5H_{11}; $R^2 = R^3$ = Pr: 81% (purity 90%)
R^1 = Me_2NCH_2; $R^2 = R^3$ = -$(CH_2)_4$-: 71% (purity 98%)

Cl_2/HCl two-phase system in the presence of $PdCl_2$ and Bu_4NCl at room temperature.[51] Usually, these conditions were found to give yields comparable to or higher than those obtained with $PdCl_2$ in acetonitrile at 60−80 °C. However, neutral conditions appear to give better results with *o*-alkynylanilines containing electron-withdrawing groups on the alkyne moiety. Amatore, Genêt, Jutand, et al. described the synthesis of 2-substituted indoles from *o*-iodoaniline or *o*-iodotrifluoroacetanilide and terminal alkynes in the presence of $Pd(OAc)_2$, triphenylphosphinetrisulfonate sodium salt (TPPTS), and Et_3N in MeCN and H_2O without any copper promoter.[52] The indole ring was suggested to arise from the intramolecular cyclization of an organopalladate intermediate.

In addition to solution-phase synthesis, the coupling−cyclization protocol was utilized both with supported palladium catalysts and in solid-phase synthesis.

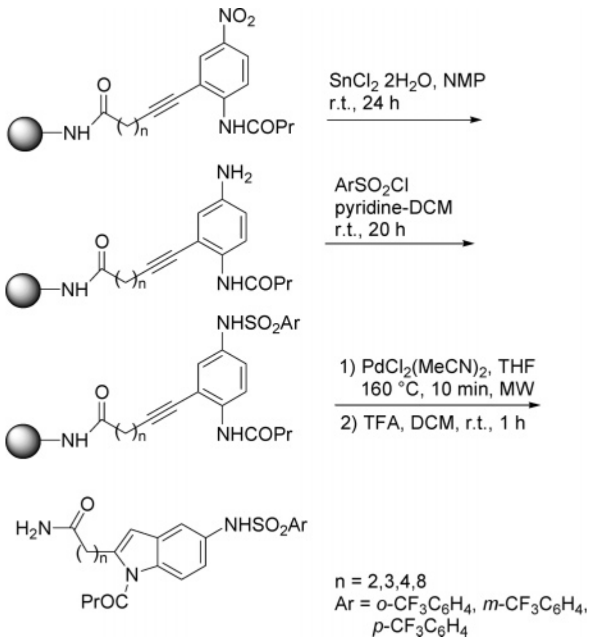
As to the construction of indole derivatives with supported palladium catalysts, palladium on activated carbon[53a] was shown to be an active and selective single catalyst for the formation of 2-phenyl indole (isolated in 72% overall yield) from phenylacetylene through a domino Sonogashira coupling−intramolecular heteroannulation. The coupling intermediate was never observed, indicating that heteroannulation is rapid under reaction conditions (1 mol % Pd/C, 1 mol % CuI, 120 °C, 6 h). Recycling experiments showed that a strong deactivation of the catalyst occurs during the first run, giving a Pd/C catalyst with an average activity of ca. 20% of the initial activity. Quite recently, a one-pot domino synthesis of 2-alkyl- and 2-aryl-substituted indoles from terminal alkynes and *o*-iodoanilides in water using 10% Pd/C was reported.[53b] The reaction was carried out in the presence of PPh_3 and CuI as the cocatalyst system and 2-aminoethanol as the base at 80 °C. Highest yields were obtained with *N*-mesylanilides (producing *N*-mesylindoles), whereas in general, the use of *o*-iodotrifluoroacetanilides did not afford good yields.

It was also shown that 2-substituted indoles can be obtained through the reactions of *o*-iodoaniline, *o*-iodoacetanilide, *o*-iodotrifluoroacetanilide, and *N*-(*o*-iodophenyl)methansulfonamide with phenylacetylene on potassium fluoride doped alumina in the presence of palladium powder, cuprous iodide, and triphenylphosphine under solvent-free and microwave-assisted conditions.[54a] Indeed, advancement in instrumentation, with the possibility of performing reactions in closed vessels in a temperature- and pressure-controlled manner, has gained increasing popularity to microwave-assisted organic synthesis. The best result was obtained with *N*-(*o*-iodophenyl)mesylamide, which afforded exclusively the indole product in 80% yield. *o*-Iodoanilides and terminal alkynes were converted into the corresponding 2-substituted indoles with a Pd(II)−NaY zeolite catalyst in DMF at 140 °C in the presence of LiCl and Cs_2CO_3.[54b] The catalyst was recycled five times with addition of LiCl and Cs_2CO_3 to each reaction, showing good catalytic reusability, though slightly lower yields were obtained and a longer reaction time was necessary each time.

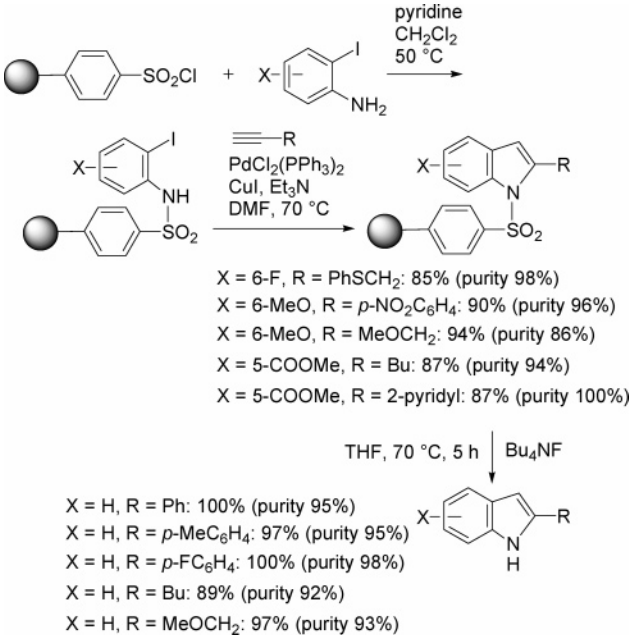
Several solid-phase syntheses of indole derivatives for the generation of indole-based combinatorial libraries were also developed. Solid-phase synthesis has had a significant impact in medicinal chemistry, and the indole ring system is an attractive scaffold for combinatorial synthesis. Structural diversity can be readily increased via ring substitution. One of the first problems to be addressed in designing a solid-phase indole synthesis is how to graft the indole precursor on the resin. Some solid-phase syntheses are based on ester[45a] and amide[55] linkers at the benzene moiety. As an example of an amide linker involving the benzene ring, 2-substituted 3-aminomethylindoles were prepared through a sequence based on the palladium-catalyzed coupling−cyclization of an *o*-iodomesylanilide bound to the resin via a benzamide linkage, followed by a Mannich condensation.[55] Some crude yields for Mannich reaction products, based on the loading level of the resin, are shown in Scheme 11.

Amide linkers involving the pyrrole nucleus were also employed (Scheme 12).[56] The palladium-catalyzed cyclization of resin-bound *o*-alkynylanilides were performed under microwave-assisted conditions. Speeding up organic reactions carried out on solid polymeric supports appears ideally suited for solid-phase combinatorial synthesis. In fact, because of its heterogeneous nature, solid-phase synthesis is often flawed by long reaction times, incomplete conversion of starting materials, or both. In the latter case, impurities may accumulate on the polymeric surface and lower the purity of compound libraries. Under

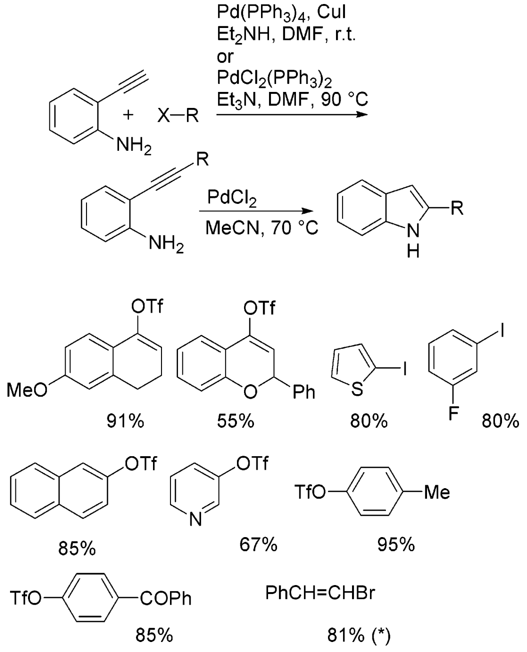
Scheme 12



Scheme 13



Scheme 14[a]



[a] (*) indicates that a commercially available *E*/*Z* mixture was used, but only the isomeric *E* derivative was isolated.

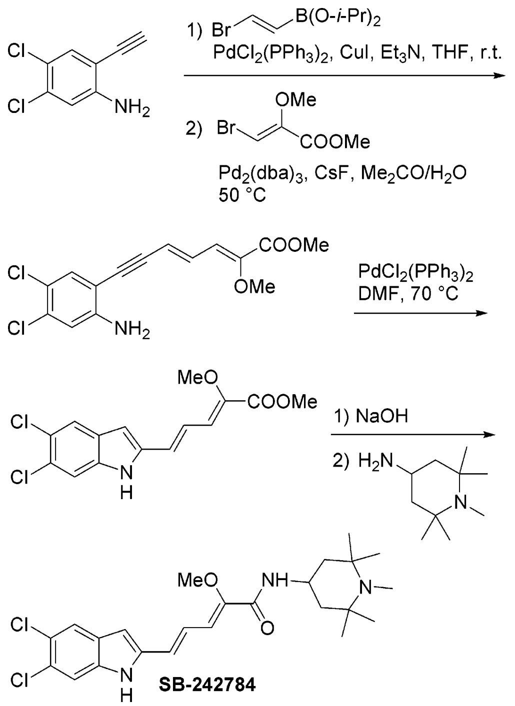
microwave-assisted conditions, 1-acyl-2-alkyl-5-arenesulfamoylindoles were obtained, after cleavage from the resin, in 95–99% purities and in 65–82% overall yields.

The preceding syntheses are examples of utilization of linkers that remain as substituents in the final indole derivatives. However, extraneous substituents such as COOH and CONH$_2$ remaining in the final product after cleavage can well be undesirable in certain indole libraries. This may represent a limit to the scope of the solid-phase approach to the synthesis of indole products and has led to the development of procedures for the solid-phase construction of indole derivatives based on traceless linkers.[57] One interesting example of such a strategy, applied by Zhang and co-workers to the synthesis of 2-substituted indoles via the coupling–cyclization methodology,[57a] is shown in Scheme 13. The linker is a sulfonyl group, which plays a doubly significant role: it serves as an activating group to facilitate the cyclization step and, after indole formation, favors the cleavage step. The cleavage step can be performed under mild conditions, which should allow the synthesis of diverse indole derivatives bearing either base- or acid-sensitive functional groups. Other reaction conditions were explored and potassium *tert*-butoxide was found to provide excellent results in the synthesis of 2-phenylindole. However, its use could be limited since strongly basic conditions may not tolerate a wide range of functional groups.

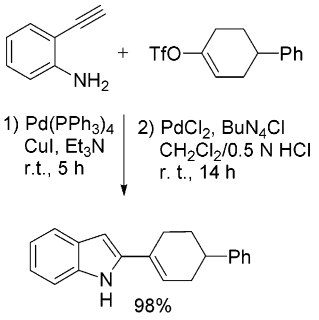
All the previously mentioned procedures require specific 1-alkynes for each indole, and this can sometimes limit their substrate scope. Furthermore, employing *o*-haloanilides usually requires an additional operative step to generate free NH indole derivatives. Cacchi et al.[58] developed an alternative approach in which free NH 2-substituted indoles can be synthesized from the same acetylenic building block: *o*-ethynylaniline. The synthesis of *o*-ethynylaniline is readily accomplished in high yield via palladium-catalyzed coupling of *o*-iodoaniline with ethynyltrimethylsilane followed by a desilylation step.[58] This indole synthesis features a palladium-catalyzed coupling of *o*-ethynylaniline with vinyl and aryl triflates or halides and a palladium-catalyzed cyclization. General reaction conditions are shown in Scheme 14.

Researchers at SmithKline Beecham exploited this strategy to develop a “three-component” approach to SB-242784, an indole derivative reported to be a potential inhibitor of the vacuolar H$^+$-ATPase for the treatment of osteoporosis[59] (Scheme 15). The key step of the process is the coupling between the alkyne and diisopropyl-(*E*)-bromovinylboronate, which was shown to occur exclusively at the carbon bearing the bro-

Scheme 15



Scheme 16

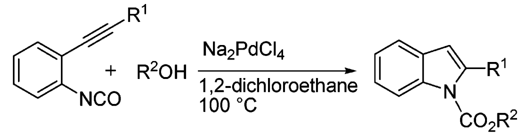


mide. Subjecting the resultant coupling intermediate to Suzuki conditions in the presence of methyl 2-methoxy-3-bromoacrylate afforded the desired yne-diene product with complete stereocontrol. No other double bond stereoisomers were observed in the crude reaction mixture.

Subsequently, Cacchi et al. implemented this approach to 2-substituted indoles by developing a procedure where the cyclization step is performed under an acidic two-phase system at room temperature.[51] This coupling/cyclization approach to 2-substituted indoles can also be conducted as a one-pot process omitting the isolation of the coupling intermediates (Scheme 16).

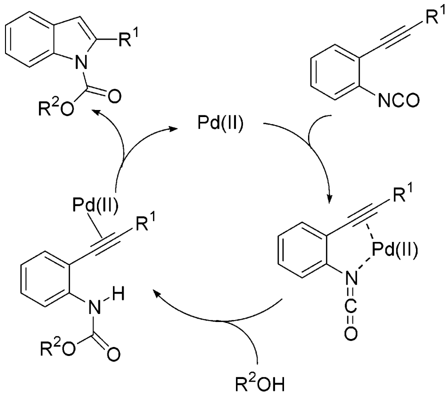
A route to 2-substituted indoles from *o*-(alkynyl)-phenylisocyanates was recently described by Yamamoto et al.[60b] (Scheme 17). Reactions were carried out in the presence of Na_2PdCl_4, but other Pd(II) catalysts, such as $PdCl_2$ and $PdCl_2(MeCN)_2$, were found to exhibit similar catalytic activities. Other transition metals were tested and Pt(II) and Au(III) exhibited catalytic activity to form indole products. Interestingly, an argon atmosphere was not necessary. The catalytic activity seemed to be high for a few hours even in the presence of oxygen. The proposed reaction mechanism is outlined in Scheme 18. The catalyst exhibits a dual role: it accelerates the addition of alcohols to the isocyanate group and activates the alkynes for the subsequent cyclization.

Scheme 17



R^1	R^2	time (h)	yield %
Pr	Pr	1.5	74
cyclopentyl	Pr	1.5	83
t-Bu	Pr	2	89
Ph	Pr	1.5	59
p-MeO-C_6H_4	Pr	1.5	58
p-CF_3-C_6H_4	Pr	1.5	55
H	Pr	2	45
Pr	Me	1.5	65
Pr	*i*-Pr	2	67
Pr	*t*-Bu	24	56

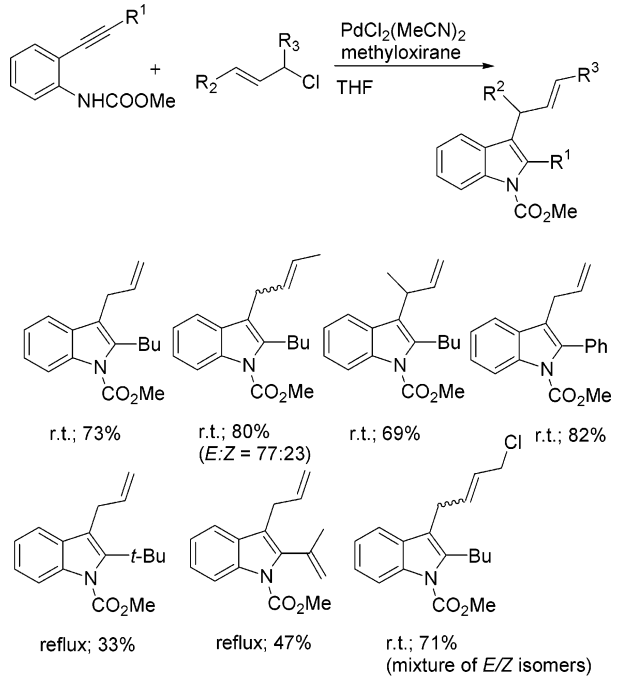
Scheme 18



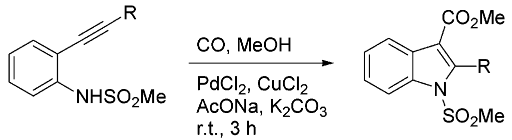
Formation of 2-substituted indoles via palladium-catalyzed cyclization of aromatic compounds containing alkyne substituents ortho to nitrogen nucleophiles involves trapping of σ-indolylpalladium intermediates with protons, so as to substitute the C−H bond for the C−Pd bond (Scheme 4). These σ-indolylpalladium intermediates, however, can be trapped by other reagents so that the cyclization step can combine with the functionalization of the indole nucleus at the position 3. The potential of this trapping approach to the synthesis of indole derivatives has not gone unnoticed, and some domino processes based on this strategy were developed.

Utimoto et al.[61] described an allylative cyclization of *o*-alkynyl-*N*-methoxycarbonylanilides (Scheme 19). The nature of the nitrogen nucleophile plays an important role in the cyclization reaction. The unprotected amino group or the acetamido group gave unsatisfactory results. With *N*-methoxycarbonylanilides the reaction usually occurs under mild conditions and proceeds through a regioselective attack of the σ-indolylpalladium intermediate on the γ position of allyl chorides. A lack of olefin geometry was observed in some cases. A large excess of the allyl chloride (10:1 allyl chloride-to-alkyne ratio) was needed to obtain the best results. The presence of an

Scheme 19



Scheme 20

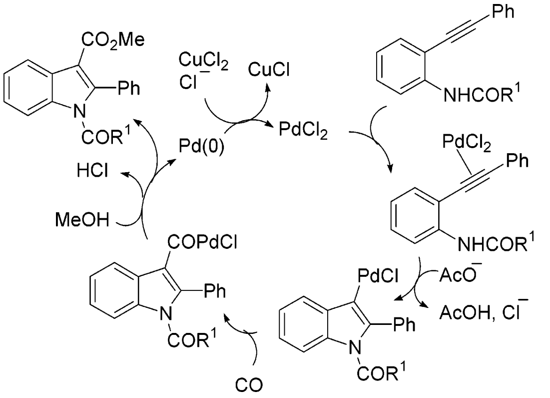


R = Ph (76%)
R = Bu (67%)

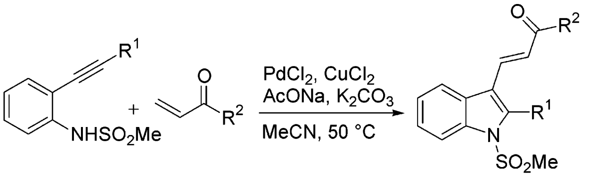
oxirane (typically methyl oxirane) as the proton scavenger was shown to be crucial for preventing the competitive protonation leading to 3-unsubstituted 2-substituted indoles. For example, when the allylative cyclization of *o*-(hexyn-1-yl)-acetanilide was attempted omitting methyl oxirane, about 30% of the allylated product and 20−35% of the protonated one were obtained. Variable amounts of 3-unsubstituted 2-substituted indoles were observed, even under the best conditions developed. Employing AcOK and proton sponge instead of methyl oxirane led to the recovery of the starting material.

It was subsequently shown that σ-indolylpalladium intermediates could be trapped by carbon monoxide[62] and electron-poor alkenes[63] to give, respectively, indole products incorporating a molecule of carbon monoxide at the C-3 position and 2-substituted 3-vinyl indole derivatives. In the first case, treatment of *o*-alkynyl-mesylanilides with $PdCl_2$ in methanol under an atmosphere of carbon monoxide afforded σ-acylpalladium derivatives, which reacted with methanol to give indolylcarboxylate esters (Scheme 20). Palladium(0) species formed in this step of the catalytic cycle were oxidized to the active palladium(II) species by $CuCl_2$. The reaction did not proceed when using 1,4-benzoquinone, disodium peroxysulfate, or molecular oxygen. *o*-Alkynylanilines, containing a free amino substituent, did not function well in this reaction: 2-phenyl- and 2-butylindole were isolated in 51% and 30% yield, respectively. The proposed catalytic cycle is outlined in Scheme 21.

Scheme 21

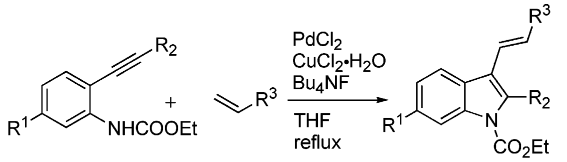


Scheme 22



R^1 = Ph; R^2 = OEt (74%)
R^1 = C_6H_{13}; R^2 = OEt (46%)
R^1 = Me_3Si; R^2 = OEt (32%)
R^1 = Ph; R^2 = Me (55%)
R^1 = Ph; R^2 = H (48%)

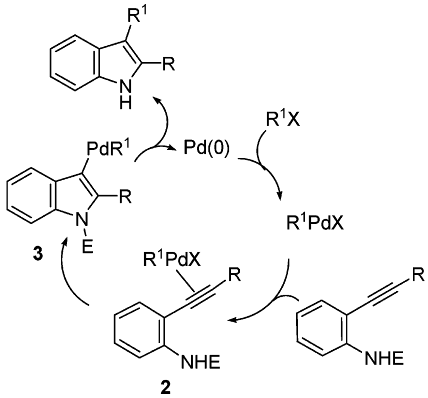
Scheme 23



R^1	R^2	R^3	time (h)	Yield %
H	Ph	COOMe	4	64
H	Ph	Bu	3	68
MeO	Ph	Bu	8	42
Cl	Ph	COOMe	6	66
CN	Ph	COOMe	22	66
Cl	Ph	CN	4.5	31

Similar conditions were used to develop a domino cyclization−Heck reaction producing 2-substituted 2-substituted 3-vinyl indoles[63] (Scheme 22). The reaction, however, appears to be limited to alkenes containing electron-withdrawing groups. Extension to styrene was attempted, but the corresponding 2-substituted 3-vinyl indole was isolated in only 19% yield, the main product being an addition derivative containing chlorine. Building on these studies, improvements in this approach to 2,3-disubstituted indoles were subsequently reported.[64] In the presence of $PdCl_2$, $CuCl_2{\cdot}H_2O$ as a reoxidant (low yields were obtained with anhydrous $CuCl_2$), and excess amounts of Bu_4NF, ethyl 2-ethynylphenylcarbamate derivatives were shown to react according to the domino cyclization−Heck reaction protocol even with alkenes lacking the activation of a carbonyl group (Scheme 23).[64] 2-Substituted indole byproducts were isolated in variable amounts. With other reoxidants such as $Cu(OAc)_2$, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and pyridine 1-oxide, the reaction failed to give the desired products. With *o*-alkynylanilides containing

Scheme 24



internal alkene groups bound to the alkyne fragment, the indolylpalladium intermediate formed in the cyclization step could undergo an intramolecular Heck reaction to give carbazole derivatives.

4.1.2. Cyclization of o-Alkynylanilides via Aminopalladation–Reductive Elimination

Disconnection a−d, Figure 1. In addition to palladium(II) salts, activation of carbon−carbon triple bonds toward intramolecular nucleophilic attack of proximate nucleophiles can be achieved via coordination to organopalladium(II) complexes. After the pioneering work of Tsuda and Saegusa in 1988,[65] who showed that π-allylpalladium complexes could activate a carbon−carbon triple bond toward the intramolecular nucleophilic attack of carboxylate anions to give lactones, this methodology has developed into a general powerful tool for the synthesis of a wide range of hetero- and carbocycles.[66]

With alkynes containing nitrogen nucleophiles close to the carbon−carbon triple bond, particularly *o*-alkynylanilides, coordination to organopalladium(II) complexes can produce indole derivatives. Organopalladium complexes, exemplified as "R^1PdX" in Scheme 24, can be generated in situ through an oxidative addition of organic halides or triflates to palladium(0) species and give the π-alkyne−organopalladium complexes **2**. The characteristic feature of this route to indoles is that the intramolecular nucleophilic attack by the nitrogen atom across the activated carbon−carbon triple bond affords σ-indolyl-σ-organopalladium intermediates **3** instead of σ-indolylpalladium halide intermediates **1** as observed with palladium(II) salts (see Scheme 4). The desired indole derivative is produced through a reductive elimination reaction (considered as the coupling of two groups coordinated to the palladium center in a cis manner), which forms a new carbon−carbon bond and regenerates the active palladium(0) catalyst. With the σ-indolylpalladium halide intermediates **1** involved in the cyclization of *o*-alkynylanilides catalyzed by palladium(II) salts, the catalytic cycle is terminated by a protonation step (see Scheme 4).

This is the basis of the indole synthesis that Cacchi and co-workers developed and thoroughly investigated. Optimum yields were obtained by using *o*-alkynyltrifluoroacetanilides ($E = CF_3CO$) as the alkyne partners, whereas *o*-alkynylanilines ($E = H$) and *o*-alkynylacetanilides ($E = MeCO$) provided unsatisfactory results. Apparently, the acidity of the nitrogen−hydrogen bond plays a major role in this cyclization reaction. Most probably, the beneficial effect of the trifluoroacetyl group on the cyclization step is due to its ability to favor the formation of a stronger anionic nitrogen nucleophile or to promote the intramolecular nucleophilic attack by proton removal in the transition state leading to the cyclization adduct. Whatever the real mechanism may be, it remains that organopalladium complexes appear to be less effective than palladium dichloride in activating the carbon−carbon triple bond toward intramolecular nucleophilic attack, as suggested by a variety of cyclizations of alkynes containing close amino[39,67,68] and amido[37,40,41,55,56,61−64,69] groups catalyzed by palladium(II) salts. The trifluoroacetyl group provides the additional advantage of being readily removed (the amide bond is broken during the reaction or the workup) so as to allow for the formation of free NH pyrrole nuclei, avoiding troublesome and time-consuming deprotecting steps. Carbonate bases were found to be better bases than Et_3N.

A broad range of 2,3-disubstituted indoles can be prepared from *o*-alkynyltrifluoroacetanilides and aryl, heteroaryl, and vinyl halides or triflates,[70] allyl esters,[71] alkyl halides,[72] and alkynyl bromides[73] by using this methodology. With aryl, heteroaryl, and vinyl halides or triflates,[70] reactions were carried out according to the conditions shown in Scheme 25. The reaction tolerates a variety of functional groups, including aldehyde, ketone, ester, nitro, and nitrile groups. Substituents close to the oxidative addition site do not hamper the reaction. As for the alkyne component, indole derivatives were obtained in high yield with alkynes containing alkyl, vinyl, electron-withdrawing, and electron-donating substituents on the alkyne moiety.

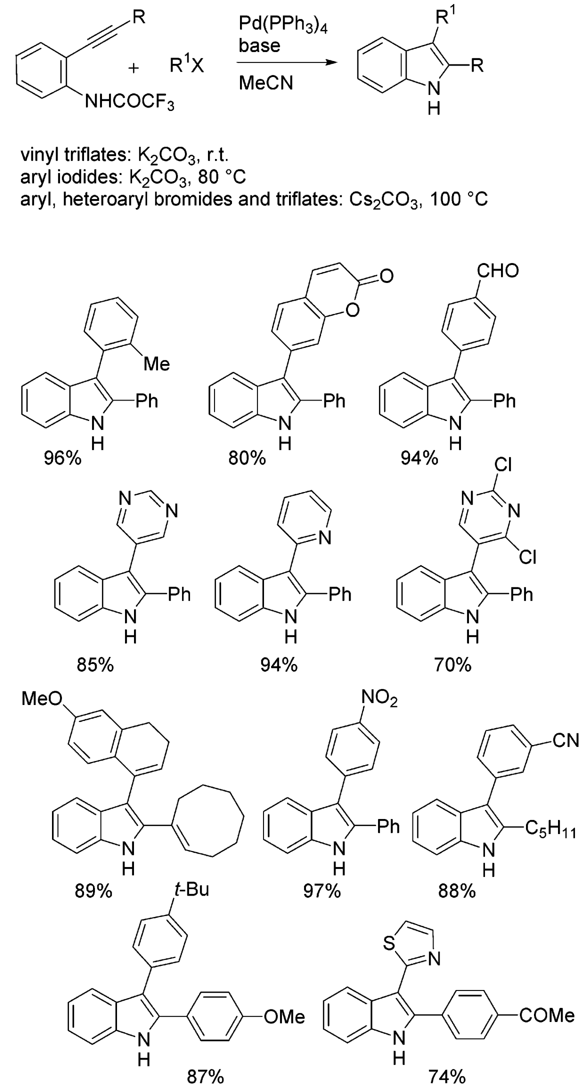
The reaction is particularly suited for a straightforward preparation of symmetrical and unsymmetrical 2,3-diarylindoles, a class compounds of which the biological activity is the object of a continuing interest. The success with the preparation of 3-thiazolyl indoles is particularly interesting since the indole−thiazole motif is incorporated in a variety of biologically active compounds such as camalexins or the naturally occurring BE 10988, an inhibitor of topoisomerase. In addition, the thiazolyl group can be readily converted into a formyl group[74] to afford 2-substituted indole-3-carboxaldehydes (Scheme 26).

Interestingly, when the methodology was applied to bis(*o*-trifluoroacetamidophenyl)acetylene, the initially formed indole derivative was found to undergo a subsequent cyclization process to afford 12-aryl- (or vinyl) indole[1,2-*c*]quinazolines, usually in high to excellent yields, with a variety of aryl and vinyl halides or triflates (Scheme 27).

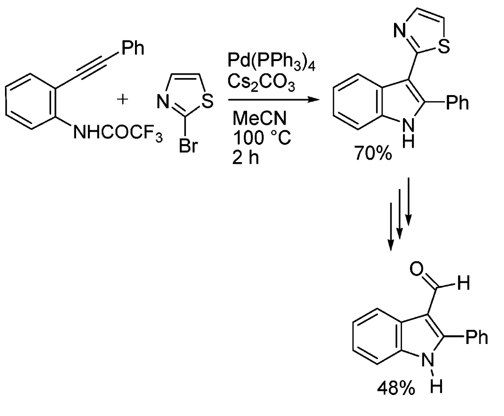
Extension of the methodology to the construction of the functionalized pyrrole nucleus on heteroaromatic scaffolds provided a new access to pyrroloquinoxaline[75] and azaindole[76] derivatives.

Alkyl halides, particularly ethyl iodoacetate and benzyl bromides, were also employed in the amino-

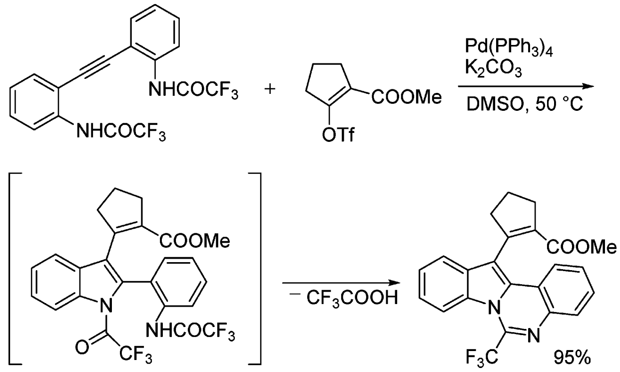
Scheme 25



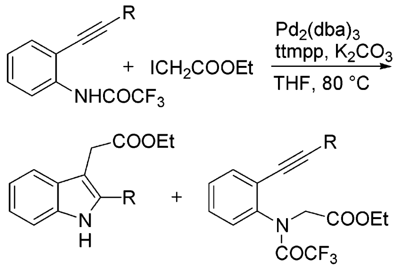
Scheme 26

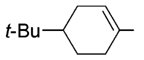
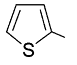


Scheme 27



Scheme 28

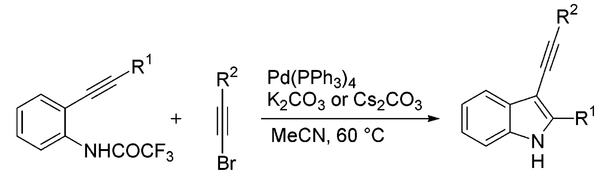


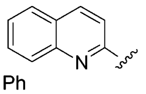
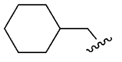
R	time (h)	indole yield %	*N*-alkyl derivative yield %
Ph-	2	73	traces
m-Me-C_6H_4-	4	70	20
p-MeCO-C_6H_4-	3	64	17
p-MeOOC-C_6H_4-	3	61	14
Bu-	4.5	44	14
 *t*-Bu	5	78	traces
 S	4	41	traces

palladation−reductive elimination route to indoles to prepare indolylcarboxylate esters and 2-substituted 3-benzylindoles.[70d,72] Under conditions successfully used for the preparation of 2,3-disubstituted indoles from aryl, heteroaryl, and vinyl halides or triflates,[69] the reaction met with failure, the main or sole product being the *N*-alkyl derivative generated through a competitive nucleophilic substitution reaction. Noteworthy, *N*-alkyl derivatives proved to be useful intermediates for the synthesis of 2-acyl-3-alkylindoles.[77] The solvent was found to play a crucial role for the success of the reaction. For example, using DMSO as the solvent but keeping all the other parameters the same, *o*-(phenylethynyl)trifluoroacetanilide produced the corresponding indolecarboxylate ester in only 12% yield, whereas 2-ethoxycarbonyl-3-benzylindole[77] was isolated in 64% yield. Investigations into the role of ligands, bases, and solvents led to the observation that best results could be obtained by using $Pd_2(dba)_3$, the strongly basic, electron-rich, sterically encumbered ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp),[78] and K_2CO_3 in THF at 80 °C. Under these conditions, good selectivity was observed in favor of the palladium-catalyzed cyclization and a number of *o*-alkynyltrifluoroacetanilides were converted into the desired indole products in satisfactory yields (Scheme 28). Similar results were obtained with benzyl bromides.

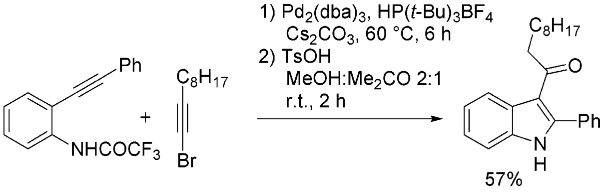
In a subsequent extension of the substrate scope of the methodology, it was shown that *o*-alkynyltrifluoroacetanilides could be treated with 1-haloalkynes to give 2-substituted 3-alkynylindoles.[73] Satisfactory yields were obtained with 1-bromoalkynes, usually under the conditions shown in Scheme 29, whereas 1-iodoalkynes did not function well in this reaction, most probably because of their tendency to undergo

Scheme 29

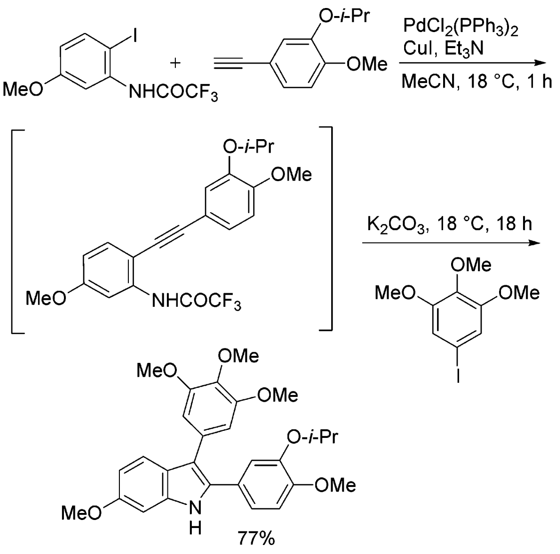


R^1	R^2	yield %
Ph	Ph	78
Ph	p-CHO-C_6H_4	86
Ph	p-MeCO-C_6H_4	65
Ph	p-NO_2-C_6H_4	66
Ph	o-NO_2-p-Me-C_6H_3	81
Ph	C_7H_{13}	48
Ph		52
p-MeO-C_6H_4	Ph	75
p-MeO-C_6H_4	p-MeCO-C_6H_4	73
p-MeO-C_6H_4	o-NO_2-p-Me-C_6H_3	85
p-MeCO-C_6H_4	Ph	52
p-MeCO-C_6H_4	p-NO_2-C_6H_4	59
Ph		53
CH_2OTHP	p-MeCO-C_6H_4	56

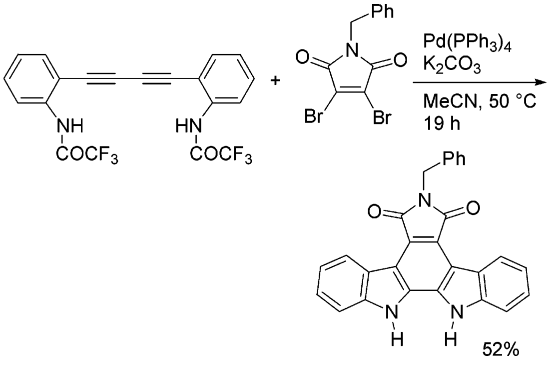
Scheme 30



Scheme 31



Scheme 32



side reactions under the conditions used. For example, 1-iodoalkynes were recently shown to undergo palladium-catalyzed homocoupling to give 1,3-diynes.[79]

2-Substituted 3-alkynylindoles were found to be useful intermediates for the regioselective synthesis of 2-substituted 3-acylindoles. The addition of water promotes the reaction regioselectivity in high yield at room temperature in the presence of catalytic amounts of TsOH. The presence of electron-withdrawing or electron-donating substituents in the C2-position or in the alkyne moiety does not influence the regioselectivity of the acid-induced hydration. 2-Substituted 3-acylindoles can be conveniently prepared from *o*-alkynyltrifluoroacetanilides and 1-bromoalkynes via a one-pot cyclization–hydration protocol, omitting the isolation of 2-substituted 3-alkynylindoles (Scheme 30).

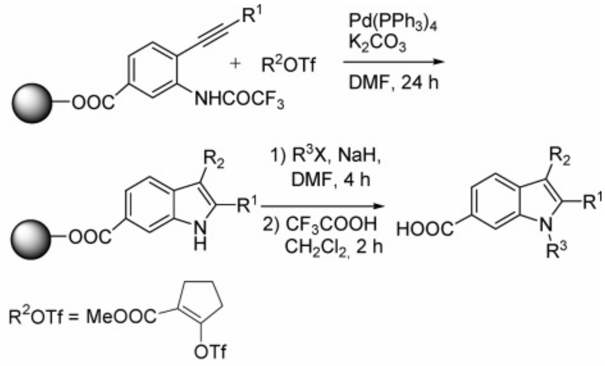
The aminopalladation–reductive elimination protocol for the synthesis of 2,3-disubstituted indoles was applied by Flynn et al.[80,81] to the preparation of indole inhibitors of tubulin polymerization through a one-pot process at room temperature (Scheme 31). The appropriate *o*-iodotrifluoroacetanilide was coupled to the terminal alkyne under Sonogashira conditions in acetonitrile to give the coupling product. When this coupling was complete, the aryl iodide and K_2CO_3 were added. After 18 h, the desired indole product was isolated in an overall 77% yield.

Extension to the synthesis of the parent indolo[2,3-*a*]carbazole ring system, common to several biologically active molecules such as arcyriaflavin A and the potent antitumor agent rebeccamycin, led to an elegant, straightforward process involving a polyannulation reaction wherein two C–C bonds and two C–N bonds are formed in a single step (Scheme 32).[43a]

The Cacchi route to substituted indoles was also adapted to a solid-phase synthesis for the preparation of libraries of three independently substituted indoles using a Wang resin[82] (Scheme 33). The Wang resin was converted into the alkyne precursor for the palladium-catalyzed cyclization through a three-step process. Interestingly, K_2CO_3 was found to be the optimal base for the cyclization step even though it could be expected that a soluble base would be needed for a solid-phase synthesis.

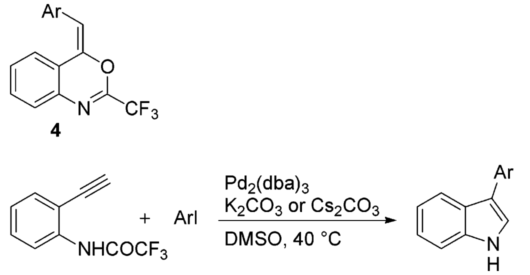
The methodology was extended to the preparation of 2-unsubstituted 3-aryl indoles from *o*-ethynyltrifluoroacetanilide.[83] The reaction of aryl iodides with this anilide, containing an ortho terminal alkyne moiety, needed much more optimization, because formation of coupling derivatives[42d,e] was a significant side reaction under the standard conditions developed for *o*-alkynyltrifluoroacetanilides. Indeed, coupling derivatives were observed under a number of reaction conditions, using a variety of phosphine ligands. With tris(*p*-chlorophenyl)phosphine, for example, the reaction of *o*-ethynyltrifluoroacetanilide with *p*-iodoacetophenone [$Pd_2(dba)_3$, THF, 60 °C, 7 h] afforded the coupling derivative in 83% yield. In

Scheme 33



R¹	R³		
	H	Me	CH₂COOEt
(CH₂)₃Me	34%	33%	55%
Ph	60%	58%	71%
(CH₂)₃O-C₆H₄-COOMe-*m*	68%	58%	40%
CH₂N(Me)CO-C₆H₄-OMe-*p*	76%	70%	73%

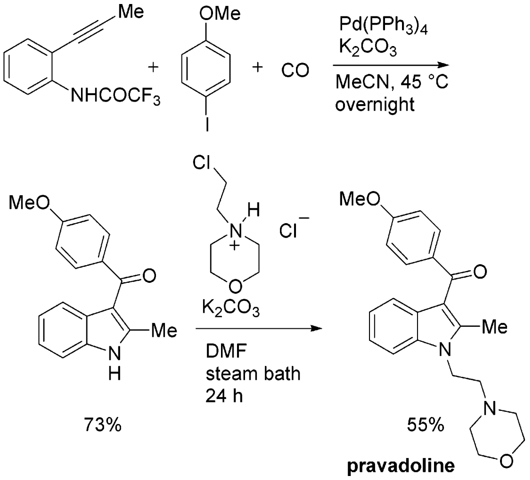
Scheme 34[a]



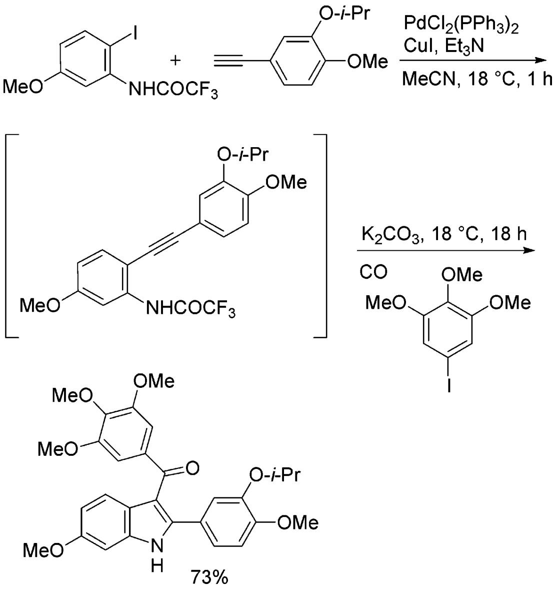
[a] ArI = PhI (67%); *p*-Me−OC₆H₄−I (56%); *p*-MeCONH−C₆H₄−I (62%); *p*-F−C₆H₄−I (71%); *m*-F−C₆H₄−I (57%); *p*-Cl−C₆H₄−I (86%); *m*-CF₃−C₆H₄−I (82%); *p*-EtOOC−C₆H₄−I (69%); *m*-EtOOC−C₆H₄−I (78%); *m*-NO₂-*p*-Me-C₆H₃−I (69%); *m*-NO₂−C₆H₄−I (85%); *p*-Me-C₆H₄−I (63%).

addition, formation of **4**, derived from the nucleophilic attack of the oxygen at the "internal" carbon of the activated carbon−carbon triple bond, was also found to be a significant side reaction. Both the nature of the solvent and the catalyst system were shown to have a strong influence on the *N*-/*O*-cyclization ratio. Best results were obtained by using $Pd_2(dba)_3$ as the palladium(0) source, DMSO as the solvent, and K_2CO_3 as the base, omitting phosphine ligands (Scheme 34). Cs_2CO_3 was also successfully employed. When *o*-ethynyltrifluoroacetanilide was subjected to the same reaction conditions omitting aryl iodides, indole was isolated in 80% yield.

Scheme 35



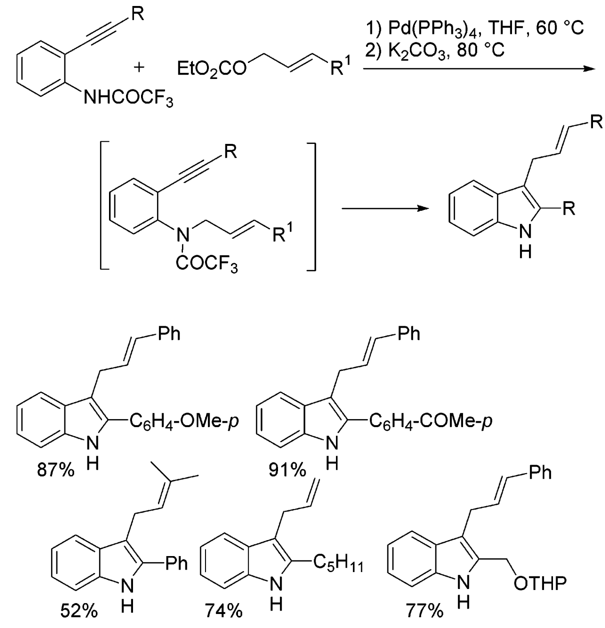
Scheme 36



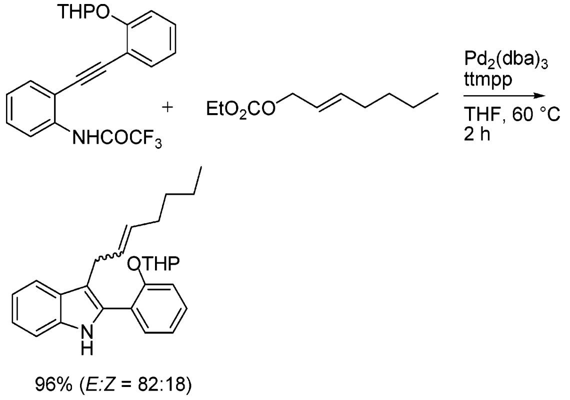
In a further extension of the scope of the aminopalladation−reductive elimination route to indoles, the above group showed that the reaction of *o*-alkynyltrifluoroacetanilides with aryl iodides and vinyl triflates in the presence of carbon monoxide afforded 2-substituted 3-acyl indoles,[70d,84] a class of compounds exhibiting a number of important therapeutic activities, in fair to good yields. With neutral, electron-rich, or slightly electron-poor aryl iodides and vinyl triflates, this three-component reaction gives satisfactory results using $Pd(PPh_3)_4$ and K_2CO_3 in MeCN at 45 °C under a balloon of carbon monoxide. With strongly electron-poor aryl iodides, such as ethyl *p*-iodobenzoate, the use of anhydrous acetonitrile and a higher pressure of carbon monoxide appeared necessary. Alternatively, good results could be obtained with $Pd(dba)_2$/P(*o*-tol)$_3$ under a balloon of carbon monoxide. Very likely, the reaction proceeds according to the following basic steps: (a) carbonylation of a σ-organopalladium complex formed in situ through oxidative addition of an organic halide or triflate to palladium(0) to give a σ-acylpalladium complex; (b) formation of a π-alkyne−σ-acylpalladium complex via coordination of the alkyne to the palladium atom of the σ-acylpalladium complex; (c) intramolecular nucleophilic attack of the nitrogen to the activated carbon−carbon triple bond to give a σ-acyl−σ-indolylpalladium complex; (d) reductive elimination. Other mechanisms involving carbonylation of a σ-organo-σ-indolylpalladium complex or the addition of a σ-acylpalladium complex to the carbon−carbon triple bond were also considered. The utility of this methodology was demonstrated in a new synthesis of pravadoline,[84] an indole derivative with analgesic activity in humans (Scheme 35) and, through a one-pot reaction at room temperature, of indole inhibitors of tubulin polymerization (Scheme 36).[80,81]

When the reaction was applied to *o*-(*o*′-aminophenylethynyl)trifluoracetanilide, 6-aryl-11*H*-indolo[3,2-*c*]quinolines were produced through a carbonylative

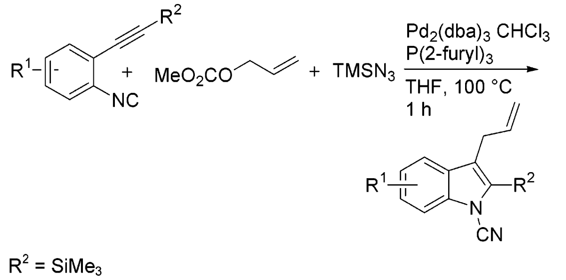
Scheme 37



Scheme 38



Scheme 39



R^1	yield %
H	59
4-MeO	69
4-MeS	67
4-PhN=N	45
4-F	56
$4\text{-}CF_3$	65
$4\text{-}CO_2Me$	53
4-MeCO	37
5-Me	65
3-MeO	62
$5\text{-}NO_2$	59
$4\text{-}NO_2$	34

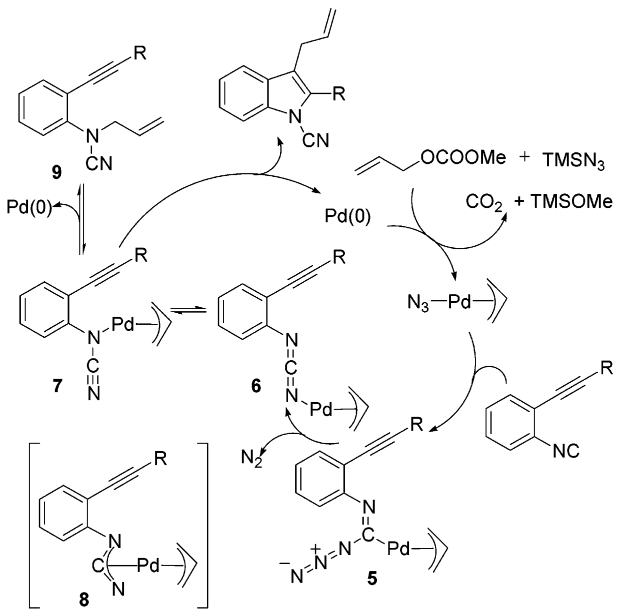
cyclization followed by the cyclization of the resulting 3-acylindoles. The synthesis was best conducted as a one-pot process.[85] Under the same carbonylative cyclization conditions, bis(*o*-trifluoroacetamidophenyl)acetylene afforded 12-acylindolo[1,2-*c*]quinazolines.[86]

Finally, the reaction of *o*-alkynyltrifluoroacetanilides with allyl esters[70d,71] provides a straightforward route to 2-substituted 3-allylindoles. Optimization studies developed three basic procedures: procedure A, a stepwise method based on the isolation of *N*-allylation products generated through a palladium-catalyzed *N*-allylation (only *N*-allyl derivatives bearing the nitrogen fragment on the less substituted allyl terminus were isolated), followed by a cyclization step; procedure B, a one-pot reaction that omits the isolation of *N*-allyl intermediates (Scheme 37); procedure C, a reaction that most probably does not involve the intermediacy of *N*-allyl intermediates (Scheme 38).

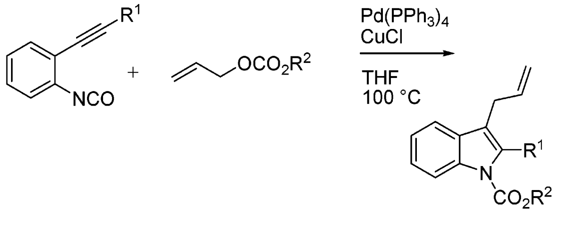
Noteworthy, procedures A and B involve an ambivalent behavior of the nitrogen atom: it intervenes in the process as a nucleophile in the *N*-allylation step and as a leaving group in the cyclization step, favoring the formation of a π-allylpalladium complex. These procedures gave good results with a variety of *o*-alkynyltrifluoroacetanilides and allylic carbonates. By use of procedure A, 2-unsubstituted 3-allylindoles were also prepared in allowable yields from *o*-ethynyltrifluoroacetanilide. The presence of a substituent on the central carbon atom of the allylic system seems to be tolerated, whereas substitution at both termini of the allylic system or sterically encumbered substituents at one end of the alkyne moiety hamper the cyclization reaction. As to the regiochemistry of the new carbon−carbon bond, the most challenging situation is posed when steric differences between the two allylic termini are small. In these cases, procedure C gave the best results. In the presence of tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) the reaction exhibits remarkable regioselectivity, and the indole unit is located almost exclusively on the less substituted terminus of the allylic system. The process is accompanied by some loss of olefin geometry.

2-Substituted 3-allylindoles were prepared by Yamamoto and co-workers via cyclization of alkynylbenzenes containing isocyano[87] and isocyanato[60] functionalities in the ortho position. In the first case, a three-component reaction of *o*-alkynylisocyanobenzenes, allyl methyl carbonate, and trimethylsilyl azide in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and tri(2-furyl)phosphine at 100 °C gave 2-substituted 3-allyl-*N*-cyanoindoles[87] (Scheme 39). Good to allowable yields are obtained with a variety of substituents in the aryl ring. The proposed mechanism is outlined in Scheme 40. An interesting and distinctive feature of this mechanism is the Curtius-like rearrangement of the π-allylpalladium intermediate **5** to the palladium−carbodiimide complex **6**. The palladium−carbodiimide complex **6** could be in equilibrium with the palladium−cyanamide complex **7**. The possible involvement of the heteroatom-containing bis-π-allylpalladium complex **8** was also suggested. *N*-Cyanoindole is generated through the insertion of the alkyne moiety into the Pd−N bond of the intermedi-

Scheme 40

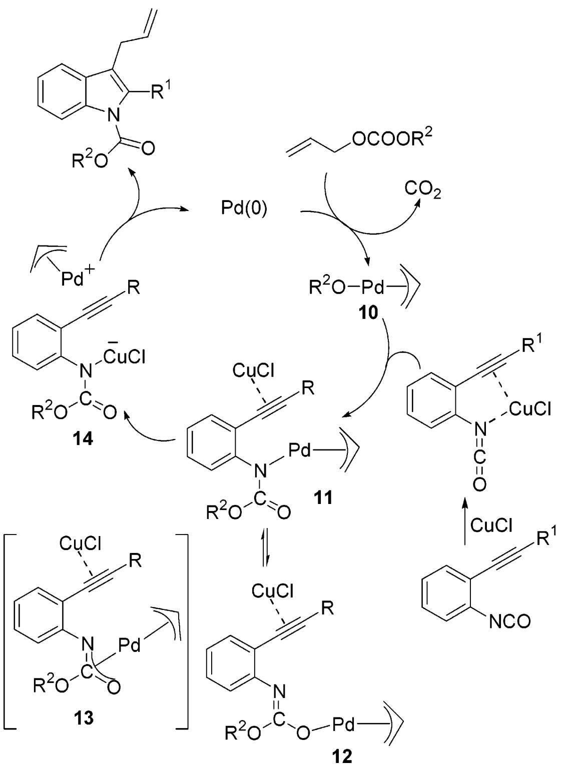


Scheme 41

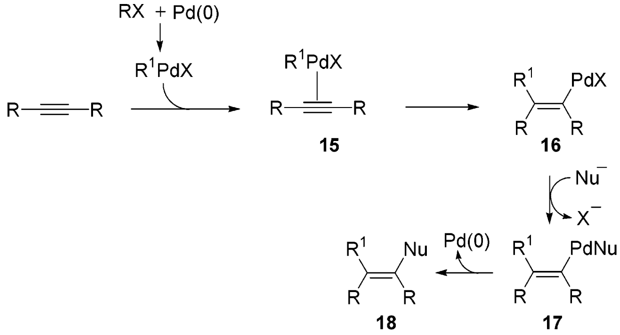


R^1	R^2	time (h)	yield %
p-MeO-C_6H_4-	Me	6	62
p-CF_3-C_6H_4-	Me	7	65
Pr	Me	1	81
cyclopentyl	Me	3	71
t-Bu	Me	5	0
Pr	*i*-Pr	1	69
Pr	*t*-Bu	1	72
Pr	Ph	1	86

Scheme 42



Scheme 43



ate **7** followed by a reductive elimination of Pd(0) (Scheme 40). Indoles are generated when the reaction is carried out at 100 °C whereas, at lower temperature (up to 40 °C), reductive elimination of Pd(0) from the palladium−cyanamide complex **7** takes place generating allyl cyanamides **9**.

In the second synthetic approach, 2-substituted 3-allyl-*N*-(alkoxycarbonyl)indoles[60] were prepared via the reaction of *o*-(alkynyl)phenylisocyanates with allyl carbonates in the presence of $Pd(PPh_3)_4$ and CuCl (Scheme 41). CuCl gave higher yields than CuBr and was found to be far superior to other copper salts such as CuI, CuOAc, $(CuOTf)_2$·benzene, and $CuCl_2$. Longer reaction times were required when R^1 was a bulky substituent, and with a *tert*-butyl group, no allylindole was obtained, the sole product being the corresponding *N*-allylaniline derivative. Electronic effects of the para substituents on the aromatic ring, as well as the bulkiness of the substituents R^2 of the allyl carbonates, did not seem to exert a significant influence on the reaction outcome.

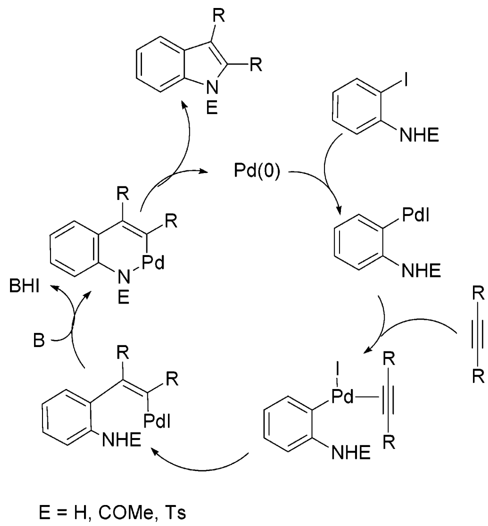
According to the authors, a likely sequence involves the reaction of the isocyanate group, activated by the coordination of CuCl, with the π-allylpalladium alkoxide complex **10** to give the π-allylpalladium complex **11** in equilibrium with **12**, which more probably could be represented as a heteroatom-containing bis-π-allylpalladium analogue **13**, a transmetalation step generating the intermediate **14**, and, most probably, a trans-aminopalladation followed by a reductive elimination (Scheme 42).

4.1.3. Intermolecular Cycloaddition of o-Iodoanilines and o-Iodoanilides with Internal Alkynes

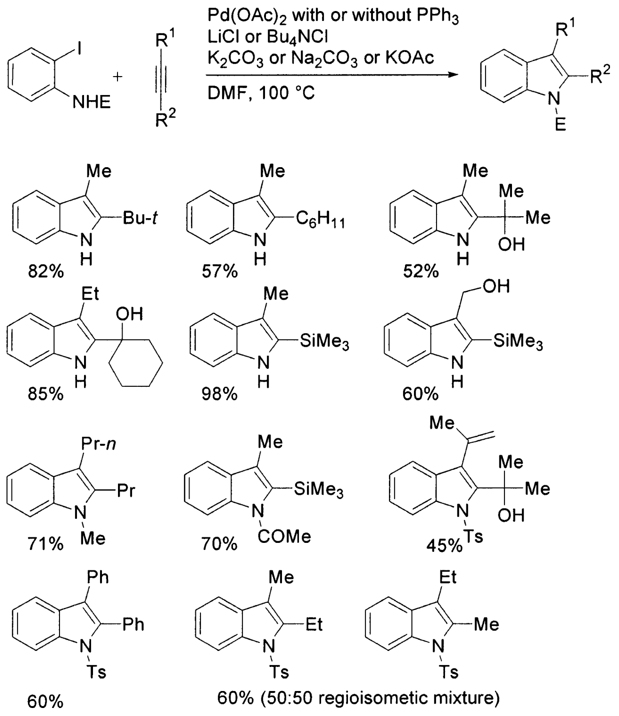
Disconnection a−e, Figure 1. In the absence of nucleophiles close to the carbon−carbon triple bond, formation of π-alkyne-σ-organopalladium complexes **15** can give rise to carbopalladation adducts **16**, which can undergo a number of transformations. For example, when they are trapped by nucleophiles such as formate anions, organometals, carbon monoxide, nitrogen, and oxygen nucleophiles,[88] halide or triflate displacement from the palladium can occur to give the intermediate **17** from which olefin derivatives **18** are formed via reductive elimination of a palladium(0) species (Scheme 43).

When the added organic moiety is an aryl group containing a nitrogen nucleophile ortho to the oxida-

Scheme 44



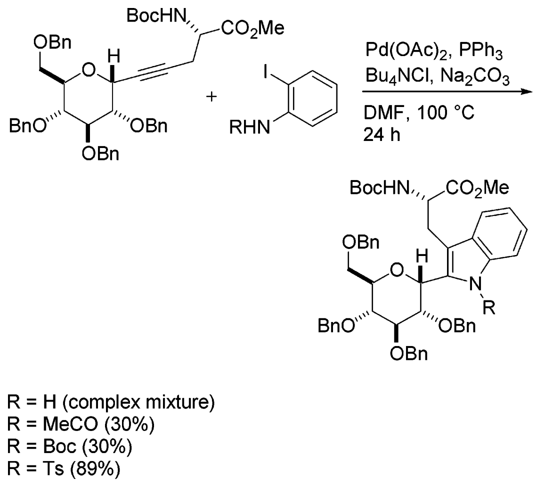
Scheme 45



tive addition site as shown in Scheme 44, intramolecular halide or triflate displacement from the palladium can occur to form a nitrogen-containing palladacycle, which subsequently affords the indole product via a reductive elimination step.

Larock et al. based his versatile and very efficient palladium-catalyzed indole synthesis on this principle. The best results were obtained treating *o*-iodoaniline or the corresponding *N*-methyl, *N*-acetyl, and *N*-tosyl derivatives with an excess of the internal alkyne and a sodium or potassium carbonate base and 1 equiv of LiCl or Bu_4NCl and occasionally adding 5 mol % of PPh_3 at 100 °C in DMF. Under these conditions, 2,3-disubstituted indoles were isolated in good to excellent yields[89c,d] (Scheme 45). With unsymmetrical alkynes the process is usually highly regioselective, the carbopalladation step being crucial to the regiochemical outcome of the reaction. Steric and coordination effects are considered to play a major role in controlling the regiochemistry of the carbopalladation step, which follows the general trend observed in related reactions.[88] Steric effects appear to control the conversion of the π-alkyne-σ-organopalladium intermediate into the carbopalladation adduct so as to direct the organic residue preferentially to the less hindered end of the carbon–carbon triple bond and the palladium moiety to the more hindered end. Coordinating effects tend to influence the formation of vinylic adducts in such a way that the added palladium ends up close to the coordinating group. In this respect, the presence of alcohol groups in the alkyne seems to have a particularly strong directing effect.

Scheme 46

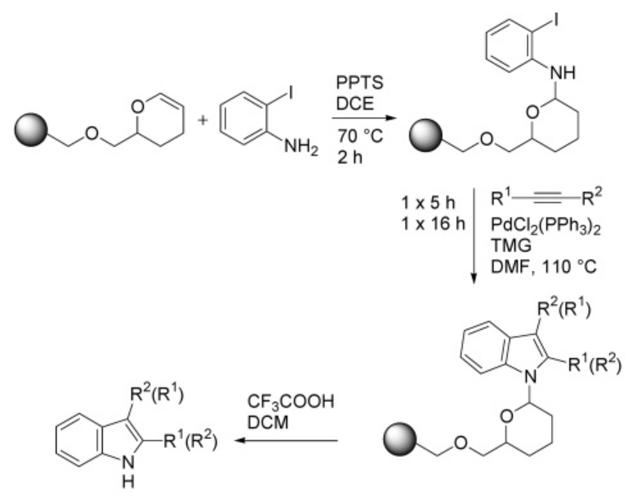


The Larock annulation reaction was widely employed for the preparation of indole derivatives. The range of products prepared demonstrates the scope and utility of the reaction. It was used in the synthesis of paramagnetic indole derivatives,[90] of 5-, 6-, and 7-azaindoles,[91] of 2,3-disubstituted pyrrolo[2,3-*b*]pyridines,[92a] of 2,3-disubstituted indoles via a reaction catalyzed by an oxime-derived, chloro-bridged palladacycle (thermally stable, not sensitive to air or moisture),[92b] and of α-*C*-glycosyl-*iso*-tryptophans[93] (Scheme 46) and in a solid-phase synthesis of trisubstituted indoles (using an amide group as a linker)[94] and in a traceless solid-phase synthesis of 2,3-disubstituted indoles[95] (Scheme 47). In the latter case, solution-phase conditions were not found to be particularly successful, incomplete reaction and large quantities of multiple acetylene insertion products being observed. Optimum yields attended the use of $PdCl_2(PPh_3)_2$ as the precatalyst, TMG as the base, and double couplings.

In most of the reactions studied, one of the acetylenic termini was a silyl group. In fact, Larock[89] showed that the annulation of silylalkynes is highly regioselective, affording 2-silylindoles, which are versatile intermediates for the synthesis of a vast array of other indole derivatives (Scheme 48).

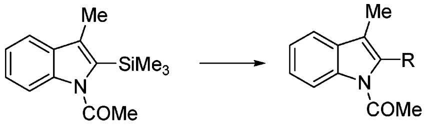
The potential of this silylalkyne approach to the synthesis of functionalized indoles was readily recognized. A range of 3-substituted 2-aryl indoles were prepared through processes featuring a silylalkyne-based Larock indole synthesis, conversion of the

Scheme 47



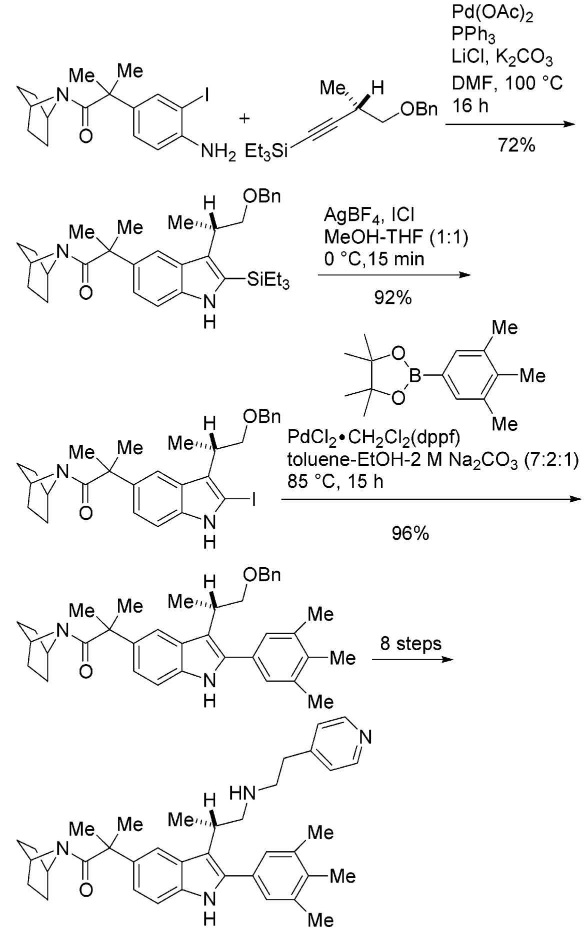
R^1	R^2	conversion (%)	isomeric ratio	mass recovery (%)
Ph	Et	100	84:15	63
TMS	Ph	100	100:0	73
Ph	Ph	93	-	97
t-Bu	Me	48	100:0	55
Pr	Pr	100	-	53

Scheme 48

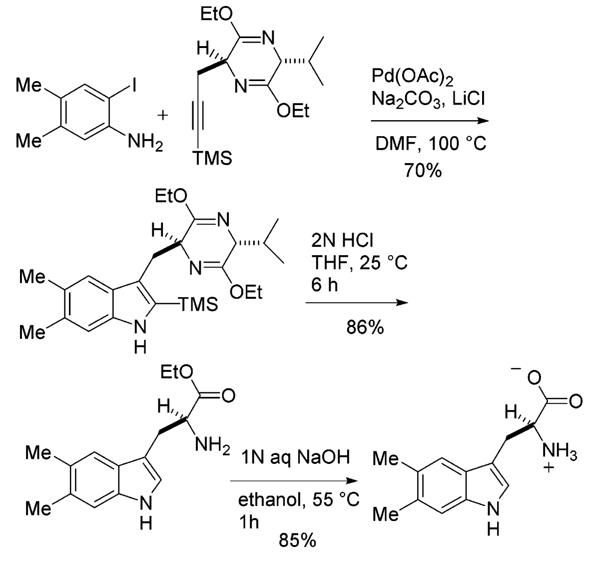


R = H (1. AlCl$_3$, 2. H$_2$O; 87%)
R = Br (NBS; 70%)
R = *E* CH=CHCOMe (CH$_2$=CHCOMe, Pd(OAc)$_2$; 50%)
R = *E* CH=CHCO$_2$Et (CH$_2$=CHCO$_2$Et, Pd(OAc)$_2$; 75%)

Scheme 49



Scheme 50

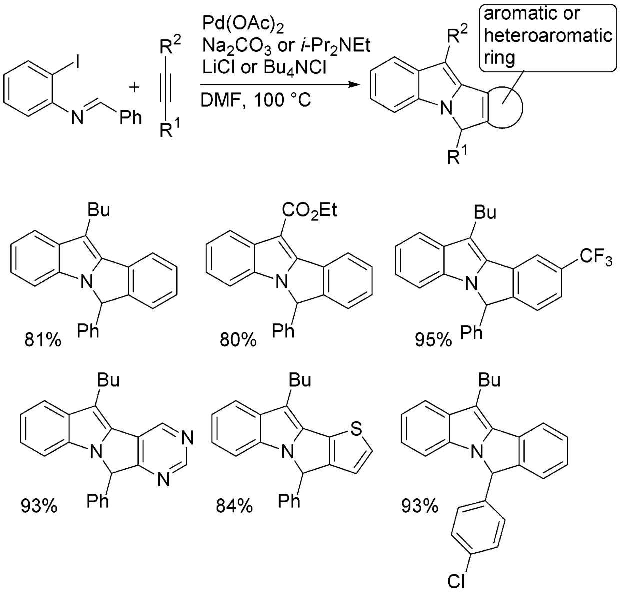


obtained 2-silylindole into the corresponding iodide derivative, and a Suzuki coupling sequence.[45d,96] For example, this route to indole derivatives was exploited to develop a convergent synthesis of (*S*)-*β*-methyl-2-aryltryptamine-based gonadotropin releasing hormone antagonists[96a] (Scheme 49). Bz-substituted tryptophans,[97a] optically active ring A substituted tryptophans[97b,c] (Scheme 50), alkoxy-substituted indole bases 16-*epi*-N_a-methylgardneral, 11-methoxyaffinisine, and 11-methoxymacroline, as well as the indole alkaloids alstophylline and macralstonine,[98a] 12-alkoxy-substituted indole alkaloids (+)-12-methoxy-N_a-methylvellosimine, (+)-12-methoxyaffinisine, (−)-fuchsiaefoline,[98b] and the 5-HT$_{1D}$ receptor agonist MK-0462,[99a] were also prepared through the annulation−desilylation sequence. This silylalkyne chemistry was also employed in the microwave-assisted solid-phase synthesis of 5-carboxamido-*N*-acetyltryptamine derivatives.[99b]

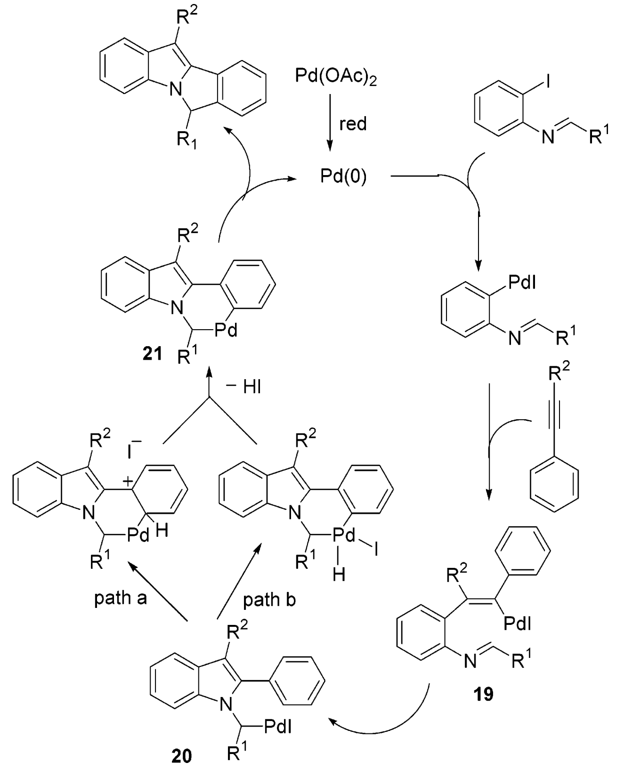
As an extension of the palladium-catalyzed annulation to indoles of *o*-iodoanilines and *o*-iodoanilides with internal alkynes, Larock et al.[89a,b] described a concise synthesis of isoindole[2,1-*a*]indoles via annulation of internal alkynes by imines derived from *o*-iodoanilines (Scheme 51). Two basic procedures were developed: procedure A [Pd(OAc)$_2$, Na$_2$CO$_3$, LiCl, DMF, 100 °C] and procedure B [Pd(OAc)$_2$, *i*-Pr$_2$NEt, Bu$_4$NCl, DMF, 100 °C]. A third procedure was developed (procedure C), which differs from procedure B in only the amount of DMF. In general, with alkyl-substituted alkynes better results attended the use of procedure B, while the alternative procedure C was favored with diarylalkynes. The other substituted alkynes (hydroxyl, esters) afforded better yields when procedure A was used. Internal alkynes containing either a phenyl or a heterocyclic ring were employed in this annulation reaction.

The proposed mechanism for this isoindoleindole synthesis is outlined in Scheme 52 and involves the

Scheme 51

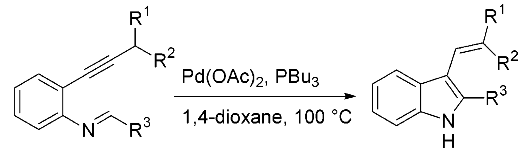


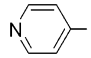
Scheme 52



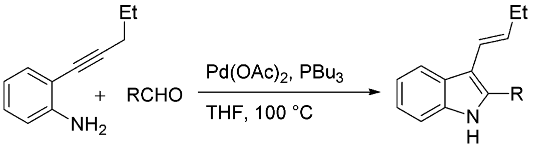
following basic steps: (a) oxidative addition of the aryl iodide to Pd(0), (b) regioselective carbopalladation of the alkyne, (c) 5-*exo* addition of the resultant σ-vinylpalladium intermediate **19** across the carbon−nitrogen double bond to give the σ-alkylpalladium intermediate **20**, (d) either electrophilic palladation of the σ-alkylpalladium moiety of **20** onto the adjacent aromatic ring (path a) or oxidative addition of the neighboring carbon−hydrogen bond to the σ-alkylpalladium moiety of **20** (path b), (e) elimination of HI by base to give the palladacycle **21**, and (f) reductive elimination of Pd(0) to give the isoindoloindole.

Scheme 53



R^1	R^2	R^3	yield %
Et	H	Ph	58
Et	H	*p*-NO$_2$-C$_6$H$_4$-	70
Et	H		64
-(CH$_2$)$_5$-		*p*-NO$_2$-C$_6$H$_4$-	71
OTHP	H	*p*-NO$_2$-C$_6$H$_4$-	56
(CH$_2$)$_2$CO$_2$Et	H	*p*-NO$_2$-C$_6$H$_4$-	59

Scheme 54[a]



[a] R = Ph$_2$CH− (30%); Ph(Me)CH− (67%; NMR yield); Me$_2$CH− (57%; NMR yield); Ph− (74%; NMR yield).

4.1.4. Cyclization of o-Alkynyl-N-alkylidene-anilines

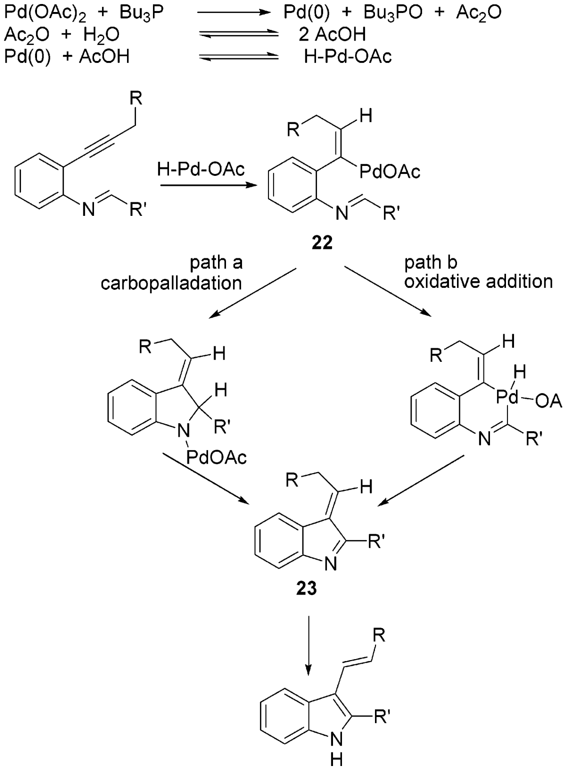
Disconnection c, Figure 1. Yamamoto et al.[100] reported a palladium-catalyzed indole synthesis in which the new bond formed via a palladium-catalyzed reaction and leading to the functionalized pyrrole ring is the carbon−carbon bond between the C-2 and the C-3. In this synthesis 2-(1-alkynyl)-*N*-alkylidene anilines undergo a palladium-catalyzed cyclization to give 2-substituted 3-vinylindoles (Scheme 53). Cyclization of 2-aryl- and 2-heteroaryl substituted imines afforded the corresponding indole derivatives in good yields. When the preparation of 2-alkyl indoles was attempted, optimum yields were obtained through a reaction involving the formation in situ of imines from 2-alkynylanilines and aldehydes, followed by subsequent cyclization (Scheme 54). In fact, preparation of alkyl-substituted imines failed because of their instability. The in situ protocol proceeds without problems even with benzaldehyde.

Most probably, the reaction proceeds through the regioselective addition of palladium-hydride species to the carbon−carbon triple bond (Scheme 55). The resultant vinylpalladium intermediate **22** can afford the indolenine **23** either through a carbopalladation step followed by a β-hydride elimination (path a) or through an oxidative addition step followed by a reductive elimination pathway (path b). Isomerization of **23** generates the indole derivative. Palladium-hydride species can be formed by the reaction of AcOH (generated in situ by the hydrolysis of Ac$_2$O) with Pd(0)[101] [formed by the reaction of Pd(OAc)$_2$ with Bu$_3$P].[102]

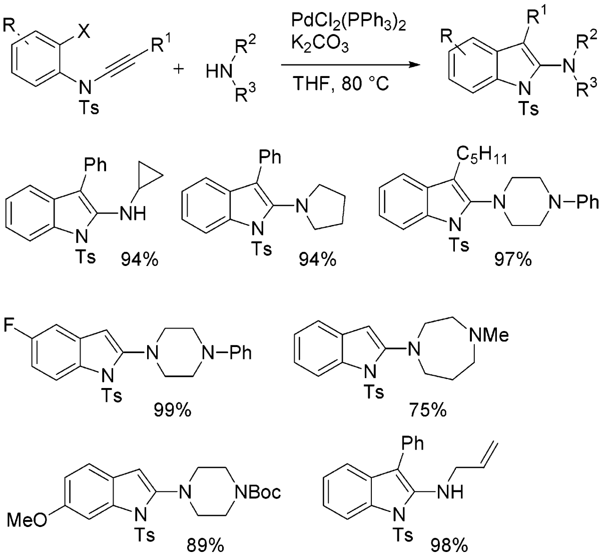
4.1.5. Cyclization of o-Halo-N-alkynylanilides and o-Iodo-N-propargylanilides

As it was shown, a variety of synthetic protocols to indole derivatives were based on the use of alkynes with the acetylenic moiety ortho to a nitrogen functionality (disconnections a, a−d, and c, Figure 1).

Scheme 55



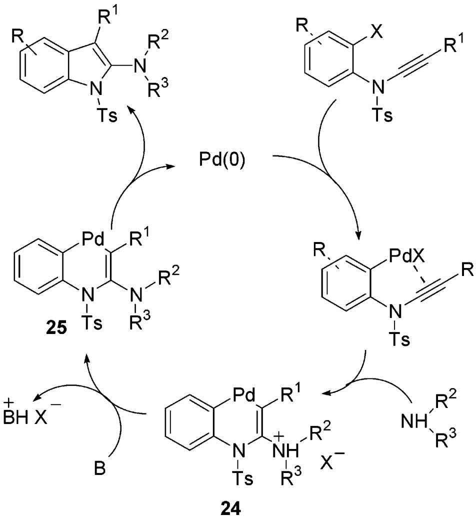
Scheme 56



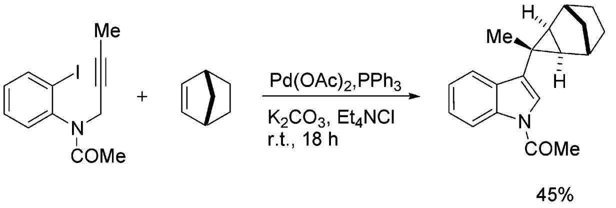
Strategies have also been developed in which the alkyne fragment is bound to the nitrogen atom. Particularly, *o*-halo-*N*-alkynylanilides (disconnection b−e, Figure 1) and *o*-halo-*N*-propargylanilides (disconnection e, Figure 1) were employed as the starting alkynes to construct the functionalized pyrrole ring.

The formation of indoles from *o*-halo-*N*-alkynylanilides was developed by Witulsky and co-workers[103] and involves the palladium-catalyzed reaction of *o*-halo-*N*-alkynylanilides with primary or secondary amines to give the interesting class of 2-aminoindoles (Scheme 56). In the search for optimal conditions, several additional bases such as DABCO, KOH, KO-*t*-Bu, K_2CO_3, and Cs_2CO_3 were tested. K_2CO_3 and Cs_2CO_3 proved to be the most efficient ones. THF was found to be more suitable than DMF or toluene. $PdCl_2(PPh_3)_2$ as the precatalyst gave higher yields than $Pd(PPh_3)_4$, very likely because of its lower phosphine content [the palladium/phosphine ratio is crucial for the success of palladium-catalyzed reactions and a relatively high phosphine content can reduce the activity of the actual Pd(0) catalyst].

Scheme 57



Scheme 58



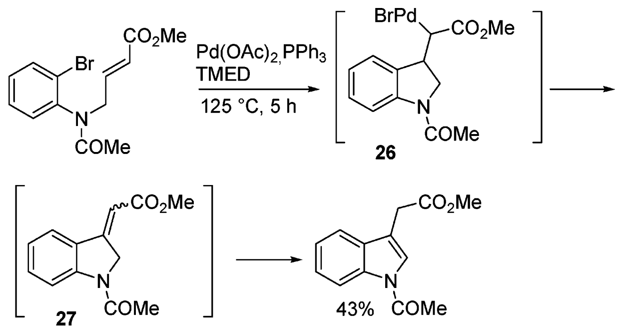
The proposed mechanism is showed in Scheme 57. The Pd(0) species generated in situ inserts into the carbon−halogen bond to give a σ-aryl−π-alkynepalladium complex. Subsequently, addition of amine to the activated carbon−carbon triple bond affords the palladacycle **24**. Deprotonation of the positively charged nitrogen atom followed by reductive elimination of the resultant intermediate **25** gives rise to the indole product and regenerates the active catalyst.

As part of their extensive work on the palladium-catalyzed polycyclization−anion capture sequence, Grigg et al.[104] reported a cascade process leading to indoles containing polycyclic substituents at the C-3 starting from *o*-iodo-*N*-propargylanilides and norbornene. The reaction proceeds through an intramolecular carbopalladation step, followed by capture of norbornene to give a σ-alkylpalladium(II) intermediate which, in turn, undergoes an intramolecular Heck reaction. One example of this chemistry is shown in Scheme 58.

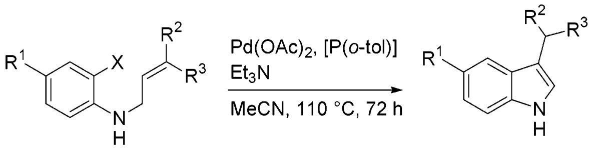
4.2. Cyclization of Alkenes

A large part of the chemistry used in the assembly of the pyrrole nucleus from acyclic precursors containing alkenes is based on the intramolecular Heck reaction, defined as a reaction involving the intramolecular carbopalladation of the carbon−carbon double bond by a σ-organopalladium complex formed in situ

Scheme 59



Scheme 60



X	R^1	R^2	R^3	yield
I	H	H	H	87
Br	H	H	H	60
I	H	H	Me	51
I	H	Me	Me	73
Br	Me	H	H	77
Br	COOEt	H	H	50

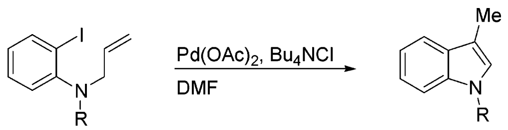
followed by the syn-β-elimination of a hydridopalladium species. The intramolecular amination of olefinic systems represents another potentially general approach to the construction of the pyrrole ring, though only a few synthetic applications were reported. Other approaches were also described, but their synthetic scope appears more limited. In the next seven subsections, we review this indole chemistry.

4.2.1. o-Halo-N-allylanilines

Disconnection e, Figure 2. The first synthesis of indoles based on the intramolecular Heck reaction was described by Mori et al. in 1977.[105] These authors prepared indole derivatives from *o*-halo-*N*-allylanilides containing the side-chain olefin conjugated to a carbonyl group. One of the original examples of this procedure is outlined in Scheme 59. Though aryl iodides are known to be more reactive in the oxidative addition step, the aryl bromide shown in Scheme 59 provided a better result, whereas the corresponding aryl chloride failed to give any of the desired indole derivative. According to the authors, the alkylidene indoline intermediate **27**, generated from the carbopalladation adduct **26** via elimination of a hydridopalladium species, isomerizes to give the indole product under reaction conditions. Formation of the desired indole product was found to be accompanied by the formation of the deallylated *o*-bromoacetanilide and the deallylated acetanilide (the latter derived from the reduction of the carbon−bromine bond).

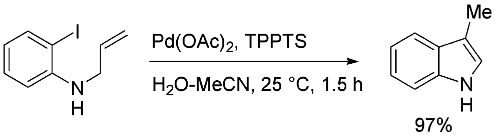
Unactivated *o*-halo-*N*-allylanilines were used by Hegedus and co-workers[106] (Scheme 60). Iodo aromatics gave good results in the presence of $Pd(OAc)_2$ and Et_3N in MeCN at 110 °C for 72 h. Because of deactivation of the catalyst during the reaction, considerably better results were obtained by periodic provision of fresh catalyst. In practice, the same total amount of catalyst was added in three successive 1% portions, one each day of reaction. Less reactive bromo aromatics required the addition of 2 equiv of tris(*o*-tolyl)phosphine per Pd to produce acceptable yields.

Scheme 61



R = H	Na_2CO_3, 25 °C, 24 h	97%
R = Me	Et_3N, 25 °C, 48 h	81%
R = COMe	NaOAc, 80 °C, 24 h	90%

Scheme 62



Subsequently, Larock et al.[107] greatly improved upon the conditions developed by Hegedus for the cyclization of *o*-halo-*N*-allylanilines. For example, 3-methylindole could be obtained in higher yield and under milder conditions omitting phosphine ligands (Scheme 61). The palladium-catalyzed cyclization of *o*-halo-*N*-allylamines was also performed in a homogeneous water−acetonitrile medium in the presence of the water-soluble tris(3-sulfonatophenyl)phosphine sodium salt (TPPTS) ligand[108] (Scheme 62), in supercritical carbon dioxide in the presence of $Pd(OAc)_2$ and a fluorinated phosphine ligand $[C_6F_{13}CH_2CH_2)_2$-PPh],[109] and on solid phase, coupling the aryl[110] and the olefin[111] moieties to the solid support.

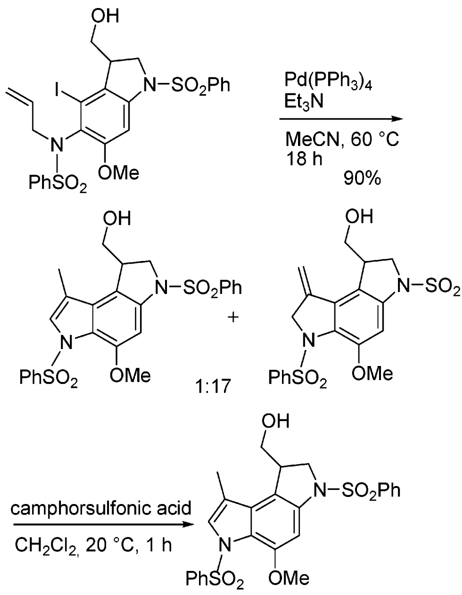
Numerous applications of this indole chemistry were described, including the preparation of cycloprop[*c*]indol-5-ones,[112] indole-3-acetic acids and hetero analogues,[113] indole-3-pyruvic acid oxime ethers,[114] 5-(sulfamoylmethyl)indoles,[115] the anti-migraine agent CP-122,288,[116] and the protected A-unit of CC-1065.[117,118] In the synthesis of the protected A-unit of CC-1065 developed by Tietze et al.[118] (Scheme 63), the cyclization step produced indole and alkylidene indoline products as a 1:17 mixture from which, without further workup, the indole derivative was obtained through quantitative isomerization with camphorsulfonic acid.

4.2.2. o-Haloanilino Enamines

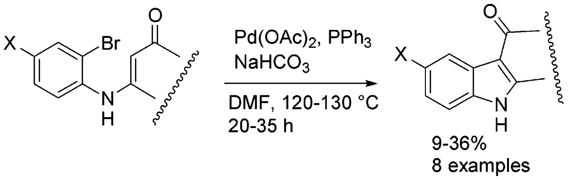
Disconnection e, Figure 2. Another application of the Heck reaction to the synthesis of indoles is based on the utilization of *o*-haloanilino enamines. Formation of indole derivatives from *o*-haloanilino enamines has been known since 1980.[119] In the first utilization of this chemistry, enaminones (derived from *o*-bromoanilines and 1,3-dicarbonyls) were subjected to cyclization conditions and afforded the desired products in low to moderate yields at high temperature (Scheme 64). The proposed mechanism is outlined in Scheme 65.

Since then, a variety of structurally diverse *o*-haloanilino enamines conjugated to ketone and ester groups (prepared from 1,3-dicarbonyls, palladium-

Scheme 63



Scheme 64



Scheme 65

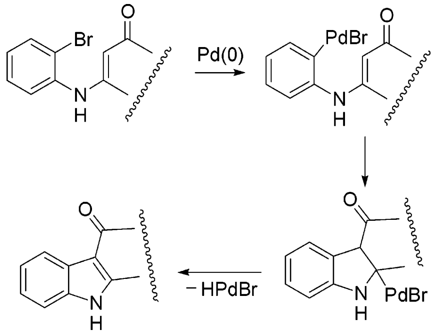
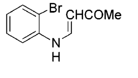
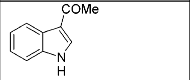
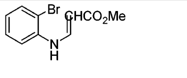
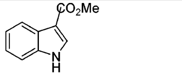
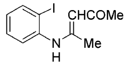
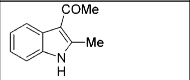
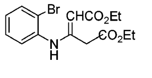
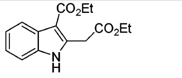
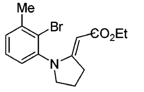
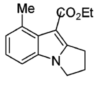
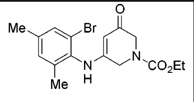
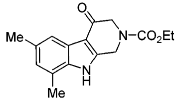
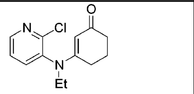
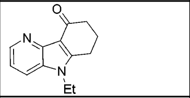
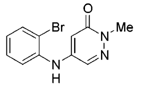
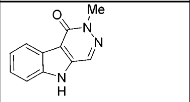
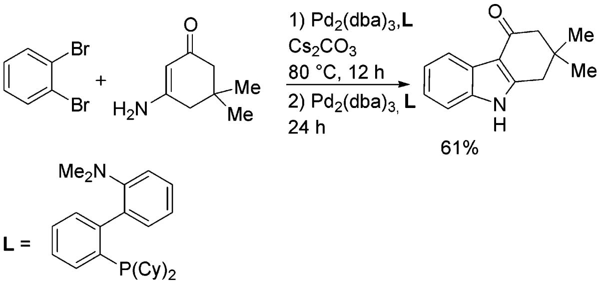


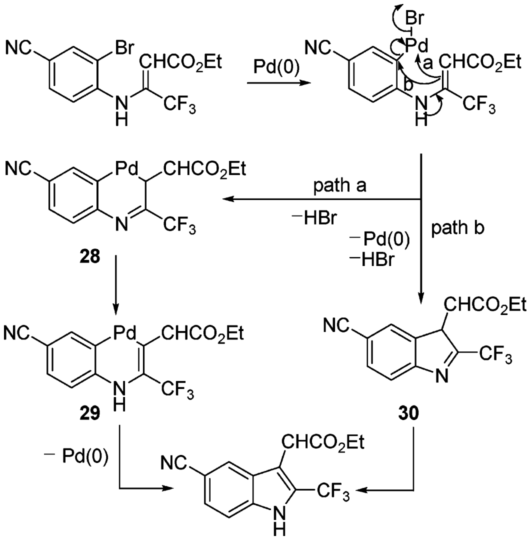
Table 1. Indoles Prepared via Palladium-Catalyzed Cyclization of *o*-Haloanilino Enamines Conjugated to Carbonyl Functionalities

o-haloanilino enamine	conditions	indole	yield %
	$Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N MeCN,100 °C, 20 h		95[121a]
	$Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N MeCN, 100 °C, 20 h		96[121a]
	$Pd(OAc)_2$, Et_3N DMF, 120 °C, 6 h		49[121b]
	$Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N DMF, 120 °C, 6 h		35[121b]
	$Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N MeCN, reflux, 19.5 h		81[121c]
	$Pd(PPh_3)_4$, $NaHCO_3$ HMPA, 140 °C, 2 h		76[121d]
	$Pd(OAc)_2$, PPh_3, $NaHCO_3$ DMF, reflux, 15 h		23[121e]
	$PdCl_2(PPh_3)_2$, NaOAc $3H_2O$ DMA, 130 °C, 3 h		73[121g]

Scheme 66



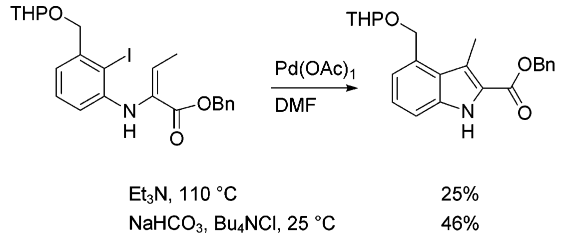
Scheme 67



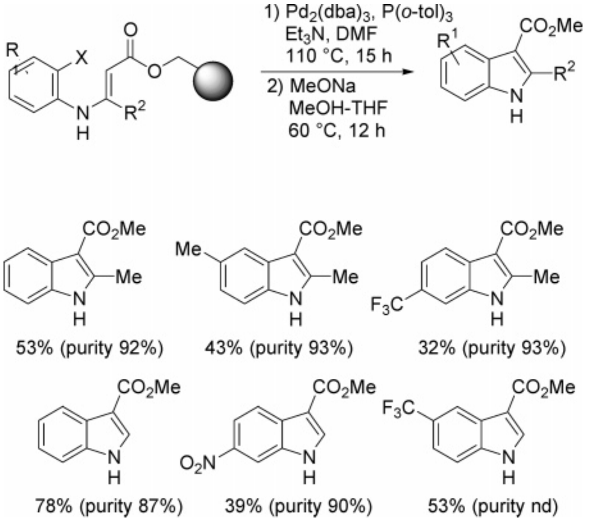
catalyzed oxidative amination of electron-deficient olefins with *o*-haloanilines,[120] Michael addition of *o*-haloanilines to ethynyl ketones and esters, and Buchwald/Hartwig amination) were shown to function well in this application of the Heck reaction[121] (Table 1). Domino processes were also described in which *o*-haloenamines conjugated to carbonyl groups, generated through the Buchwald/Hartwig palladium-catalyzed C–N bond formation from vinylogous amides and aryl halides[121f] (Scheme 66) or vinylogous acyl chlorides and *o*-haloanilines,[121g] undergo an in situ Heck cyclization.

o-Haloanilino enamines conjugated to an ester group (prepared through a Wittig reaction) were also utilized in the preparation of 2-trifluoromethylated indoles possessing electron-deficient 5-substituents.[122] In this case, however, the cyclization was proposed to proceed through a mechanism that does not involve the classical Heck sequence (i.e., carbopalladation of the carbon–carbon double bond followed by a syn-β-elimination of hydridopalladium species). The two possible mechanistic pathways are shown in Scheme 67: one pathway (arrow a) involves the formation of palladacycles **28** and **29**, the latter being

Scheme 68



Scheme 69



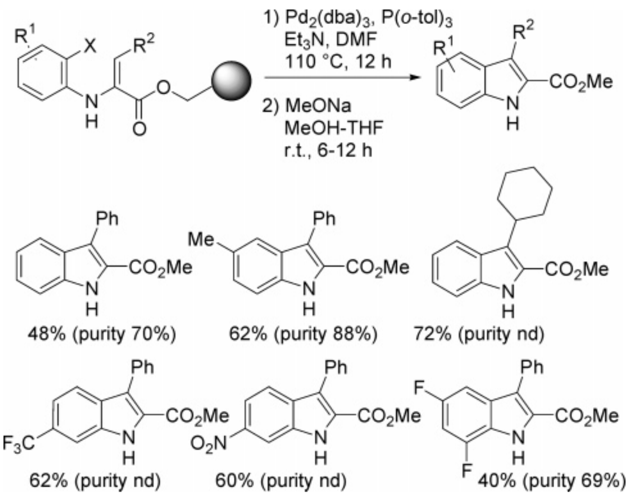
converted into the indole product via reductive elimination of Pd(0); the alternative pathway (arrow b) involves the intermediacy of the 3*H*-indole **30** from which indole is formed by isomerization.

o-Haloanilino enamines containing an ester substituent on the same carbon bearing the aniline group were used in the synthesis of the 2,3,4-trisubstituted indole motif found in the antibiotic nosiheptide[123] (Scheme 68). The substrate required for the cyclization reaction was obtained via condensation of a properly substituted *o*-iodoaniline with the benzyl ester of 2-ketobutyrric acid.

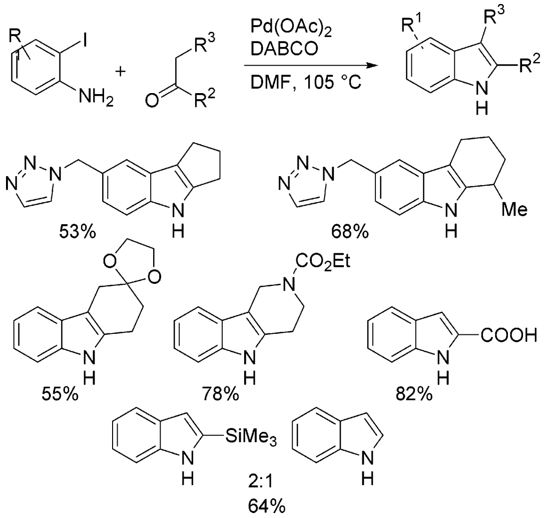
Kondo et al. developed the enamine approach to the construction of the indole skeleton into a solid-phase synthesis in which immobilized *o*-iodo- and *o*-bromoanilino enaminoesters are cyclized to give, after a transesterification step, indolecarboxylate derivatives[124] (Schemes 69 and 70). Adding P(*o*-tol)$_3$ increased the isolated yield, and with *o*-bromoanilino enaminoesters, $Pd_2(dba)_3 \cdot CHCl_3$ worked better than $Pd(OAc)_2$.

A significant extension of the *o*-haloenamine route to indoles is based on the in situ preparation of *o*-iodoanilino enamines from *o*-iodoanilines and simple cyclic and acyclic ketones,[125] though with the latter the procedure is not as effective. Best conditions are shown in Scheme 71. Most reactions proceeded efficiently in DMF, but in the more sluggish cases, the addition of $MgSO_4$, presumably acting as a dehydrating agent, was found to be beneficial. Though the presence of an amine base was found to be critical to the success of the process, the ability of palladium to oxidize amines[126] made it necessary to use an amine such as DABCO, able to resist oxidation to imine.

Scheme 70



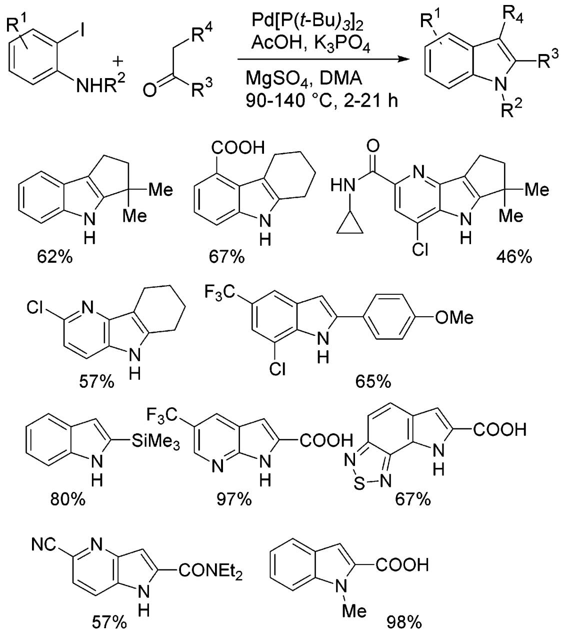
Scheme 71



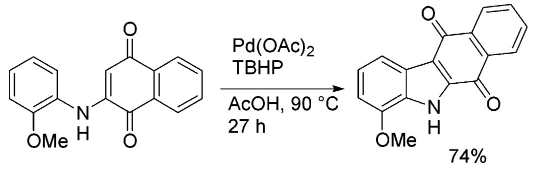
More recently, the reaction was further extended to *o*-chloroanilines.[127] Under the optimized reaction conditions (Scheme 72), a variety of electron-rich and electron-poor *o*-chloroanilines and simple cyclic and acyclic ketones containing diverse functional groups (including amides and free acids), as well as *N*-alkylated anilines, could be converted into the corresponding indoles. *o*-Chloroaminopyridines were cyclized smoothly to give azaindoles.

In the context of the construction of the indole system via cyclization of enamines, a related approach disclosed by Åkermark and co-workers involves the palladium-catalyzed cyclization of 2-arylamino-1,4-quinones.[121h] The cyclization was performed in acetic acid in the presence of catalytic amounts of $Pd(OAc)_2$ and an excess of *tert*-butyl hydroperoxide (TBHP) as oxidant to give indole derivatives in 30−74% yield (Scheme 73). The reaction was found to be strongly dependent on the quality of both palladium acetate and *tert*-butyl hydroperoxide. This catalytic process was subsequently exploited in a key step of a total synthesis of carbazoquinocin C, a potent lipid peroxidation inhibitor.[121i,j]

Scheme 72



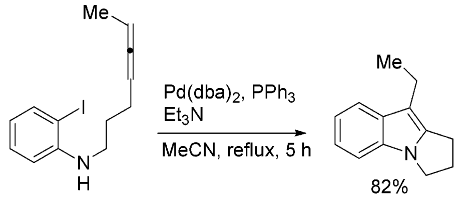
Scheme 73



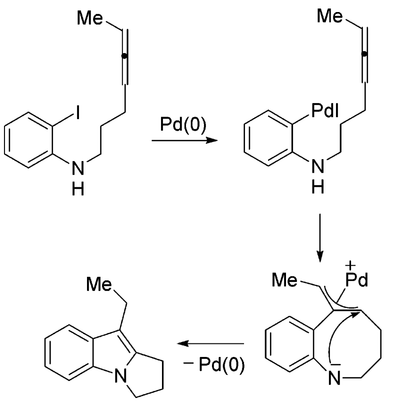
4.2.3. o-Iodoanilines with an Allene Functionality Connected to the Nitrogen Atom

Disconnection a−e, Figure 2. The palladium-catalyzed reaction of allenes with organic halides or triflates in the presence of nucleophiles represents a useful three-component reaction to afford products via intermolecular nucleophilic attack of the nucleophile to one of the allylic termini of the π-allylpalladium intermediate, which is generated from the starting allene and the organopalladium complex formed in situ.[128] The reaction was exploited to develop a new approach to indoles from compounds containing the three components (allene, aryl halide, and nucleophilic functionalities) in the same molecule. *o*-Iodoanilines with an allene functionality connected to the nitrogen atom were indeed cyclized to indoles.[129] Pd(dba)$_2$ gave better results than Pd(OAc)$_2$. Using refluxing MeCN or DME resulted in higher yields. Phosphine ligands, as well as the nature of the starting allene, were found to influence the reaction outcome. The presence of Et$_3$N or K$_2$CO$_3$ was essential to achieve cyclization products. In some cases, 3-alkylidene indolines were obtained as the main products. An example of this reaction is shown in Scheme 74. The proposed reaction mechanism is outlined in Scheme 75.

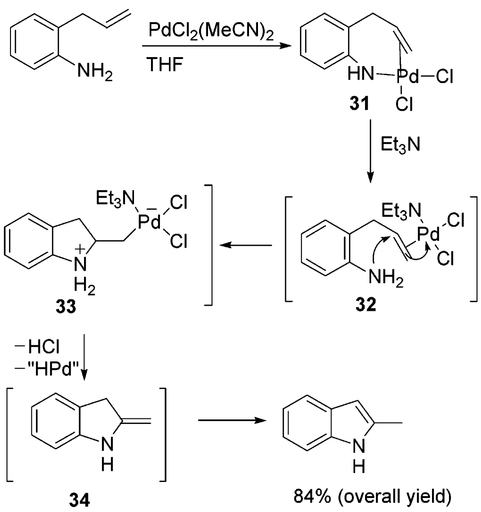
Scheme 74



Scheme 75



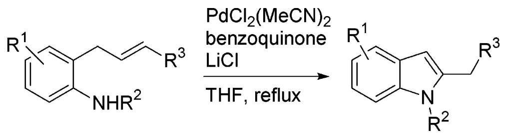
Scheme 76



4.2.4. o-Allylanilines

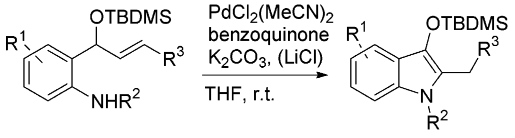
Disconnection a, Figure 2. After reporting the palladium-assisted amination of simple monoolefins by secondary amines to give tertiary amines, in 1976 Hegedus et al.[130] described an intramolecular version of the reaction in which *o*-allylanilines underwent palladium-assisted cyclization to 2-methylindoles. One of the original examples is shown in Scheme 76. The reaction of *o*-allylaniline with PdCl$_2$ affords the complex **31** which, upon addition of Et$_3$N, undergoes the displacement of the weakly basic aromatic amine to generate complex **32**. Nucleophilic attack of the aromatic amine across the coordinated olefin results in the σ-alkylpalladium complex **33**, which upon elimination of HCl and "HPd" gives compound **34**. Spontaneous isomerization of the latter affords the observed 2-methylindole. While this chemistry provided a new simple synthesis of indoles under mild conditions, it suffered from requiring stoichiometric amounts of palladium dichloride (palladium is in fact reduced to metallic Pd). Improvements to this method were clearly needed, and in a subsequent paper,[131] these authors described a catalytic version of the process using benzoquinone to reoxidize Pd(0) to Pd(II) (Scheme 77). In some cases, indole products were formed in higher yield under catalytic conditions than

Scheme 77

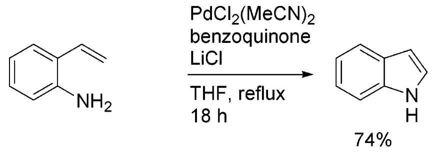


2-methylindole	86%
1,2-dimethylindole	89%
N-acetyl-2-methylindole	71%
2-methyl-5,6-dimethoxyindole	48%
2-methyl-5-methoxyindole	32%
2-ethylindole	79%

Scheme 78



Scheme 79



under stoichiometric conditions. The source of Pd(II) used was $PdCl_2(MeCN)_2$, as in the stoichiometric process. Neither palladium acetate nor lithium chloropalladate were as effective.

The reaction has rarely been applied to the preparation of indoles. One of the few examples was the preparation of 3-alkoxyindoles[132] (Scheme 78).

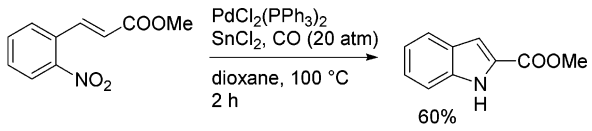
4.2.5. o-Vinylanilines

Disconnection a, Figure 2. In 1978, in the same paper describing the cyclization of *o*-allylanilines to indoles in the presence of catalytic amounts of palladium, Hegedus and co-workers reported the successful palladium-catalyzed preparation of indole from *o*-vinylaniline[131] (Scheme 79). Remarkably, no cyclization of the same substrate was observed under stoichiometric conditions. Subsequently, the procedure was applied to the cyclization of *o*-vinyl-*N*-tosylanilines,[133b−e] *o*-vinylacetanilides,[134] *o*-vinylanilines, and *o*-vinyl-*N*-alkylanilines.[135] However, despite the potential of this chemistry, its applicability remained essentially unexplored, possibly because the routes to *o*-vinylanilines are somewhat difficult due to the number of steps necessary[133d,136a−d] or because more direct approaches usually proceed only in moderate yield.[136e]

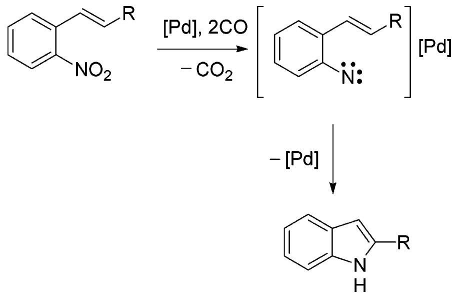
4.2.6. o-Nitrostyrenes

Disconnection a, Figure 2. The direct involvement of *o*-nitrostyrenes as substrates in the palladium-catalyzed synthesis of indoles was first observed by Kasahara et al.[134] who, upon Heck reactions of *o*-bromonitrobenzenes with ethylene in the presence of palladium acetate to prepare *o*-nitrostyrenes, isolated in some cases significant amounts of indole products. For example, *o*-bromonitrobenzene led to a mixture of *o*-nitrostyrene (43% yield) and indole (22% yield). These authors suggested a mechanism consisting of the reduction of *o*-nitrostyrenes (formed via Heck reaction) to *o*-vinylanilines by hydridopalladium species (generated in the Heck reaction as well), followed by a Pd(II)-catalyzed cyclization. Subsequently, Watanabe et al.[137] described the preparation of indoles in moderate to good yields via reductive *N*-heteroannulation in the presence of carbon monoxide, catalytic amounts of $PdCl_2(PPh_3)_2$, and an excess of $SnCl_2$ (Sn/Pd = 10:1). Other additives such as $SnCl_4$, $CuCl_2$, $FeCl_3$, and $BF_3{\cdot}Et_2O$ were ineffective. An example of this reaction is shown in Scheme 80. Since this reaction proceeds in the presence of carbon monoxide, a different mechanism is probably in operation. The proposed reaction mechanism (Scheme 81) involves (a) the deoxygenation of the nitro group of the nitroarene by carbon monoxide, (b) the attack of the resultant active transition metal nitrene intermediate to the olefinic carbon, and (c) the hydrogen transfer via [1,5]-sigmatropic rearrangement.

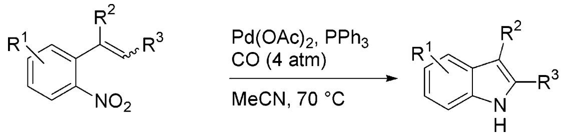
Scheme 80



Scheme 81

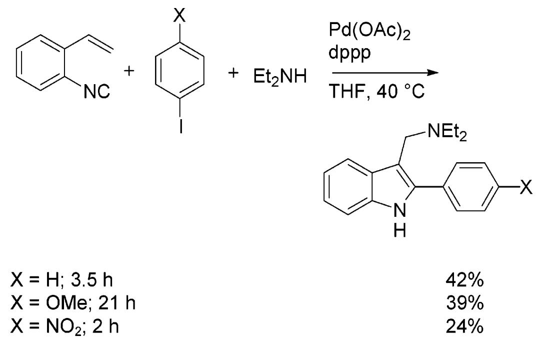


Scheme 82

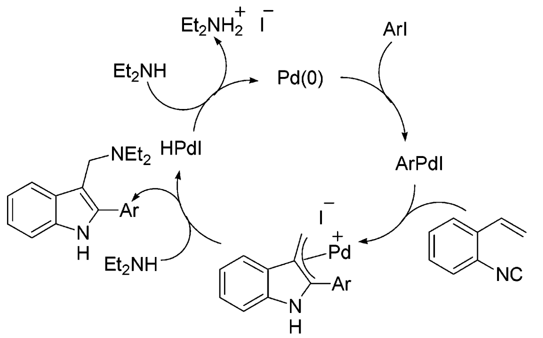


A significant improvement upon the conditions developed by Watanabe et al. was made by Södeberg et al.[138a] The protocol developed by these authors proceeds at a substantially lower temperature and pressure and does not require the presence of tin dichloride. The optimized reaction conditions are shown in Scheme 82. The stereochemistry of the alkene moiety does not affect the reaction outcome. In general, the reaction appears to be independent of the substituents on the aromatic ring. *o*-Nitrostyrenes containing either electron-withdrawing or electron-donating substituents give indoles in moderate to excellent yields. In subsequent papers, Södeberg and co-workers applied the reaction to the synthesis of indoles isolated from *Tricholoma* species[138b] and fused indoles.[138c] In the latter case, the highest yields were obtained under slightly modified reaction conditions: $Pd(OAc)_2$, dppp, CO (60 psi), DMF, 120 °C.

Scheme 83



Scheme 84



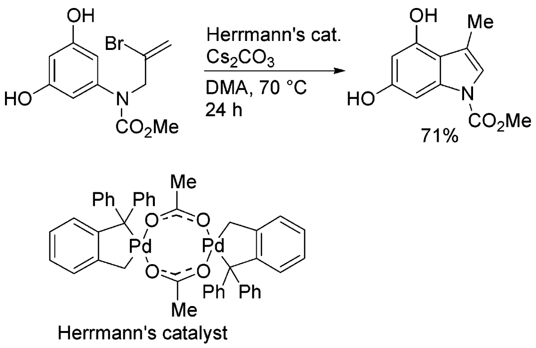
4.2.7. o-Vinylphenyl Isocyanide

Disconnection c, Figure 2. The three-component reaction of aryl iodides, *o*-vinyl isocyanide, and diethylamine was found to give 2,3-disubstituted indoles according to Scheme 83.[139] Using PPh_3, 1,2-bis(diphenylphosphino)ethane (dppe), or 1,4-bis(diphenylphosphino)butane (dppb) instead of 1,3-bis(diphenylphosphino)propane (dppp) decreases the yields. Though the yields of the few examples investigated range only from low to moderate, this is one of the few palladium-catalyzed reactions involving isocyanides. The tentative reaction mechanism is shown in Scheme 84.

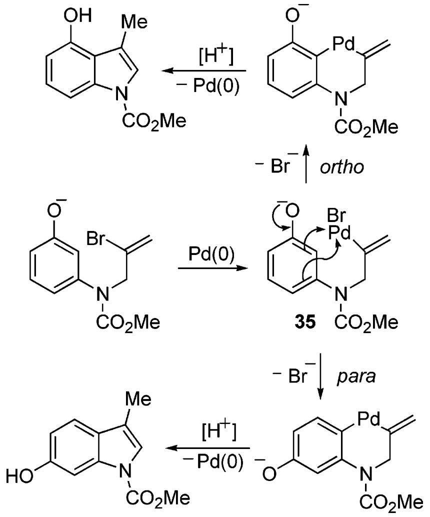
4.3. Cyclization via Intramolecular Coupling of Vinyl Halides onto Aromatic Positions

Unlike procedures where the site of the oxidative addition step is located on the benzenoid ring, such as the cyclization of *o*-halo-*N*-allylanilines (section 4.2.1), *o*-haloanilino enamines (section 4.2.2), and allene-containing *o*-iodoanilines (section 4.2.3), in this type of cyclization the oxidative addition site is located in a vinylic fragment tethered to the benzenoid ring. This synthetic strategy was applied to the preparation of indole carbamates from phenolic carbamates containing a bromovinylic fragment bound to the nitrogen atom[140] (Scheme 85). Optimum yields were obtained by use of the Herrmann's catalyst. The reaction involves a palladacycle intermediate, formed via nucleophilic attack of a carbon nucleophile on the σ-vinylpalladium moiety of **35**, which is converted to the indole product via reductive elimination (Scheme 86). Cyclization both at the ortho and at the para position can occur, generating mixtures of indole derivarives. The issue of ortho versus para selectivity can be avoided by blocking one of the cyclizable positions with a substituent or using a symmetrical phenol such as in that Scheme 85.

Scheme 85



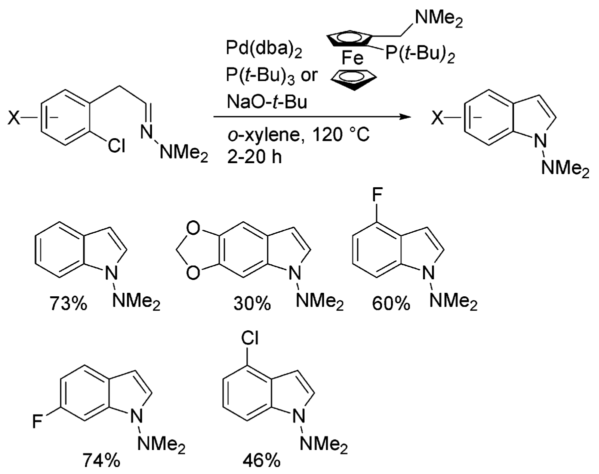
Scheme 86



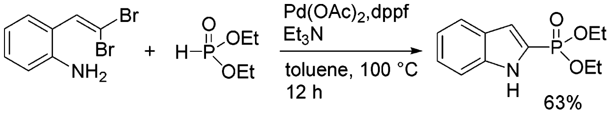
4.4. Cyclization via Intramolecular C–N Bond Forming Reactions

After the pioneering work of Buchwald et al. and Hartwig et al. on the palladium-catalyzed C−N bond forming reaction from aryl halides or triflates and amines, amides, and carbamates, the methodology has gained enormous popularity. Its utility and enormous substrate scope has been demonstrated by the vast amount of published material available describing the preparation of a wide range of *N*-aryl derivatives.[36] Recently, the first extensions of the C−N bond forming reaction to the direct formation of indole rings by intramolecular *N*-arylation were also reported. Watanabe et al.[141] described the synthesis of *N*-aminoindoles via palladium-catalyzed cyclization of *o*-chloroarylacetaldehyde *N*,*N*-dimethylhydrazones. Best results were obtained under the conditions shown in Scheme 87. The ligand 2-(dimethylaminomethyl)-1-(di-*tert*-butylphosphinyl)ferrocene was chosen because it could be readily synthesized in one step from commercially available dimethylaminomethylferrocene. In some cases, the use of the bulky electron-rich P(*t*-Bu)$_3$ gave satisfactory results. Cs_2CO_3 and Rb_2CO_3 could also be used as bases. Yields of chloroindoles are lower than those of unsubstituted indoles or fluoroindoles because oxidative addition of chloroindoles to Pd(0) species takes place under reaction conditions. Since indole

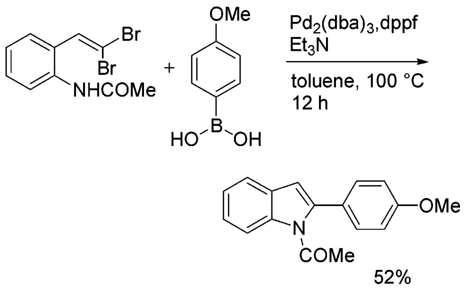
Scheme 87



Scheme 88



Scheme 89

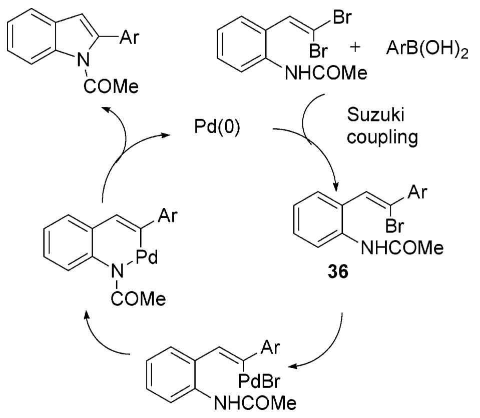


derivatives bearing a chloro substituents on the carbocyclic ring could be useful substrates for increasing the molecular complexity of indole products, the authors developed a domino process based on the palladium-catalyzed intramolecular cyclization to chloroindoles followed by the palladium-catalyzed functionalization of their carbocyclic rings (see section 5.2.4).

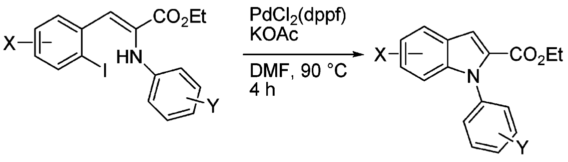
Another example of this chemistry involves the conversion of o-(2,2-dibromovinyl)-phenylaniline and o-(2,2-dibromovinyl)-phenylacetanilide into 2-functionalized indoles through domino palladium-catalyzed coupling–cyclization reactions according to the conditions shown in Schemes 88 and 89.[142] The indole synthesis based on the Suzuki coupling (Scheme 89) required the utilization of the acetanilide derivative (unsatisfactory results were obtained with the free aniline or the Boc derivative) and the presence of $Pd_2(dba)_3$ instead of $Pd(OAc)_2$.

The suggested mechanism for the domino Suzuki coupling–cyclization reaction is shown in Scheme 90. The known higher reactivity of the trans C–Br bond relative to the cis C–Br bond toward oxidative addition[143] should favor the formation of the coupling intermediate **36**. A subsequent oxidative addition step followed by the intramolecular halide displacement from the palladium forms a nitrogen-containing palladacycle from which the indole product is generated via reductive elimination.

Scheme 90



Scheme 91



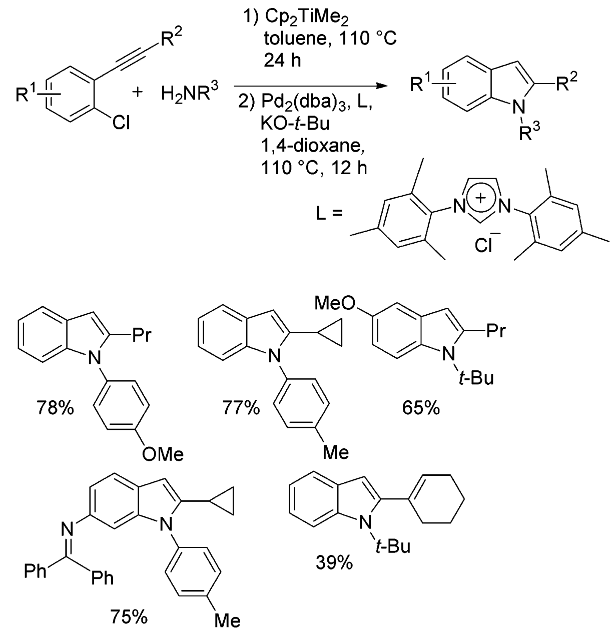
X = H, Y = p-CO_2Et (89%)
X = H; Y = m,p-OCH_2O (92%)
X = 6-NO_2; Y = o-Br ((83%)
X = 6-NO_2; Y = p-CH_2CO_2Et (93%)
X = 6-NO_2; Y = m,p-OCH_2O (94%)
X = 5-NO_2; Y = o-Br (90%)
X = 5-MeO; Y = p-CO_2Et (94%)
X = 5-MeO; Y = m,p-OCH_2O (90%)

N-Aryl indole-2-carboxylates were prepared through an intramolecular palladium-catalyzed cyclization of (*Z*)-didehydrophenylalanine derivatives[144] (Scheme 91). The reaction was extended to the preparation of *N*-acylindoles starting from (*Z*)-*N*-acyldidehydroamino acid derivatives.

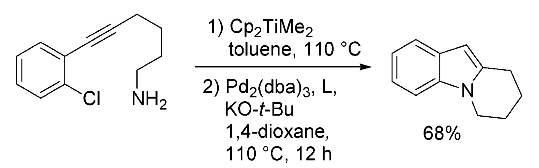
An interesting one-pot procedure for the synthesis of *N*-alkyl- and *N*-arylindoles from 1-(o-chloroaryl)-2-alkyl alkynes, in which two new C–N bonds are formed, was developed by Doye et al.[145] (Scheme 92). The alkynes were first subjected to a titanium-catalyzed regioselective hydroamination with a primary amine to give imines, which under reaction conditions are in equilibrium with the corresponding enamines. Subsequently, $Pd_2(dba)_3$, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (precursor of a carbene ligand), and KO-t-Bu were directly added to the reaction mixture to allow for the conversion of the enamines into indoles by a palladium-catalyzed intramolecular C–N bond forming reaction. Indoles could be isolated usually in good yield. Only the reaction of a 2-vinyl alkyne with *tert*-butylamine gave the corresponding indole in modest yield (39%), most probably because the regioselectivity of the titanium-catalyzed hydroamination of 2-vinyl alkynes is worse than that of 2-alkyl alkynes. The reaction was extended to the preparation of cyclic indole derivatives starting from 1-(o-chloroaryl)-2-(aminoalkyl) alkynes. In this case, the titanium-catalyzed hydroamination occurs intramolecularly. An example of this chemistry is shown in Scheme 93.

A solid-phase indole synthesis based on the intramolecular cyclization of immobilized α-acetamido-

Scheme 92



Scheme 93



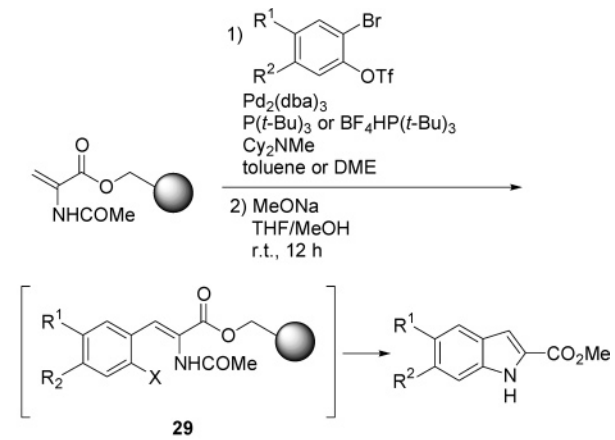
β-(*o*-bromophenyl)acrylates by the Buchwald/Hartwig intramolecular *N*-arylation was developed by Kondo and co-workers.[146] $Pd_2(dba)_3$ was used as the source of Pd(0). The search for optimal phosphine ligands and bases was made under solution-phase conditions and showed that the use of P(*t*-Bu)$_3$ or the air stable, robust BF_4HP(*t*-Bu)$_3$ introduced by Fu et al.[147] and Cy_2NMe afforded the highest yields. Consequently, the N-arylation under solid-phase conditions was carried out in the presence of P(*t*-Bu)$_3$ and Cy_2NMe in toluene at 80 °C when it involved the substitution of the C−N bond for a C−Br bond and in the presence of BF_4HP(*t*-Bu)$_3$ and Cy_2NMe in DME at 100 °C when the reaction involved the substitution of the C−N bond for a C−OTf bond. This indole synthesis could also be carried out as a domino process via the Heck reaction of the solid-supported *N*-acetyl-dehydroalanine with 1,2-dibromobenzenes or 2-bromophenyl triflates, followed by the in situ intramolecular cyclization of the resultant α-acetamido-β-(*o*-bromophenyl)acrylate intermediates **29** (Scheme 94).

5. Functionalization of the Preformed Indole System

5.1. Indoles

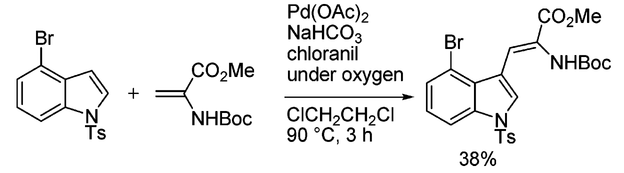
Although the functionalization of indoles via palladium-catalyzed substitution of C−H bonds with C−C bonds could represent a convenient tool for the direct elaboration of the indole core motif, eliminating the need for introducing reactive functionalities such as carbon−halogen or carbon-triflate bonds or "anionic" sites via stoichiometric metalation, relatively few processes were developed in this area. Nevertheless, despite the limited number of such processes reported so far, two main approaches have been highlighted: the reaction of indoles with Pd(II) salts and the reaction of indoles with organopalladium complexes generated in situ.

Scheme 94



R¹	R²	X	yield %
H	H	I	46
H	H	Br	78
H	H	OTf	41
Me	Me	Br	82
MeO	H	Br	39

Scheme 95

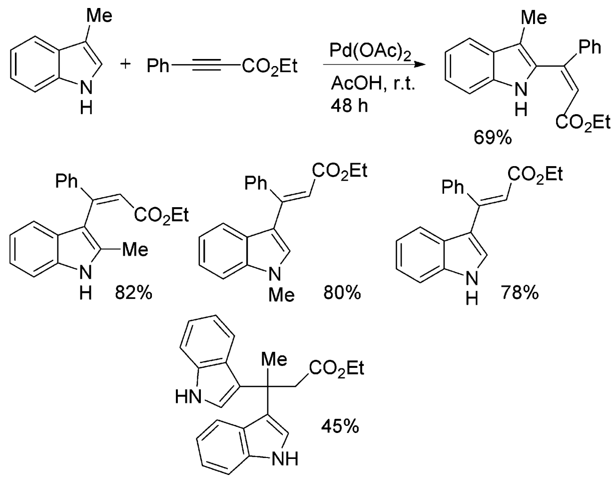


5.1.1. Reaction with Pd(II) Salts

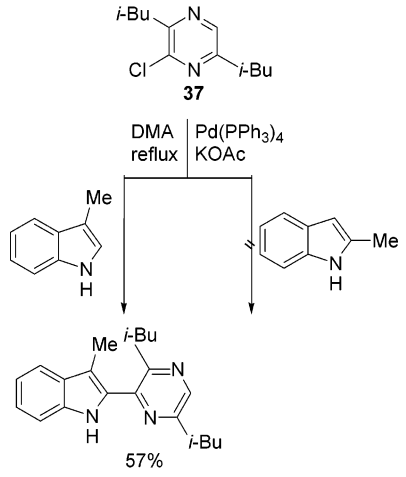
Some of the published procedures involving Pd(II) salts are flawed by the efficiency of the catalyst systems used. For example, the selective vinylation of a bromo indole at the C-3 position in the presence of 0.25 equiv of $Pd(OAc)_2$ produced the desired indole product only in 38% yield[148] (Scheme 95).

Very recently, however, the Pd(II)-catalyzed functionalization of indoles was developed into some synthetically useful processes. Fujiwara and co-workers described a reaction in which the indolyl unit is involved in the regioselective addition to the carbon−carbon triple bonds of ethyl alkynoates (Scheme 96).[149] The new C−C bond is formed at the β-carbon of the ynoate system. The reaction occurs in the presence of 5% of $Pd(OAc)_2$ under mild conditions. The unsubstituted indole forms 3-vinyl derivatives, while 3-substituted indoles give 2-vinyl derivatives. Both (*E*) and (*Z*) addition products[150] were isolated. With alkynoate esters containing small groups in the C-3 position, such as Me, the reaction in AcOH affords diaddition products, while with a relatively bulky group, such as Ph, the reaction gives monoaddition products. The suggested reaction mechanism involves (a) the electrophilic substitution of a pyrrole C−H bond by a cationic Pd(II) species, (b) the

Scheme 96



Scheme 97



regioselective addition of the resultant indolylpalladium(II) intermediate to the alkyne, and (c) substitution of the C−Pd bond of the carbopalladation adduct with the C−H bond. The presence of AcOH would facilitate both the formation of the cationic Pd(II) species and the protonation step.

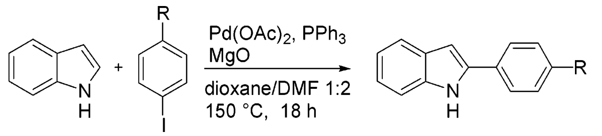
5.1.2. Reaction with Organopalladium Complexes

The second straightforward approach to the direct palladium-catalyzed functionalization of the core motif of indoles is based on the reaction of indoles with organopalladium complexes generated in situ. This strategy was utilized to functionalize free NH indoles,[151a,c] *N*-methyl[151d] and *N*-benzylindoles[151b] at the C-2 position, and *N*-tosylindoles[151b] at the C-3 position.

In the first application of this chemistry, 2-(pyrazin-2-yl)indoles, which constitute the carbon skeleton of the *Cypridina* luciferin, were prepared via palladium-catalyzed reaction of free NH indole with chloropyrazines.[151a] Two procedures were developed: (procedure A) $Pd(PPh_3)_4$, KOAc, DMA, reflux; (procedure B) $PdCl_2(PPh_3)_2$−CuI, K_2CO_3, DMA, reflux. Interestingly, the reaction of 2-methylindole with the choropyrazine **37** failed, whereas 3-methylindole gave the indole derivative in 57% yield (Scheme 97).

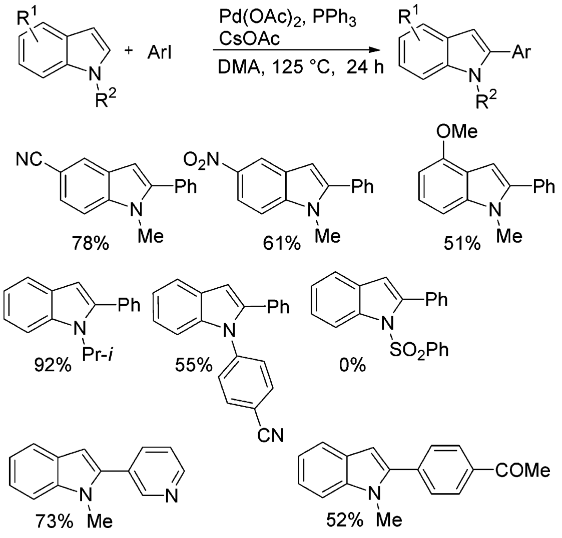
In a more recent work, the selective targeting of C−H bonds in the presence of free NH functionality[151c] was carried out in the presence of the inexpensive and easy to handle MgO, which presumably affords an indolylmagnesium hydroxide (Scheme 98). In the search for a suitable base, alkali metal bases such as LiOH, NaOMe, K_3PO_4, KOAc, or Cs_2CO_3 failed completely, and ZnO gave the desired product only in moderate yield. Under the best conditions, the reaction gave arylated indole derivatives in high yields exclusively at position 2 with iodobenzenes containing both electron-donating and electron-withdrawing groups. In contrast, when the aryl iodide contained a substituent in the ortho position, a regioisomeric mixture of C-2 and C-3 arylation products was obtained. *o*-Iodotoluene afforded the C-2 and C-3 arylation products in 39% and 12% yield, respectively. The authors suggested two possible mechanistic modes: (a) carbopalladation of the double bond, followed by anti-elimination of hydrogen palladium species; (b) electrophilic metalation with ArPdX, followed by reductive elimination.

Scheme 98[a]



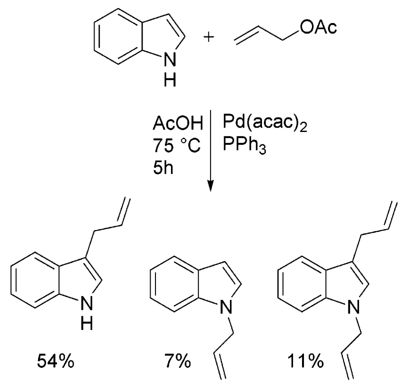
[a] R = H (84%); Me (81%); OMe (87%); F (74%); CF_3 (75%); COMe (79%).

Scheme 99



N-Protected indoles were also subjected to this derivatization protocol. With these substrates, regioselectivity was found to depend on the nature of the protecting group. Alkyl substituents gave preferentially 2-heteroarylation and 2-arylation products. The palladium-catalyzed reaction of *N*-methyl- and *N*-benzylindoles with 2-chloro-3,6-dialkylpyrazines [$Pd(PPh_3)_4$, KOAc, DMA, reflux][151b] and *N*-methylindoles with aryl iodides[151d] gave 2-functionalized derivatives. In the latter case, good to high yields were obtained under the conditions shown in Scheme 99. CsOAc gave higher yields than MgO, ZnO, Cs_2CO_3, KOAc, or $CsOCOCF_3$. As observed with free NH indoles, aryl iodides containing ortho substituents afforded mixtures of C-2 and C-3 arylation products. Formation of homocoupling biaryl products, a com-

Scheme 100



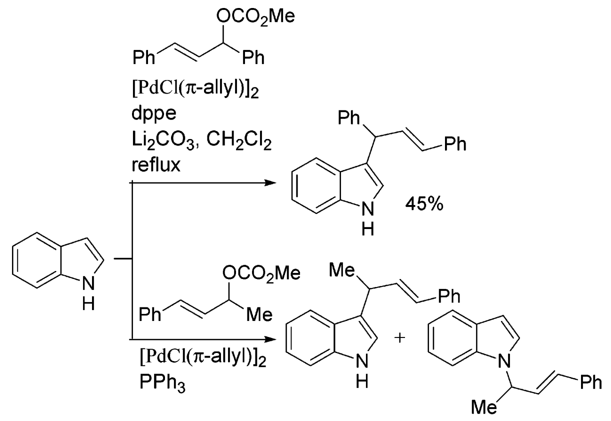
petitive side reaction assumed to require a bimolecular transmetalation of σ-arylpalladium species formed in the oxidative addition step, was limited by decreasing the catalyst loading. Typically, arylations were carried out with 0.5 mol % of $Pd(OAc)_2$.

With *N*-tosylindole and 2-chloro-3,6-dialkylpyrazines, the C-3 position was preferentially targeted, whereas functionalization at the C-2 position occurred with *N*-methyl- and *N*-benzylindoles.[151b]

The Tsuji–Trost reaction was also applied to the direct functionalization of indoles.[152] In the first application of this chemistry to the synthesis of indole derivatives, it was shown that the reaction of indole with allyl acetate in the presence of triphenylphosphine and $Pd(acac)_2$ (palladium acetylacetonate) in a 1:1 ratio in glacial acetic acid afforded 3-allylindole along with minor amounts of *N*-allylindole and bisallylindole[152a] (Scheme 100). This chemistry probably involves the nucleophilic attack of the indole to a π-allylpalladium complex as the key step. The product distribution and the rate of the reaction were found to be strongly dependent on the catalyst/ligand ratio. When the ligand/catalyst ratio was increased to 3:1, the overall rate became significantly lower and *N*-allylindole was obtained as the major product. In the same work, it was also demonstrated that allyl alcohol could serve as the allylating agent. Interestingly, this reaction seemed to work best in benzene (85 °C, 18 h) in the presence of $Pd(acac)_2$ and triphenylphosphine in a 3:1 ratio. Under these conditions, 3-allylindole was obtained in 45% yield.

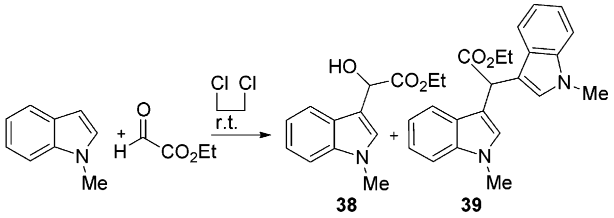
More recently, the palladium-catalyzed allylation of free NH indoles was investigated using allyl carbonates as allylating agents.[152b] The C/N-allylation ratio was found to be extremely sensitive to the base and the solvent. The authors suggested that low-coordinating solvents (i.e., CH_2Cl_2) in combination with bases bearing relatively small cations (i.e., Li_2CO_3) would favor the formation of intimate indolyl–metal ion pairs, which, in turn, would afford preferentially 3-allylated indoles. Highly coordinating solvents (i.e., THF, DMF) in combination with bases bearing larger cations (i.e., K_2CO_3, Cs_2CO_3) would favor the intermediacy of solvent-separated ion pairs and drive the reaction toward the formation of *N*-allylated indoles. Some examples from that study are outlined in Scheme 101. Notably, under both reaction conditions, only attack at the less hindered position of the allylic system was observed with the asymmetric allylic carbonate.

Scheme 101



BSA, Li_2CO_3 CH_2Cl_2,reflux	91% (10:1)
Cs_2CO_3,DMF r.t.	84% (1:50)

Scheme 102



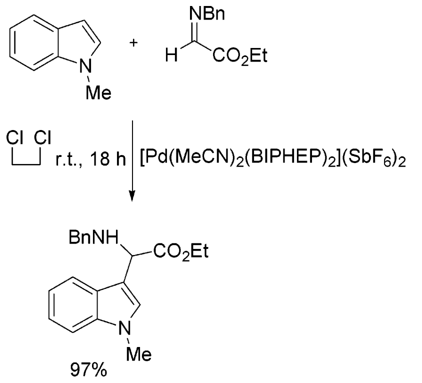
	38	39
$PdCl_2(MeCN)_2$, 18 h	96%	-
$[Pd(MeCN)_2(BIPHEP)_2](SbF_6)_2$, 12 h	-	95%

In the context of functionalization of indoles via reaction with organopalladium complexes, a related straightforward approach to the functionalization of indoles involves the utilization of Pd(II) complexes as Lewis acids to perform Friedel–Crafts C–C bond forming reactions. This type of chemistry was used in the reaction of *N*-methylindole with ethyl glyoxylate.[153] In dichloroethane as solvent and in the presence of a neutral palladium(II) complex, such as $PdCl_2(MeCN)_2$, the reaction led to the formation of the α-hydroxy indolyl acetate **38**, while in the presence of the cationic complex $[Pd(MeCN)_2(BIPHEP)_2](SbF_6)_2$**,** the reaction afforded the diindolyl acetate **39** (Scheme 102). In addition to the nature of the Pd(II) complex, the product ratio (**38** vs **39**) was found to be affected by solvents and reaction temperature. This palladium(II)-catalyzed Friedel–Crafts reaction was found to be applicable also to imine counterparts. With these substrates the reaction afforded α-amino indolyl acetates (Scheme 103).

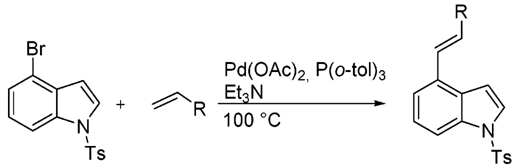
5.2. Indolyl Halides and Triflates

Indolyl halides and triflates were used in the synthesis of a large number of indole derivatives. The first step of this chemistry involves the oxidative addition of the carbon–halogen or carbon-triflate bond to Pd(0) species. Subsequently, the resultant indolylpalladium(II) intermediate is converted into the desired indole derivatives via reaction with a variety of reagents, such as alkenes, alkynes, organometallic reagents (organostannanes, arylboronic

Scheme 103

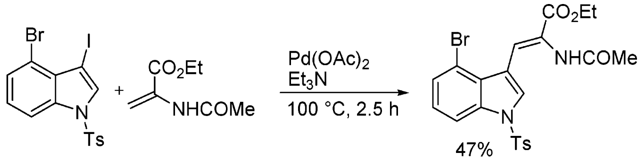


Scheme 104[a]



[a] R = CO_2Me (1 h, 86%); $C(Me)_2OH$ (5 h, 97%); Ph (7 h, 74%); NPhth (MeCN, 24 h, 74%).

Scheme 105

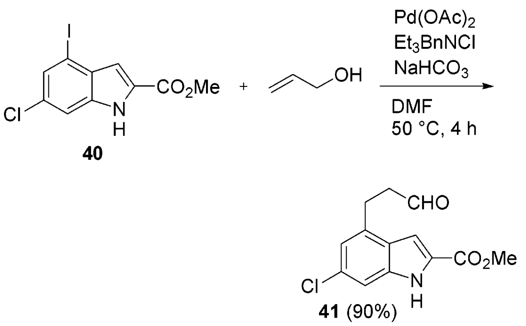


acids, organozinc compounds), and nonorganometallic nucleophiles. Though the preparation of indolyl halides and, particularly, triflates is not always a straightforward process, this derivatization strategy has received attention by synthetic organic chemists most probably because it provides the interesting advantage of utilizing a single indolyl partner for a wide range of palladium-catalyzed reactions.

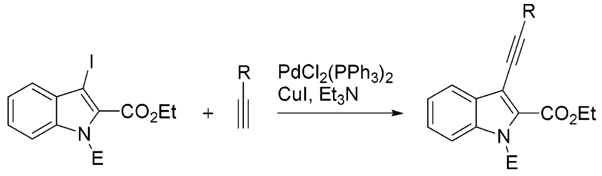
5.2.1. Reaction with Alkenes

In 1978, in a study devoted to palladium-catalyzed vinylic substitution reactions with heterocyclic bromides, Heck and co-workers[133a] showed that 5-bromoindole reacted with methyl acrylate to give the corresponding vinylated indole in 53% yield. 3-Bromoindole gave no identifiable product. However, subjecting *N*-acetyl-3-bromoindole to the same conditions produced the vinylic substitution derivative in 50% yield. Subsequently, during his studies on the synthesis of the ergoline framework, Hegedus et al.[133b] showed that 4-bromo-1-tosylindole could be readily converted into a number of 4-substituted 1-tosylindoles via the Heck reaction with electron-poor, neutral, and electron-rich olefins (Scheme 104). In the same paper, the selective functionalization of 4-bromo-3-iodo-1-tosylindole at the C-3 position was reported. Methyl acrylate and *N*-vinylphthalimide gave the desired indole derivatives in high yield (61% and 77%, respectively). Of particular interest is the reaction with methyl α-acetamidoacrylate (Scheme 105), which would allow access to optically active tryptophans via catalytic asymmetric reduction. Only one stereoisomer was observed. Unfortunately, olefin polymerization was found to be a significant competitive side reaction under the high-concentration conditions employed and the use of a larger excess of the olefin did not increase the yield of the indole product.

Scheme 106



Scheme 107



E = H (60 °C)	R = $SiMe_3$(75%); Ph (89%); Bu (28%)
E = SO_2Me (60 °C)	R = $SiMe_3$(64%); Ph (49%); Bu (62%)
E = SO_2Me (DMF, r.t.)	R = $SiMe_3$(45%); Ph (64%)

Other indolyl halides and triflates were subsequently utilized as indolyl donors in palladium-catalyzed Heck reactions with terminal olefins. 7-Iodoindole was treated with methyl acrylate to give methyl 3-(indol-7-yl)-acrylate in excellent yield,[154a] *N*-tosyl-4-bromoindole was treated with methyl α-acetamidoacrylate to give the corresponding vinylic substitution product in 57% yield,[154b] 3-substituted-2-iodoindoles were converted into the corresponding 2,3-disubstituted indoles,[155] *N*-(tosyl)indol-3-yl triflate gave 3-vinylic indoles with a number of electron-poor and neutral olefins,[156] while the corresponding 2-carboxylate derivative did not give satisfactory results.[157] The procedure was successfully applied to the functionalization of N-substituted 2-iodo-5-azaindoles and N-substituted 2-iodo-7-azaindoles.[158]

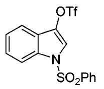
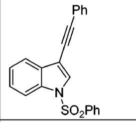
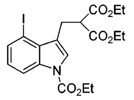
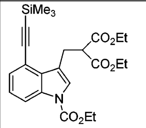
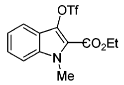
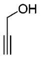
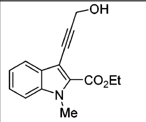
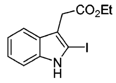
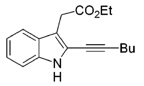
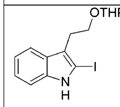
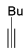
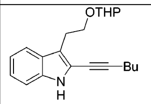
As part of a synthetic route to a series of tricyclic indole 2-carboxylic acids, a class of potent *N*-methyl-D-aspartate (NMDA)−glycine antagonists, the 4-iodo derivative **40** was subjected to allylic alcohol under the conditions shown in Scheme 106 to give the corresponding aldehyde derivative **41**.[159]

5.2.2. Reaction with Alkynes

In 1988, Yamanaka et al.[160] described the palladium-catalyzed cross-coupling of 3-iodoindole derivatives with terminal alkynes under Sonogashira[42a] conditions (Scheme 107).

Other coupling reactions of terminal alkynes with indolyl halides and triflates[155,156,157b,161] were subsequently reported under Sonogashira[42a] or Heck−Cassar[42d,e] conditions (Table 2). This chemistry was also applied to the elaboration of the C-5 position in a solid-phase synthesis of 2,3,5-trisubstituted in-

Table 2. Alkynyl Indoles Prepared via Palladium-Catalyzed Reaction of Indolyl Halides and Triflates with Terminal Alkynes

indolyl halide or triflate	alkyne	conditions	alkynyl indole	yield %
		$PdCl_2(PPh_3)_2$, *i*-Pr_2EtN LiCl, DMF		81[156]
		$Pd(OAc)_2$, PPh_3, CuI Et_3N, DMF, 70 °C, 14 h		69[161a]
		$Pd(OAc)_2$, PPh_3 Et_3N, DMF, 100 °C, 6 h		80[157b]
		$PdCl_2(PPh_3)_2$, CuI, Et_2NH r.t., 8 h		89[155]
		$PdCl_2(PPh_3)_2$, CuI, Et_2NH r.t., 8 h		93[155]

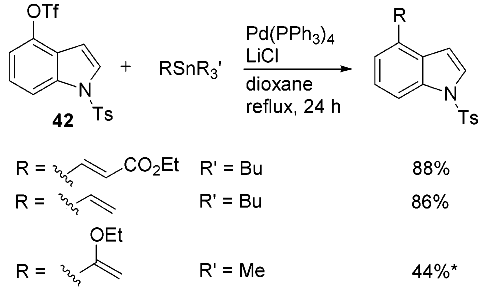
doles.[162] In this case, the Sonogashira coupling was carried out using 20% $PdCl_2(PPh_3)_2$ and 40% CuI (70 °C, 24 h).

5.2.3. Reaction with Organostannanes

The palladium-catalyzed coupling of organohalides or triflates with organostannanes, commonly known as the Stille reaction, is in widespread use in organic synthesis. This is due to the stability of organostannanes to moisture and air and to their compatibility with a wide range of functionalities. However, the toxicity of organotin compounds, organostannane reagents and byproducts, can represent a significant drawback that, in some cases, may limit the Stille reaction. This disadvantage can be limited by using organostannanes of lower toxicity[163] and solid-phase synthesis, which can allow an easy separation of the desired product from the bulk of the reaction containing an excess of the reagent and byproducts.

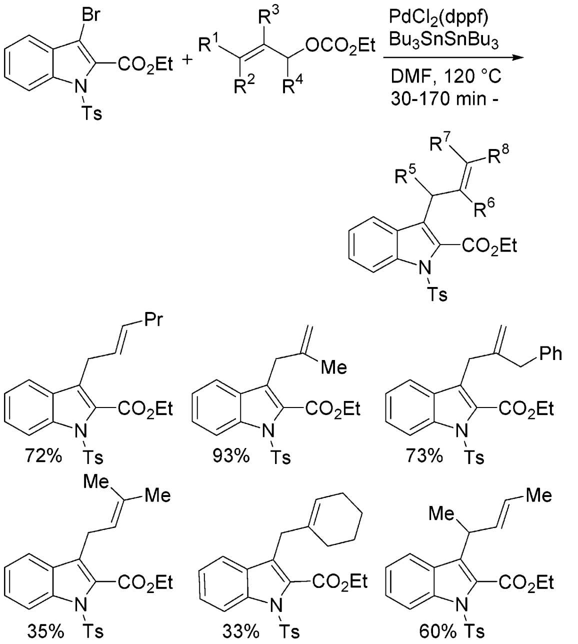
The Stille reaction has been widely used in indole synthesis and part of this chemistry involves the utilization of indolyl halides or triflates as the coupling partners. The first example of this type of cross-coupling approach to the functionalization of the indole nucleus is just due to Stille et al.,[133d] who showed that the indolyl triflate **42** could be converted to 4-substituted indoles (Scheme 108) utilizing the procedure previously developed for the coupling reaction of vinyl triflates. In that study,[23] Stille had found that the presence of LiCl was crucial for the success of the reaction with vinyl triflates and suggested that chloride anions could be involved in a ligand exchange step converting initially formed σ-vinylpalladium triflate intermediates to σ-vinylpalladium chlorides, more prone to enter a cross-coupling catalytic cycle.[164]

Scheme 108[a]



[a] The * indicates that the product hydrolyzed on workup to give R = COMe.

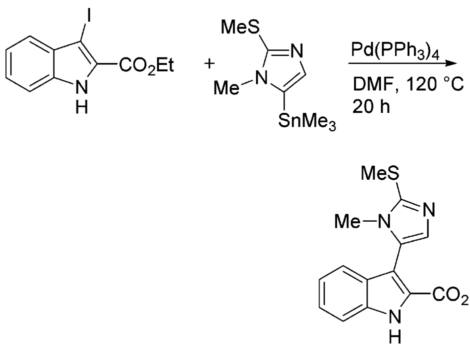
Scheme 109



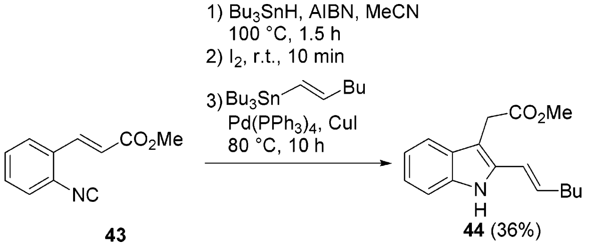
This cross-coupling methodology, employing LiCl as additive, was utilized by other groups to functionalize 2- and 3-indolyl triflates.[156,157b,c,165] Indolyl halides,[158,161a,166,167] in some cases in the presence of ammonium chlorides,[167a,e,g] were also subjected to cross-coupling conditions, usually with aryl-, heteroaryl-, and vinylstannanes. Sakamoto et al.[168] applied this derivatization protocol to the alkynylation at the C-3 position of a 3-iodoindole. Snieckus et al.[169] described the bisallylation of a 3,4-dibromoindole derivative. A 3-bromoindole was allylated with allyl esters in the presence of hexabutyldistannane through a reaction featuring an in situ formation of organostannanes[167b] (Scheme 109). Allyl carbonates gave better yields than the acetate counterparts. The new carbon−carbon bond was found to occur at the less substituted end of the allyl moiety with formation of (*E*)-isomers as a result of the isomerization or allylic rearrangement of the double bond.

The Stille reaction was employed in key steps of several syntheses of biologically active compounds such as borrerine[167a] (a naturally occurring alkaloid), grossularines-1 and -2[167d,e] (pyrido[2,3-*b*]indoles possessing interesting antitumor properties; Scheme 110), carazostatin and hyellazole[167h] (poly-substituted carbazole alkaloids), tetracyclic oxazolocarbazoles[167g] (prepared as functionalized precursors of antiostatins and carbazoquinocins), (±)-vincadifformine and (−)-

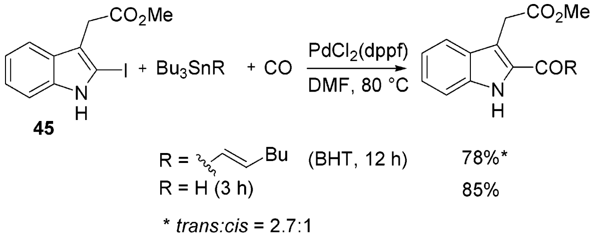
Scheme 110



Scheme 111



Scheme 112[a]



[a] The * indicates trans/cis = 27:1.

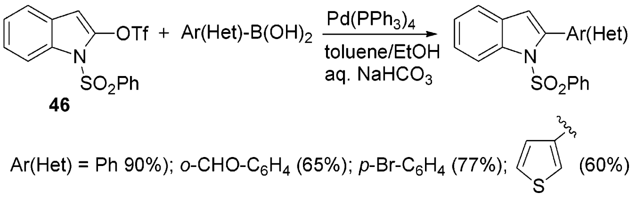
tabersonine[167j] (prominent members of aspirioderma alkaloids), and 2-arylindole NK_1 receptor antagonists.[167k] In a one-pot procedure,[155] the isocyanade **43** was converted into the indole **44** via a 2-iodoindole prepared in situ (Scheme 111).

Under an atmosphere of carbon monoxide, the Sn-based cross-coupling was utilized to convert the 2-iodoindole **45** into the corresponding α,*β*-unsaturated ketone and aldehyde via reaction with *trans*-1-tributylstannylhexene and tributyltin hydride, respectively[155] (Scheme 112). Best results were obtained in the presence of $PdCl_2$(dppf). With *trans*-1-tributylstannylhexene, a loss of olefin geometry was observed and a trans/cis mixture of olefinic derivatives was isolated. Under similar conditions, omitting the organostannane and adding methanol, the same 2-iodoindole gave the corresponding methyl ester in 89% yield.

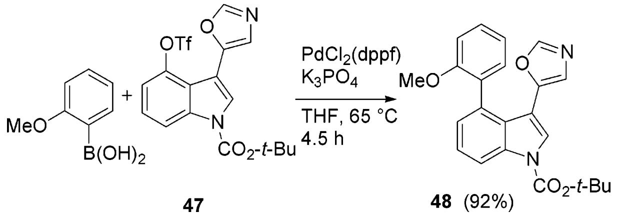
5.2.4. Reaction with Arylboronic Acids

Among the cross-coupling methodologies based on palladium catalysts and additional organometallic reagents, the Suzuki coupling[170,171]—usually the palladium-catalyzed reaction of an aryl halide or triflate with an arylboronic acid as the nucleophilic part of the reaction (arylboronate esters can be used as well, though they were utilized less frequently)—is most probably the one that has attracted more interest from academic and industrial chemists. There are several advantages of the Suzuki reaction over all the other procedures using organometallic reagents: boronic derivatives can tolerate a broad range of functional groups; their toxicity, and that of byproducts, is low, particularly if compared to tin-containing compounds; they are easy to handle and can be manipulated with less risk than other organometallics; typically, steric effects play a minor role in controlling the reaction outcome. Apparently, the only drawback of this reaction is the difficulty of preparing boronic acids. Boronic acids, in fact, are usually prepared via a three-step process involving the reaction of aryl halides with butyllithium, the formation of an aryl boronate ester via reaction of the resultant lithiated aryl intermediate with a boric acid ester, and the hydrolysis of the obtained aryl boronate ester.[172] This butyllithium route to aryl boronic acids has important deficiencies in flexibility, yield, and costs. Nevertheless, the Suzuki coupling is widely practiced in procedures assembling biaryl units. Commercial examples include the antihypertensive drug valsartan and the fungicide boscalid. The reaction is particularly used in the discovery of new bioactive compounds. Availability of libraries of aryl halides and arylboronic acids may allow for ready access to a whole range of drug candidates.

Scheme 113



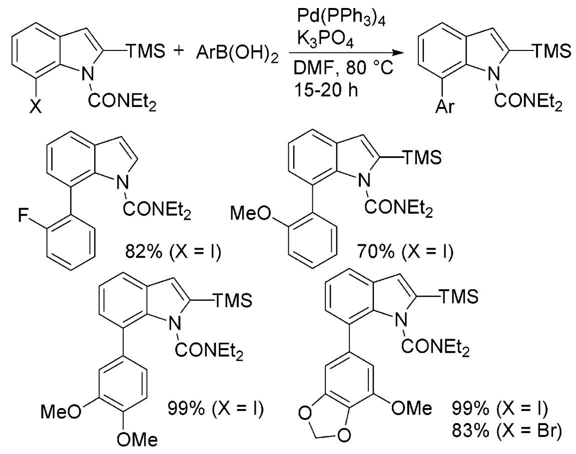
Scheme 114



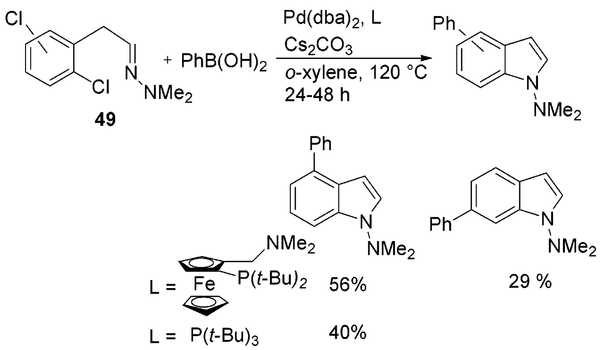
The Suzuki reaction has been widely used in the functionalization of indoles, and part of this chemistry involves the utilization of indolyl halides and triflates as coupling partners. Particularly, all the positions of the indole skeleton were functionalized by using the cross-coupling of indolyl halides or triflates with aryl- and heteroarylboronic acids. Only a few examples involving indolyl triflates, however, were described. The reaction of the 2-indolyl triflate **46** with a variety of aryl- and heteroarylboronic acids was reported to afford the coupling products in moderate to excellent yields[157c] (Scheme 113), a 3-indolyl triflate was converted to the corresponding phenyl derivative,[157b] and 4-indolyl triflate **47** gave the aryl derivative **48**, a model compound of the biaryl and 3-(oxazol-5-yl)indole segment of diazonamide A[173] (Scheme 114).

Most of this derivatization chemistry deals with the utilization of indolyl halides. Methyl 2-(2-iodo-1*H*-

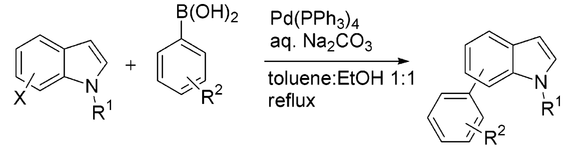
Scheme 115



Scheme 116

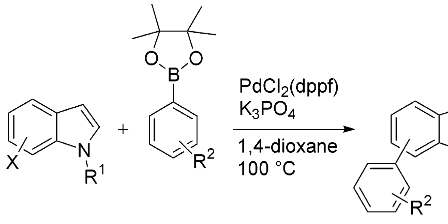


Scheme 117



X	R^1	R^2	Yield (%)
5-Br	H	*p*-Me	97
5-Br	H	*p*-OMe	85
5-Br	H	*o*-Me	99
5-Br	H	*o*-OMe	91
6-Br	H	*p*-OMe	76
6-Br	H	*o*-OMe	80
7-Br	H	*p*-OMe	67
7-Br	H	*o*-OMe	66
5-Br	Boc	*p*-Me	79
5-Br	Boc	*p*-OMe	70
5-Br	Boc	*o*-Me	99
5-Br	Boc	*o*-OMe	94
6-Br	Boc	*p*-OMe	67
6-Br	Boc	*o*-OMe	84
5-Br	Ts	*p*-Me	70
5-Br	Ts	*p*-OMe	93
5-Br	Ts	*o*-Me	74
5-Br	Ts	*o*-OMe	97
6-Br	Ts	*p*-OMe	80
6-Br	Ts	*o*-OMe	89

Scheme 118

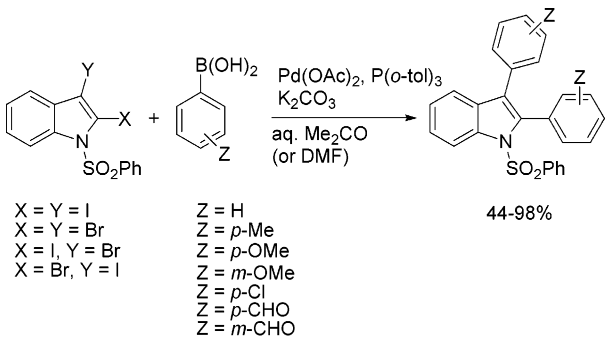


X	R^1	R^2	Yield (%)
5-Br	H	*p*-OMe	traces
5-Br	H	*o*-OMe	traces
6-Br	H	*p*-OMe	traces
5-Br	Boc	*p*-OMe	22
5-Br	Boc	*o*-OMe	8
6-Br	Boc	*p*-OMe	19
6-Br	Boc	*o*-OMe	34
5-Br	Ts	*p*-OMe	62
5-Br	Ts	*o*-OMe	45
6-Br	Ts	*o*-OMe	55
6-Br	Ts	*p*-OMe	40

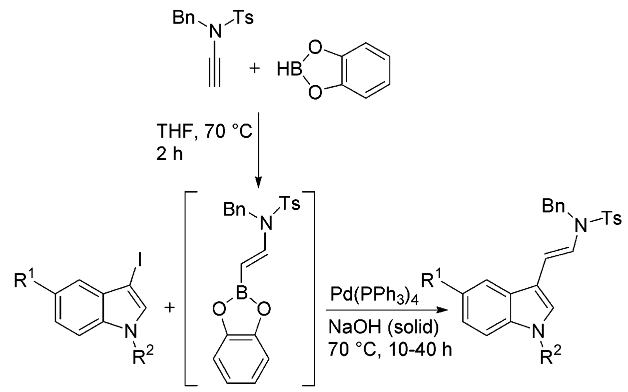
indol-3-yl)acetate was converted to the corresponding 2-phenyl derivative via reaction with phenylboronic acid,[155] a 2-iodoindole derivative was coupled with an arylpinacolboronate ester in a convergent synthesis of (*S*)-*β*-methyl-2-aryltryptamine-based gonadotropin releasing hormone antagonists[96a] (see Scheme 49), and 6- and 7-bromoindoles were converted to 6-(*p*-fluorophenyl)indole and 7-(*p*-methoxyphenyl)indole via coupling with the appropriate boronic acid.[174] No indole protection or functionalization was required in these coupling reactions. 3-Pyridyl-5-bromo-1-tosylindole was coupled with aryl and heteroarylboronic acids to give 3-pyridyl-5-aryl(heteroaryl)indoles.[166] 5-Bromoindoles were converted into their dimers via reaction with 5-indolylboronates prepared in situ.[175a] Snieckus et al.[176] described the arylation of some 7-iodo and 7-bromoindole derivatives (Scheme 115). An example of coupling of 3- and 5-indolyl bromides with heteroaryl boranes, particularly with diethyl-(3-pyridyl)-borane, was also reported.[177] The reaction affords the corresponding heteroaryl-substituted indoles in moderate yields. In the same work describing the construction of the indole ring through an intramolecular *N*-arylation process[143] (section 5.2.5), Watanabe et al. developed a procedure for the synthesis of 4- and 6-aryl-1-aminoindoles through a domino Buchwald/Hartwig–Suzuki process. Cyclization of **49** in the presence of phenyl boronic acid gave 4- and 6-phenylindole products in moderate overall yield (Scheme 116). Using 2-(dimethylaminomethyl)-1-(di-*tert*-butylphosphinyl)ferrocene as ligand provided a slightly higher yield. In this reaction, the authors observed that Suzuki coupling took place five times faster than the formation of chloroindole (2 h at 120 °C).

A recent detailed comparative study on the cross-couplings of 5-, 6-, and 7-bromoindoles with substituted arylboronic acids (Scheme 117) and arylpinacolboronate esters[178] (Scheme 118) showed that when arylboronic acids were used as coupling partners, the position of the bromo substituent has little influence on the yield, the effect of increased steric hindrance

Scheme 119



Scheme 120



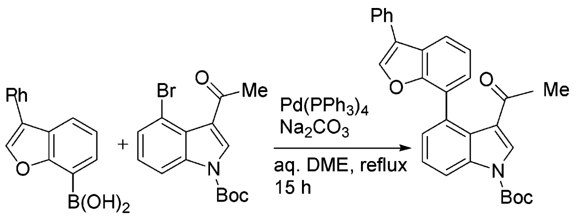
R^1	R^2	Yield %
H	Boc	58
H	Ts	71
OMe	Boc	74
OMe	Ts	84

in the arylboronic acid is negligible, and yields are similar both with protected and with free NH indoles. With arylpinacolboronate esters, a remarkably different picture emerged. For example, an evident effect of increased steric hindrance in the arylboronate partner was observed (ortho-substituted arylpinacolboronates usually gave lower yields than their para-substituted counterparts), and the reaction outcome depended on whether the heterocyclic nitrogen was protected. In general, arylpinacolboronate esters were less reactive than arylboronic acids, and this led to lower yields and longer reaction times.

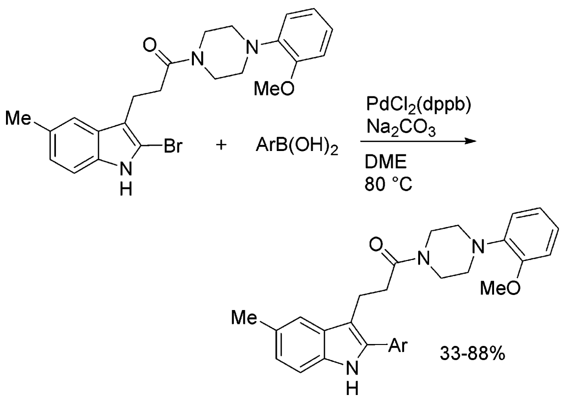
The Suzuki coupling was used to functionalize the C-2 position of various 5- and 7-azaindoles.[158] The authors found that 7-azaindoles provided higher yields of 2-aryl-7-azaindoles and required shorter reaction times than 5-azaindoles. Gribble et al.[179] described a convenient synthesis of symmetrical 2,3-diarylindoles via a domino bis-Suzuki cross-coupling reaction of 2,3-dihalo-1-(phenylsulfonyl)-indoles (Scheme 119). Attempts to achieve domino bis-Suzuki couplings leading to unsymmetrical 2,3-diarylindoles were unsuccessful.

Though less frequently, vinylation of the indole backbone via Suzuki coupling of indolyl halides has also been used to prepare indole derivatives. This protocol was utilized to functionalize the C-3[180] (Scheme 120) and the C-7[161a] positions starting from the corresponding indolyl iodides.

Scheme 121



Scheme 122



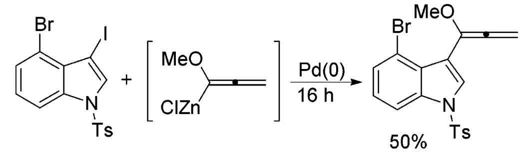
A variety of key precursors of bioactive compounds or their simplified analogues were prepared utilizing the Suzuki cross-coupling chemistry, such as in the preparation of *N*-(acyloxyalkyl)pyridinium salts as soluble prodrugs of a potent platelet activating factor antagonist,[181a] in abbreviated syntheses of pyrrolophenanthridinone alkaloids anhydrolycorinone and oxoassoanine,[181b] in model studies toward the synthesis of the cytotoxic marine natural product diazonamide A[182] (Scheme 121), in the synthesis of 2-aryltryptamines,[183] in arylation studies directed toward the synthesis of simplified eastern subunits of chloropeptin I and II and kistamycin,[184b] and in coupling reactions toward the total synthesis of the natural product diazonamide A.[173] Researchers at Merck exploited the Suzuki coupling of a 2-bromoindole with arylboronic acids to prepare novel 2-aryl indole hNK_1 receptor ligands[167k] (Scheme 122).

Cross-coupling chemistry on solid support is an active area. Solid-phase versions of the coupling of indolyl halides with aryl and heteroarylboronic acids evolved and were used to prepare 3-substituted 2-aryl indoles via elaboration of C-2 or C-3 positions and C-2, C-3 positions (in the latter case, the reaction was performed via a one-pot bis-Suzuki coupling of a 2,3-dibromoindole),[45d] 3-aryl(heteroaryl)-2-carboxyindoles (via elaboration of the C-3 position),[185] and 2,3,5-trisubstituted indoles (via elaboration of the C-5 position).[162]

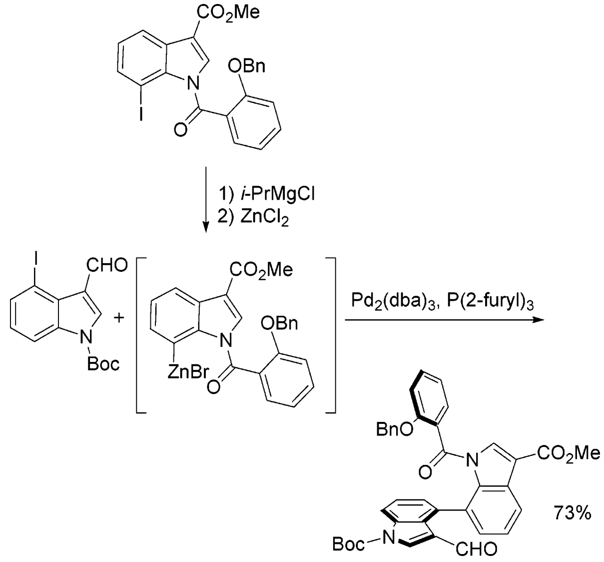
5.2.5. Reaction with Organozinc Compounds

Of the palladium-catalyzed cross-coupling reactions involving additional organometallics, the Zn-based methodology, known as the Negishi reaction, is the less frequently used with indolyl halides or triflates. Apparently, the first example dates back to 1989, when Hegedus et al.[186] applied this chemistry to the selective functionalization of the C-3 position of a 3-iodo-4-bromo indole (Scheme 123). The required allenylzinc reagent was prepared via reaction of

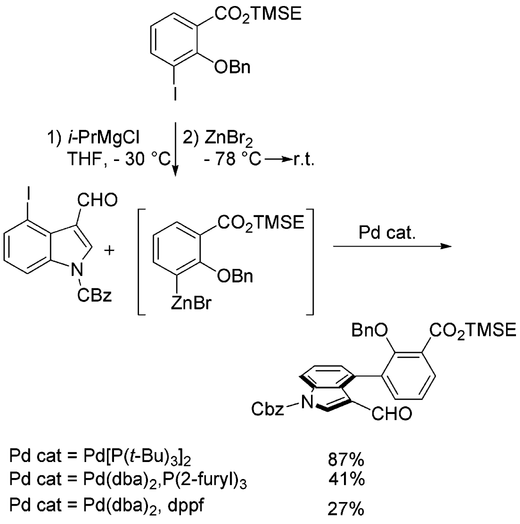
Scheme 123



Scheme 124

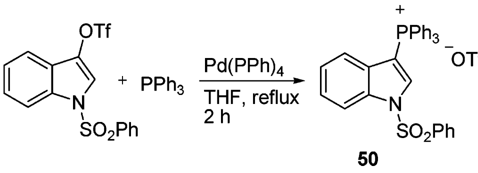


Scheme 125

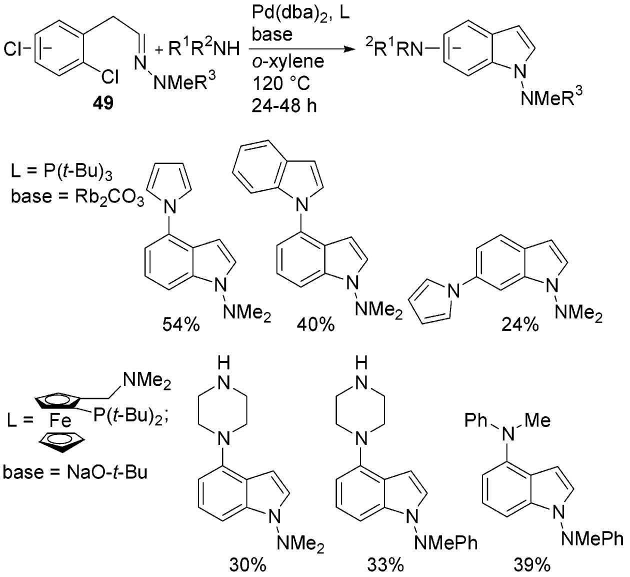


1-methoxy-1,2-propadiene with *tert*-butyllithium in the presence of TMEDA in THF, and the Pd(0) species was obtained through the reduction of $PdCl_2(PPh_3)_2$ with diisobutylaluminum hydride. The Negishi reaction was also applied to the preparation of a 2-vinylindole derivative via reaction of 2-iodo-1-methylindole with an α-(phenylthio)vinylzinc halide,[187] of 5-(indol-2′-yl)pyridin-2-ones and 5-(indol-2′-yl)pyran-2-ones from 2-iodoindole derivatives, though in very low yields (10−12%),[188] and of a bisindole (Scheme 124) and an indole salicylate (Scheme 125) with the required axial chirality for diazonamide A.[189] Interestingly, optimum yields were obtained with P(*t*-Bu)$_3$ as ligand in the latter case, in contrast to the P(2-furyl)$_3$ alternative favored with the indole-derived zinc reagent.

Scheme 126



Scheme 127



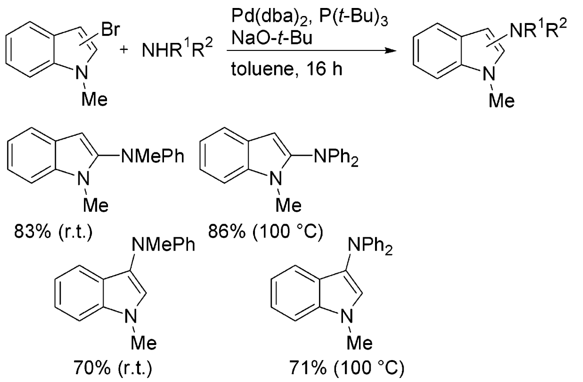
5.2.6. Reaction with Nonorganometallic Nucleophiles

Only a few examples of this methodology were described using P-, N-, and C-nucleophiles. Indolyl halides were usually employed as substrates. An example involving the reaction of an indolyl triflate with a nonorganometallic nucleophile was described by Gribble et al.,[156] who prepared the triphenylphosphonium salt **50** from 1-(phenylsulfonyl)-3-indolyl triflate and triphenyl phosphine (Scheme 126).

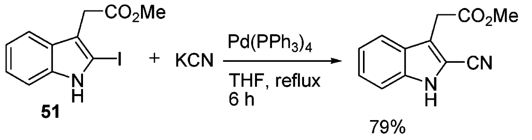
Watanabe et al.[143] prepared azolyl- and aminoindoles from dichlorophenylhydrazones **49** through a domino process based on a bis amination protocol (Scheme 127). With azoles, Rb_2CO_3 was preferably used as base and P(*t*-Bu)$_3$ was found to be superior to 2-(dimethylaminomethyl)-1-(di-*tert*-butylphosphinyl)ferrocene, whereas with amines the latter ligand gave better results than P(*t*-Bu)$_3$ and NaO-*t*-Bu was used as base. In sharp contrast to the reaction of **49** in the presence of phenylboronic acid (see Scheme 116), where the Suzuki coupling occurs before cyclization, in this case formation of the pyrrole ring was found to precede the amination of the benzenoid ring. As part of a study conducted to determine the activity of palladium catalyts for the amination of a variety of five-membered heterocyclic halides, Hartwig et al.[190] presented the amination of some *N*-methyl bromoindoles. The reaction could be best performed under the conditions outlined in Scheme 128. Interestingly, reactions with *N*-methylaniline proceeded to completion at room temperature, whereas reactions with diarylamines required 100 °C.

A couple of examples of palladium-catalyzed reactions of indolyl halides with alkali metal cyanide were reported. Cyanation of 5-bromoindole [Pd(PPh$_3$)$_4$,

Scheme 128



Scheme 129



51

CuI, NaCN, in valeronitrile, 115 °C, 2 h] was reported to give 5-cyanoindole in 76% yield,[191] and the 2-iodoindole **51** was converted to the corresponding cyano derivative[155] according to the conditions shown in Scheme 129.

5.3. Indolylmetal Compounds

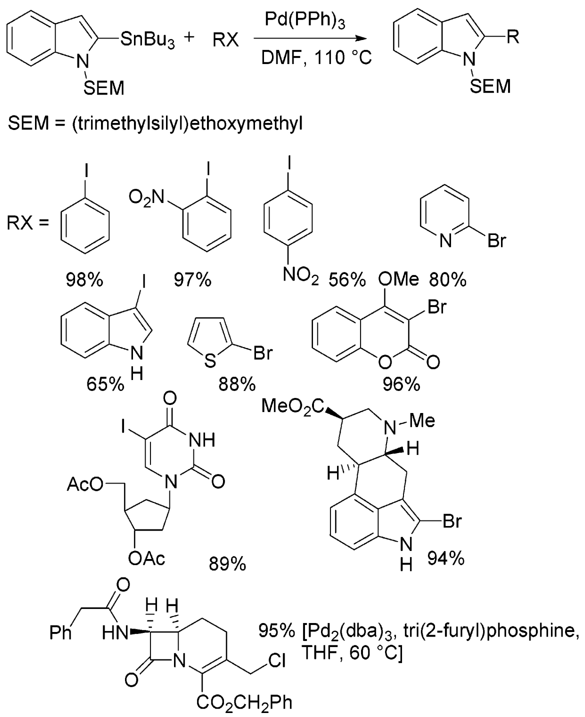
Apart from the occasional utilization of other indolylmetal intermediates, such as in the palladium-catalyzed Heck reaction of a thallated indole derivative with butenone and methyl acrylate[192a,b] or the palladium-catalyzed cross-coupling of indolylmagnesium halides,[192c−e] this derivatization chemistry has been usually based on indolylstannanes, indolylboronic acids, and indolylzinc compounds. The next three subsections are focused on this subject.

5.3.1. Indolylstannanes

Indolylstannanes were mostly utilized in the functionalization of the C-2, C-3, and, less extensively, C-5 positions. The scope of the reaction was expanded by incorporating different partners, reaction conditions, and procedures to allow access to the required stannylindoles. These developments led to a potentially general methodology for the functionalization of indoles, though the lithiation step typically used for the preparation of indolylstannanes can limit its flexibility. Alternative procedures for their preparation, which avoid the lithiation step, were developed. For example, *N*-tosyl-3-trimethylstannylindole was prepared via palladium-catalyzed coupling of *N*-tosyl-3-bromoindole with hexamethylditin.[193] These procedures, however, have not found widespread application.

First reports on the palladium-catalyzed replacement of the stannyl residue in stannylated indoles deals with 2-indolylstannanes prepared via lithiation of the *N*-SEM-,[194] *N*-methyl-, and *N*-Boc-[194c] protected indoles and dates back to the early 1990s. *N*-SEM-2-(tributylstannyl)indole was prepared on a multigram scale in excellent yield by metalation with BuLi followed by quenching of the resultant lithio complex with Bu_3SnCl. The authors ascribed the selective metalation at the C-2 position to the electron-withdrawing effect of nitrogen and the chelating ability of the oxygen contained in the protecting group. *N*-SEM-2-(tributylstannyl)indole could be stored at 0 °C for several weeks without significant decomposition. The reagent's versatility was illustrated by synthesizing a number of aryl, heteroaryl, alkynyl, vinyl, and benzyl indoles in 45−95% yields with reaction times ranging from 1 to 76 h. Best results were usually obtained under conditions shown in Scheme 130.

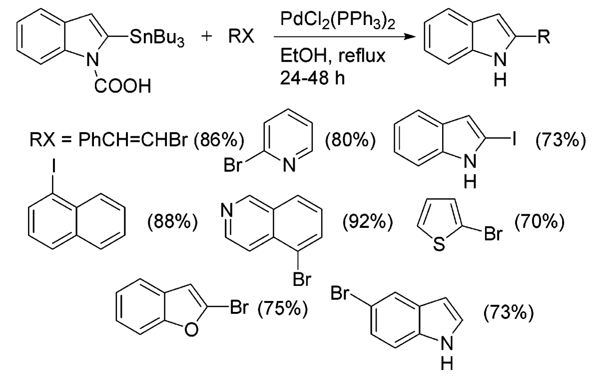
Scheme 130



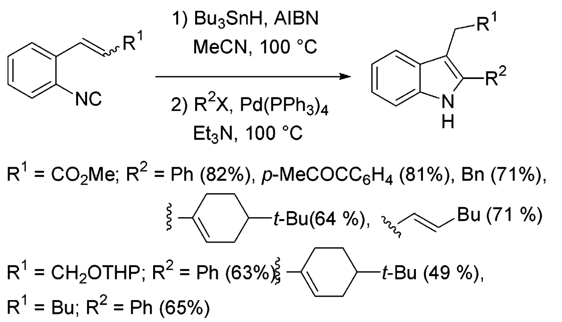
The use of the *N*-Boc protecting group has the advantage of the easy protection and deprotection. However, the *N*-Boc-protected indole reportedly gave poor yields in the formation of the *N*-Boc-2-stannyl intermediate. The *N*-SEM protecting group [subsequently employed in the synthesis of 5-(indol-2′-yl)-pyridin-2-ones and 5-(indol-2′-yl)pyran-2-ones][188] is not without faults. In some cases, it was reported to be difficult to remove.[194b] Attempts to use *N*-sulfonyl-protected stannyl indoles such as *N*-(benzensulfonyl)-2-(trimethylstannyl)indole[195] or *N*-(*p*-methoxybenzensulfonyl)-2-(trimethylstannyl)indole[188] were unsuccessful or produced the desired indole derivatives in very low yields.

In the search for alternative protecting groups, it was demonstrated that the utilization of carbon dioxide as a source of protection of the indole NH (and of an α-carbanion stabilizing group) could provide an efficient tool for the preparation of 2-substituted 1-*H*-indoles.[167f] Indeed, 2-substituted 1-*H*-indoles were prepared in high yield via palladium-catalyzed coupling of aryl, heteroaryl, and vinyl halides with *N*-carboxy-2-(tributylstannyl)indole (Scheme 131). This stannane was found to be stable for periods up to one month when stored at −20 °C under nitrogen.

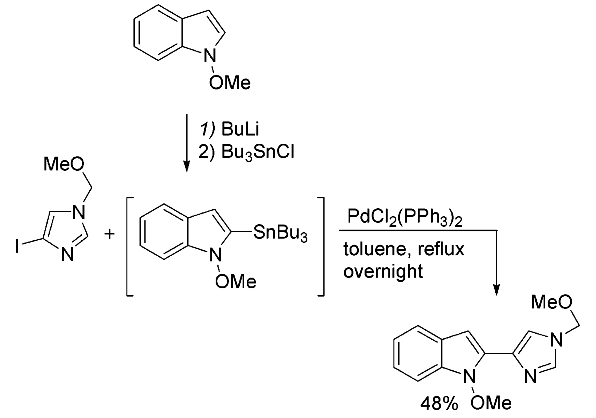
Scheme 131



Scheme 132



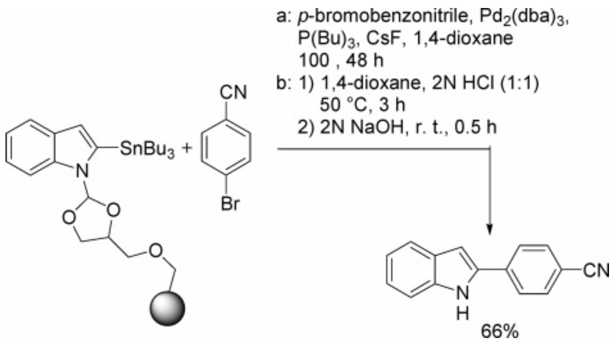
Scheme 133



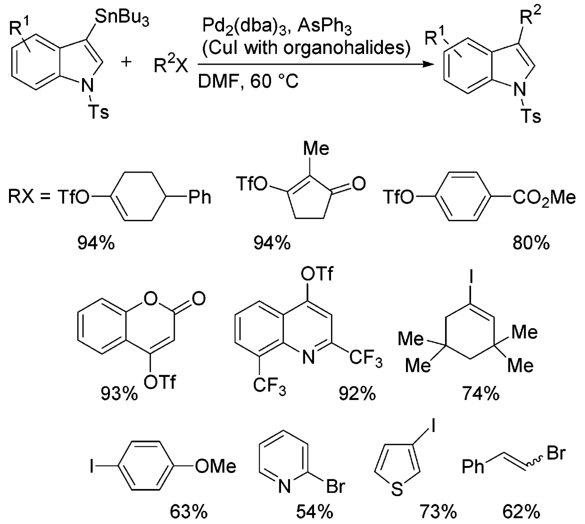
Fukuyama et al.[196] described a completely different approach to the synthesis of 2-stannylindoles. This approach, which affords 2-stannylindoles via cyclization of isonitriles in the presence of tributyltin hydride and catalytic amount of AIBN and avoids the lithiation step, was applied to the preparation of N-unprotected 3-substituted 2-stannylindoles. Since 2-stannylindoles were found to undergo destannylation during workup, the Stille coupling with aryl and vinyl halides and triflates was best performed through a one-pot protocol omitting the isolation of stannyl intermediates (Scheme 132).

In a new synthetic approach to the alkaloid granulatimide and its structural analogues, the pyrrole nitrogen was protected with the methoxy group. Indeed, *N*-methoxy-2-(tributylstannyl)indole was coupled with 4-iodoimidazoles to give the corresponding indole imidazole products in satisfactory yields (48−65%).[197] An example of this chemistry is outlined in Scheme 133. Deprotection of the *N*-methoxy group was achieved with Mg-MeOH.

Scheme 134



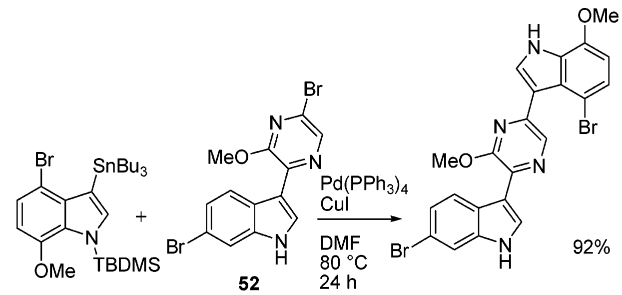
Scheme 135



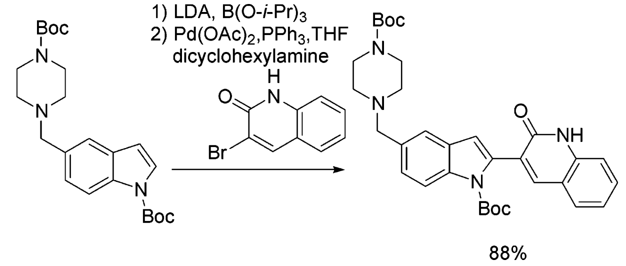
An application of the Stille coupling to a solid-phase synthesis of a 2-arylindole, based on the traceless linker methodology,[198] is shown in Scheme 134.

In an extension of the Stille coupling to the C-3 position of the indole backbone, it was shown that the palladium-catalyzed reaction of *N*-tosyl-3-tributylstannylindoles with a wide range of aryl, heteroaryl, and vinyl triflates and halides provided a general and efficient method for the synthesis of 3-substituted indoles[199] (Scheme 135). Interestingly, the *N*-tosyl protecting group was successfully used in the stannylation of the C-3 position, whereas other *N*-sulfonyl protecting groups[188,195] were found unsuitable for the preparation of 2-stannylindoles. Preliminary studies were conducted on cholest-2-en-3-yl triflate as vinyl triflate model. Classical Stille conditions[23] [Pd(PPh_3)$_4$, LiCl, THF at reflux] proved unsatisfactory. The use of $Pd_2(dba)_3$, tri(2-furyl)phosphine, and LiCl in DMF at 60 °C gave the indole product only in 39% yield, and omitting LiCl led to a moderate improvement (53%). A dramatic increase of the yield (93%) was achieved by using $AsPh_3$ as ligand without added chloride. These conditions were extended to include a large number of vinyl, aryl, and heteroaryl triflates, and the range of products prepared demonstrates the scope and utility of the reaction. With vinyl, aryl, and heteroaryl halides, optimum yields were obtained by adding CuI as cocatalyst.

Scheme 136



Scheme 137



A sulfonyl-protected stannane, *N*-(phenylsulfonyl)-3-indolylstannane, was subsequently used in a three-component coupling approach to the marine bis-indole alkaloids topsentin, deoxytopsentin, and bromotopsentin.[200] A 3-indolylstannane was also utilized in the construction of the skeleton of the dragmacidin D,[201] a significant bis-indole alkaloid belonging to an emerging class of bioactive marine natural products. In this case, the *tert*-butyldimethylsilyl (TBDMS) moiety was the protective group (Scheme 136). The reaction was carried out subjecting the indolylpirazine **52** to the crude stannane reagent.

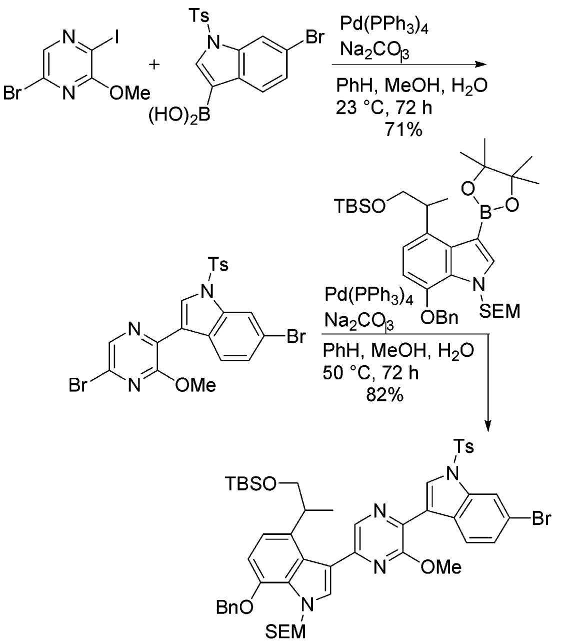
A couple of 5-heteroaryl-substituted 1-(*p*-fluorophenyl)-1*H*-indoles were prepared through the Stille coupling of a 5-stannylindole with heteroayl halides.[202]

5.3.2. Indolylboronic Acids

The Suzuki coupling of indolylboronic acids and indolylboronates has known widespread application in the functionalization of the indole ring. All the positions of the indole skeleton were functionalized with this cross-coupling protocol using a vast array of N-protecting groups (Me, allyl, Bn, MOM, SO_2Ph, Boc, SEM, TBDMS, TIPS). Since preparation and purification of indolylboronic acids in a pure state is not always easy to accomplish,[3f,178] often they are used directly as crude products.

N-Boc-2-indolylboronic acid was used to prepare some 2-arylindole derivatives.[203] 2-Indolylboronates were utilized in the synthesis of indolecarbazoles[204] and, recently, in a key step of a concise synthesis of a novel antiangiogenic tyrosine kinase inhibitor[205] (Scheme 137). In the latter case, the Suzuki coupling was carried out on a multikilogram scale. The indole was lithiated selectively at the C-2 position and was quenched in situ by triisopropyl borate using a noncryogenic protocol. Dicyclohexylamine was found to be an excellent activator, whereas usual basic aqueous system led to substantial deboronation.

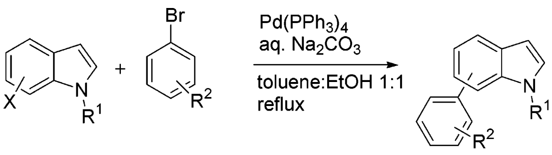
Scheme 138



The palladium-catalyzed cross-coupling between *N*-tosyl-3-indolylboronic acids and vinyl triflates was shown to be an efficient method for the regioselective introduction of the vinyl group into the indole C-3 position.[206] 3-Indolylboronic acids were successfully used in the total synthesis of the marine alkaloids nortopsentins A–D,[207] in the synthesis of mono-(indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines[208] (novel analogues of marine alkaloids), in the construction of the skeleton of dragmacidin D by stepwise cross-coupling reactions,[201] in the synthesis of bisindole alkaloids,[209] in the preparation of some analogues of camalexins.[210] In convergent and short-step syntheses of *dl-Cypridina* luciferin and its analogues,[211] *N*-tosyl-3-indolylboronic acid was coupled with a bromopyrazine to afford the corresponding free NH coupling derivative in 80% yield after hydrolysis with a 1:1 mixture of 5 M NaOH (aq) and 1,4-dioxane. *N*-Tosyl-3-indolylboronic acid, *N*-SEM-3-indolylboronate, and *N*-SEM-4-indolylboronate intermediates were involved in key steps of the first total synthesis of dragmacidin D.[212] An example of this chemistry is shown in Scheme 138. The authors emphasized that precise temperature control is needed for this sequence of coupling reactions, particularly for the second step, which involves the coupling of the pyrazinyl bromide in the presence of the indolyl bromide. They observed that at temperatures approaching 80 °C, coupling of the bromoindole unit becomes competitive with the desired cross-coupling.

Free NH and *N*-methyl-protected 5-indolylboronates prepared in situ through the reaction of bis(pinacolato)diborane and 5-bromoindoles in the presence of $PdCl_2$(dppf) and KOAc in DMF were used in the synthesis of new melatonin analogues,[175a] and *N*-methyl-protected 4-indolylboronates were found to be useful intermediates in the synthesis of novel quinolinequinone antitumor agents.[175b] Unprotected 5-indolylboronic acid was coupled with a variety of aryl and heteroaryl halides in the presence of

Scheme 139



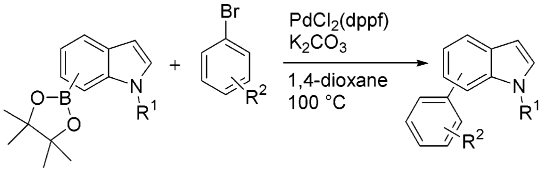
X	R^1	R^2	yield (%)
5-$(BOH)_2$	H	*p*-Me	65
5-$(BOH)_2$	H	*p*-OMe	80
5-$(BOH)_2$	H	*o*-Me	60
5-$(BOH)_2$	H	*o*-OMe	94
6-$(BOH)_2$	H	*p*-OMe	75
6-$(BOH)_2$	H	*o*-OMe	65
7-$(BOH)_2$	H	*p*-OMe	52
7-$(BOH)_2$	H	*o*-OMe	87
5-$(BOH)_2$	Boc	*p*-Me	34
5-$(BOH)_2$	Boc	*p*-OMe	50
5-$(BOH)_2$	Boc	*o*-Me	18
5-$(BOH)_2$	Boc	*o*-OMe	8
5-$(BOH)_2$	Ts	*p*-OMe	10
5-$(BOH)_2$	Ts	*o*-OMe	traces

$Pd(PPh_3)_4$ and aqueous sodium bicarbonate in ethylene glycol dimethyl ether.[184a] Unprotected 5-, 6-, and 7-indolylboronic acids were employed to develop an access toward analogues of the eastern subunits of chloropeptin I and II and kistamycin.[184b] In this work, a brief comparative study was made between Suzuki cross-coupling reactions involving bromoindoles and those involving indolylboronic acids. The yields with indolylboronic acids were higher than those provided by indolyl bromides.

The general picture emerging from literature data on the partner role swapping in the functionalization of the indole core motif via Suzuki coupling, however, is not unambiguous and straightforward, most probably because of the number of the reaction variables involved in the reaction. The cross-couplings of unprotected and N-protected (Boc and Ts) 5-, 6-, and 7-indolylboronic acids (Scheme 139) and 5-, 6-, and 7-indolylboronate esters (Scheme 140) with aryl bromides were subsequently investigated in an extensive and systematic work and a comparison was made with the reactivity of the 5-, 6-, and 7-indolyl bromide counterparts.[178] In general, cross-couplings with indolyl bromides gave the highest yields, which were unaffected by incorporating *N*-Boc or *N*-tosyl protection.

With indolylboronic acids and indolylboronates, which were subjected to coupling conditions directly as crude products, the reaction outcome was found to be influenced by the functionalization at the pyrrole nitrogen. In particular, with indolylboronic acids yields were almost independent of the position of the boronic acid group within indole. Nevertheless, they were usually lower in comparison to the series of reactions performed with indolyl bromides (see Scheme 117), most probably as a consequence of the reduced effectiveness with which the more electron-rich aryl bromides can participate in the oxidative addition to Pd(0) species.[213] Furthermore, the effect of steric hindrance was found to be dependent on the substituents at the pyrrole nitrogen. It was negligible in those couplings involving unprotected indoles (yields ranged from 52% to 94%) and became noticeable in couplings involving *N*-Boc-protected indolylboronic acids (8−50%). With the *N*-tosyl-protected counterparts, yields were very low (<10%) and no reliable relationship could be established. The authors suggested that the variation with respect to the substituents at the nitrogen atom could be explained by the higher reluctancy of more electron-deficient indolylboronic acids to undergo transmetalation.[170] The possibility that the results with indolylboronic acids might reflect the yields in which the different boronic acids themselves were formed was not ruled out.

Scheme 140



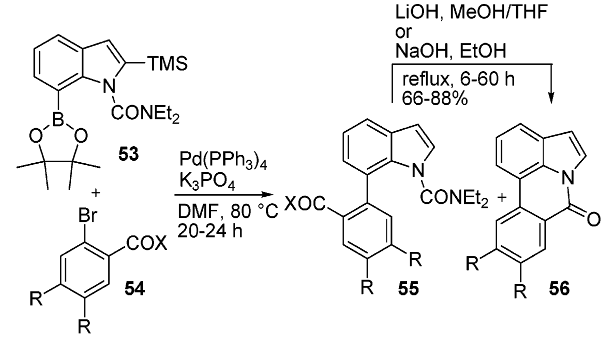
X	R^1	R^2	yield (%)
5-Bpin	H	*p*-OMe	traces
5-Bpin	H	*o*-OMe	traces
6-Bpin	H	*p*-OMe	traces
5-Bpin	Boc	*p*-OMe	36
5-Bpin	Boc	*o*-OMe	16
6-Bpin	Boc	*p*-OMe	39
6-Bpin	Boc	*o*-OMe	30
5-Bpin	Ts	*p*-OMe	43
5-Bpin	Ts	*o*-OMe	24
6-Bpin	Ts	*p*-OMe	62
6-Bpin	Ts	*o*-OMe	42

Indolylboronate esters gave yields significantly lower than indolylboronic acids (Scheme 140). The effect of increased steric hindrance in the ortho position of aryl bromides was again noticeable. Markedly, an inversion of the trend of the yields for *N*-tosyl-protected, *N*-Boc-protected, and free NH boronates was observed in comparison to the reactions employing boronic acids. The highest yields were in fact obtained with *N*-tosyl-protected boronates and the lowest ones with free NH boronates. *N*-Boc-protected boronates gave intermediate values.

Snieckus et al. applied the Suzuki coupling of 7-indolylpinacolboronate esters with aryl bromides to the synthesis of some representative members of pyrrolophenanthridone alkaloids exhibiting antitumor and other biological activities.[176] The indolylboronate **53** was coupled with aryl bromides **54** to give products **55** in moderate to high yields along with **56** as side products (Scheme 141). Prolonged cross-coupling reaction times or hydrolysis of isolated compounds afforded the tetracyclic derivatives in good yields.

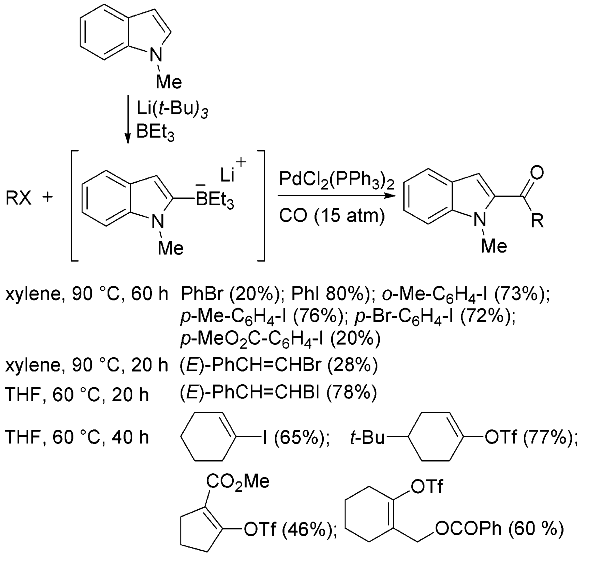
Indolylborates, generated in situ from lithioindoles and triethylborane, were also used to form functionalized indoles. Ishikura et al. employed indolylborates in cross-couplings with aryl, heteroaryl, and vinyl halides,[214] in domino cyclization/cross-couplings to

Scheme 141



R = OMe, X = NEt$_2$	40%	18% (pratosine)
R = OCH$_2$O, X = OEt	90%	7% (hippadine)
R = H, X = OEt	76%	13%

Scheme 142

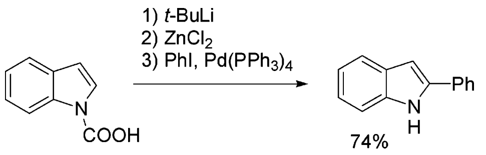


provide access to ellipticine derivatives,[215] and in cyclization/carbonylation/cross-coupling[214a] reactions. Carbonylative cross-coupling of *N*-methylindolylborate with 2-propynyl carbonates produced cyclopenta[*b*]indole derivatives in a one-pot manner.[216] An adequate set of conditions was developed to allow for the isolation of indol-2-yl allenyl ketone intermediates. With aryl halides and vinyl halides and triflates,[217a] carbonylative cross-coupling of triethyl(*N*-methylindol-2-yl)borate produced *N*-methylindol-2-yl ketones (Scheme 142). Variable amounts of cross-coupling products not incorporating carbon monoxide and *N*-methyl-2-ethylindole were also isolated. The usefulness of this approach to indolyl ketones was demonstrated by using the palladium-catalyzed carbonylative cross-coupling of triethyl(*N*-Boc-indol-2-yl)borate and triethyl(*N*-methoxyindol-2-yl)borate with vinyl triflates in a key step of a concise preparation of yuehchukene (a novel class of bisindole alkaloids) and its analogues.[217b]

5.3.3. Indolylzinc Compounds

The Negishi reaction represents the third methodology widely employed in the functionalization of indoles based on indolylmetal intermediates. Typically, indolylzinc compounds are prepared via lithiation of *N*-protected indoles. As observed with indolylstannanes and indolylboronic acids, however, this butyllithium route may limit the scope of the process in terms of flexibility, yields, and costs. To solve the problem of synthesizing indolylzinc intermediates via lithiation of indoles, Sakamoto et al. proposed an alternative preparation based on the oxidative addition of active zinc to indolyl iodides.[218] This method appears to be suitable for the functionalization of indoles containing functional groups such as acyl, alkoxycarbonyl, or cyano.

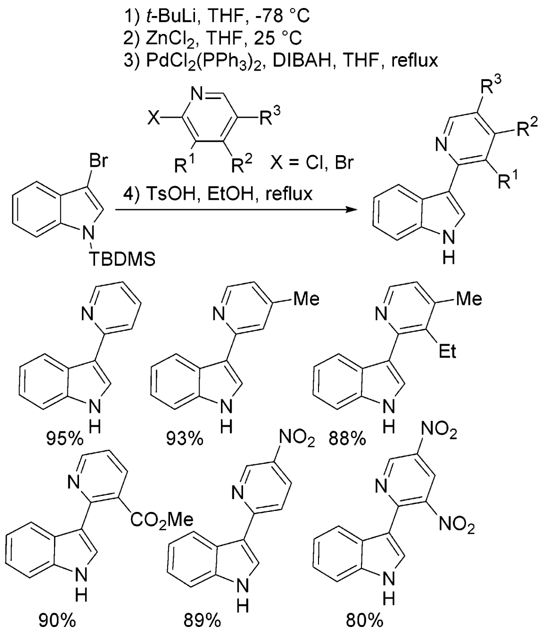
Scheme 143



First applications of indolylzinc halides to the functionalization of indoles dates back to the early 1990s. In 1993, Sakamoto, Yamanaka, et al.[219] described the synthesis of some 2-aryl- and 2-heteroarylindoles in 29−74% yield by the palladium-catalyzed reaction of aryl and heteroaryl iodides with *N*-COOH-protected 2-indolylzinc. A typical example of this chemistry is shown in Scheme 143. Other *N*-protecting groups such as $-SO_2Ph$, $-CH_2OMe$, and $-CH_2NMe_2$ gave unsatisfactory results. The reaction of iodobenzene with *N*-COO-*t*-Bu protected 2-indolylzinc gave the cross-coupling product in similar yield (68%), but the use of indole-*N*-carboxylic acid, which has a structural relationship with *N*-*tert*-butoxycarbonylindole, provides the significant advantage of allowing for easy removal of the protecting group during the workup. Almost at the same time, Amat, Bosch, and co-workers showed that *N*-(benzenesulfonyl)-2-indolylzinc chloride, prepared by treatment of *N*-(benzenesulfonyl)indole with LDA followed by transmetalation with anhydrous $ZnCl_2$, underwent smooth reaction with a variety of 2-chloro- and 2-bromopyridines to give 2-(2-pyridyl)indoles.[220a]

In subsequent papers, these two research groups reported further studies on the preparation of 2-aryl,[218b] 2-pyridyl,[220b,c] and 3-aryl/heteroaryl[218,220b,c] indoles. For the preparation of 3-functionalized indoles, two different approaches were developed. Since selective preparation of 3-indolylzinc chlorides from 3-lithioindoles unsubstituted at the C-2 position is difficult because of the easy rearrangement of the latter to the 2-lithio isomer, the required 3-indolylzinc intermediate was prepared via oxidative addition of active zinc to 3-iodo-*N*-(phenylsulfonyl)indole at room temperature.[218] Palladium-catalyzed cross-coupling of *N*-(benzenesulfonyl)-3-indolylzinc chloride with aryl halides gave 3-arylindoles in moderate to good yields. The procedure was developed into a new approach to camalexin. Alternatively, the C-3 position was successfully functionalized by using the bulky *tert*-butyldimethylsilyl group as the protecting group (Scheme 144).[220b,c] Indeed, most probably because the steric requirements of the bulky alkyl substituents on the silicon atom provide lateral protection of the C-2 position and noncoordinating abilities, *N*-(*tert*-butyldimethylsilyl)-3-lithioindole was found to be a stable species which does not rearrange

Scheme 144



to the 2-lithio isomer, even upon warming at room temperature.

Organozinc species derived from trasmetalation of the dilithio derivative of *N*-butylindole-3-carboxylic acid with $ZnCl_2$ produced 2-benzyl derivatives upon treatment with benzyl bromides in the presence of catalytic amounts of $Pd(Ph_3)_4$,[221a] (*N*-Methylindol-2-yl)zinc chloride was used to prepare 2-(2-arylethenyl)-*N*-methylindoles in good yield,[221b] and (*N*-SEM-indol-2-yl)zinc chloride was coupled with 5-bromopyridin-2-ones and 5-bromopyran-2-ones to give the corresponding 5-(indol-2′-yl)pyridin-2-ones and 5-(indol-2′-yl)pyran-2-ones in low to moderate yields.[188] A methodology for the phenyl ring functionalization of indoles via combined directed ortho metalation/cross-coupling was developed by Sniekus et al. to prepare some indole derivatives functionalized at the C-4 position.[169,222] The Negishi cross-coupling protocol was applied to the preparation of 5-hereroaryl *N*-(*p*-fluorophenyl)indoles in gram scale in 38−85% yield[202] (the use of reverse addition techniques in the lithiation step was found to be crucial to avoid formation of byproducts) and in the syntheses of a bisindole (Scheme 124) and an indole salicyclate (Scheme 125) with the required axial chirality for diazonamide A.[189]

5.4. *N*-Arylation and *N*-Vinylation of Indoles

As part of an investigation dedicated to the extension of the palladium-catalyzed C−N bond couplings to the formation of the aryl-nitrogen bonds in azoles, Hartwig et al.[223a] recently reported that *N*-arylindoles could be efficiently prepared from indoles and aryl bromides in the presence of $Pd(OAc)_2$ and dppf. Typically, reactions were carried out at 100 °C using Cs_2CO_3 as base with aryl bromides containing electron-withdrawing substituents in the para position, whereas neutral aryl bromides required higher temperature (120 °C), NaO-*t*-Bu as base and longer reaction times. On the basis of their data, the authors concluded that reductive eliminations that form *N*-aryl azoles require higher temperatures than do reductive eliminations that form C−C bonds in biaryls or C−N bonds in anilines. Subsequently, Hartwig et al.[223b] showed that the catalyst system involving $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as ligand allowed for much milder arylation of indoles than the combination of $Pd(OAc)_2$ and dppf. Electron-rich aryl bromides and *p*-chlorotoluene could arylate indoles at 100 °C in toluene. The use of Cs_2CO_3 as base rather than NaO-*t*-Bu was crucial to the success of the reaction. When reacted with unsubstituted indoles, hindered aryl halides such as *o*-bromotoluene generated products derived from the arylation at the nitrogen, at the C-2 position, and at both sites. The prototypical reaction is shown in Scheme 145. Practically parallel to the work of Hartwig et al. on the role of $P(t\text{-}Bu)_3$ in favoring the *N*-arylation of indoles, Watanabe and co-workers[224] showed that the $Pd(OAc)_2/P(t\text{-}Bu)_3$ combination in the presence of K_2CO_3 or Cs_2CO_3 (xylene, 120 °C) could effectively catalyze the *N*-arylation of indoles, pyrroles, and carbazoles. Interestingly, with their catalytic system, Cs_2CO_3 and NaO-*t*-Bu did not function very well.

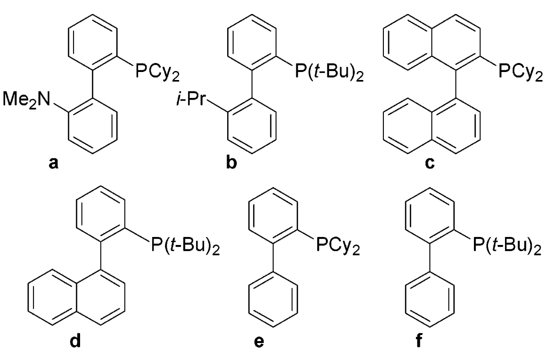
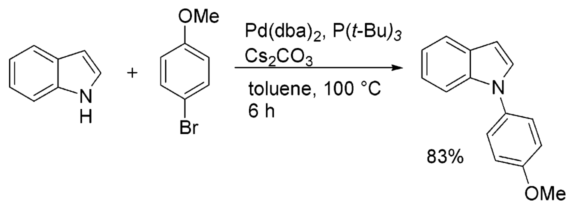


Figure 3.

Scheme 145



In another recent development, taking into account the dramatic influence of the ligand on C−N bond forming reactions, Buchwald and co-workers[225] investigated the use of bulky, electron-rich phosphines (Figure 3) as the supporting ligand in combination with $Pd_2(dba)_3$ in the arylation of indole. They were able to arylate a variety of substituted indoles with aryl iodides and bromides and also chlorides and triflates. Some examples from that study are depicted in Scheme 146. Building on these studies, Buchwald and co-workers[226] reported further improvements to the catalytic variation of the formation of C−N bonds. Indeed, in a study devoted to the arylation of a variety of nitrogen-containing compounds, they showed that the air-stable ligand **j** (Figure 4) is well suited for *N*-arylation and *N*-vinylation reactions. This ligand was found to be the best compromise between ligand **k** with the largest PR_2 group (moderately effective) and ligand **i** with the smallest PR_2 group

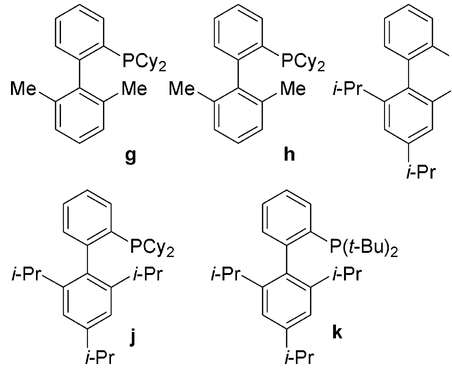
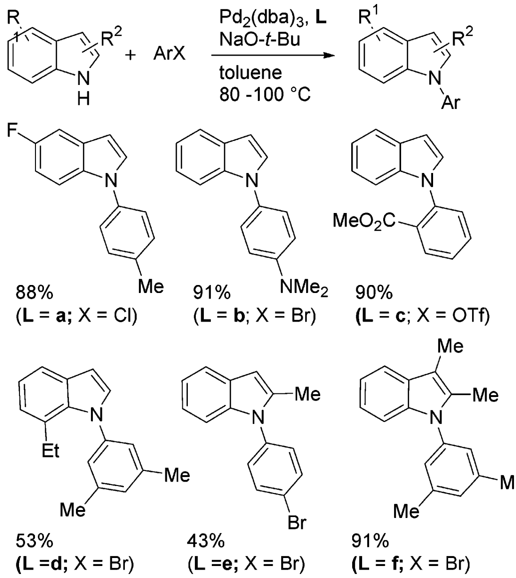
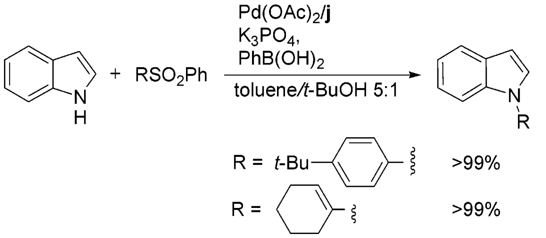


Figure 4.

Scheme 146



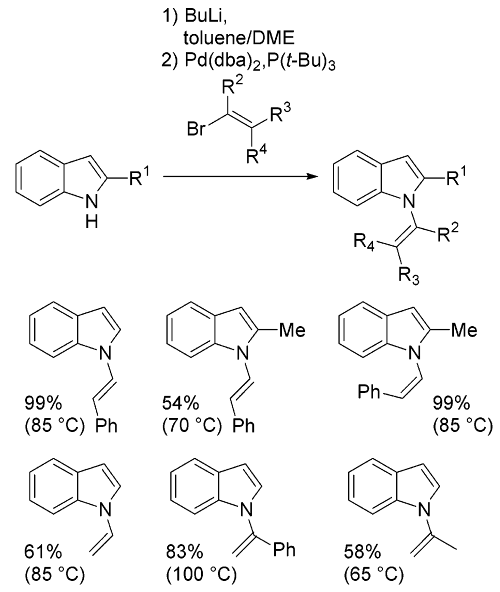
Scheme 147



(ineffective). It was also far superior to ligands **g** and **h** (Figure 4). Although only two indole examples were reported, it was demonstrated that indole underwent efficient *N*-arylation and *N*-vinylation in the presence of the $Pd_2(dba)_3$/**j** combination with aryl and vinyl sulfonates, a class of compounds less expensive than their triflate counterparts and usually reluctant to enter palladium-catalyzed reactions with other Pd/ligand combinations (Scheme 147). Noteworthy, in many cases excellent results were obtained using the $Pd_2(dba)_3$/**j** combination and KOH in water. Under these conditions, indole was arylated with *p*-butylchlorobenzene in 92% yield.

The palladium-catalyzed vinylation of indoles with vinyl bromides was also performed by treating preformed indolyllithium in the presence of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$,[227] though the catalyst based on the more expensive $t\text{-}Bu_2PC_6H_4Ph\text{-}o$ was shown to possess a very high activity. Either preformed indolyllithium or indole/LiO-*t*-Bu were found to be the most reactive and selective reagents for this type of reaction, whereas potassium and sodium salts as well as indole/K_2CO_3 gave poor results. Satisfactory yields were provided by indole/K_3PO_4 and indolylmagnesium bromide. The addition of a coordinating solvent such as DME to toluene was found to favor the vinylation reaction. The reactions with both (*Z*)- and (*E*)-bromostyrenes were stereospecific, giving the respective products with full retention of configuration. Some examples of this chemistry are shown in Scheme 148.

Scheme 148



6. Concluding Remarks

In this review, we showed that over the past decades palladium catalysis has achieved an important place in the arsenal of organic chemists involved in the construction and functionalization of indole derivatives. Palladium-catalyzed reactions, usually tolerant of a wide range of functionalities—thus providing the significant advantage of avoiding protection group chemistry—have become a very powerful tool in this area. In general, it is apparent from a synthetic perspective that the application of palladium catalysis to indole chemistry has had a considerable impact on the synthesis of this important class of compounds. It is used almost routinely in today's preparation of a vast number of indoles, ranging from simple to complex molecular targets.

Several areas of the palladium-catalyzed indole chemistry have been the object of an increasing number of studies, which include the development of new synthetic strategies, the optimization of reaction conditions (ligands, bases, additives, solvents), the utilization of solid-phase synthesis and microwave-assisted conditions, the construction of indole libraries, and the application to the synthesis of bioactive derivatives.

Despite the impressive number of contributions and results obtained, however, many challenges remain. A better understanding of various processes is necessary, and there is room for improvement in both scope and mildness of the reaction conditions for many of the methods described. Achieving higher turnover numbers of the catalytic cycles to favor a major impact on industry can also be expected to be an area of major interest. Finally, one can reasonably anticipate that future studies will provide new applications to the preparation of complex molecules, particularly in the area of biologically active compounds.

7. Acknowledgments

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