ORGANIC CHEMISTRY
FRONTIERS

REVIEW

View Article Online
View Journal | View Issue

**Cite this:** *Org. Chem. Front.*, 2020, **7**, 155

# Recent advances in the synthesis of indoles from alkynes and nitrogen sources

José Sebastião Santos Neto and Gilson Zeni *

Received 28th October 2019,
Accepted 22nd November 2019

DOI: 10.1039/c9qo01315f

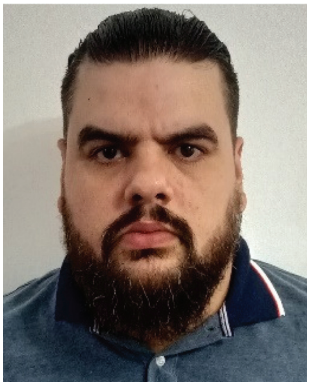
rsc.li/frontiers-organic

Transition metal-catalyzed cyclization reactions of unsaturated substrates have become one of the most important and useful methodologies for the preparation of heterocycles. To this end, the association between alkynes and nitrogen compounds results in versatile substrates for the synthesis of N-heterocycles, including indole derivatives. In order to demonstrate the growth in this area, this review highlights ten years of success in the synthesis of indoles using alkynes and nitrogen sources as substrates in the cyclization reactions catalyzed by metals. We believe that summarizing these methods would be very useful for the chemists who are interested in the synthesis of N-heterocycles.

## 1. Introduction

Indoles are the most important core structures in many biologically active natural products, exhibiting therapeutic properties over a wide range of targets.[1–5] Indole systems exhibit pharmacological activities, and are also present in commercially important products such as agrochemicals, essential oils, cosmetics, flavoring fragrance, dyes, and photosensitizer compounds.[6–8] Because they have been studied for more than one hundred years, an impressive number of well-established classical methods are now available for their synthesis.[2,9–19] The methodologies for the synthesis of indoles are normally associated with the name of the discoverer, such as Fischer indole synthesis,[20] Bischler indole synthesis,[21] Reissert indole synthesis,[22] Madelung indole synthesis,[23] Nenitzescu indole synthesis,[24] Sundberg indole synthesis,[25] Hemetsberger indole synthesis,[26] Gassman indole synthesis,[27] Leimgruber–Batcho indole synthesis,[28] Julia indole synthesis,[29] Bartoli indole synthesis,[30] Larock indole synthesis,[31] and Fukuyama indole synthesis[32] (Scheme 1).[33] Among all the existing synthetic methods to obtain indoles, those using alkynes as substrates

*Laboratório de Síntese, Reatividade, Avaliação Farmacológica e Toxicológica de Organocalcogênios CCNE, UFSM, Santa Maria, Rio Grande do Sul, 97105-900, Brazil. E-mail: gzeni@ufsm.br; http://www.ufsm.br*

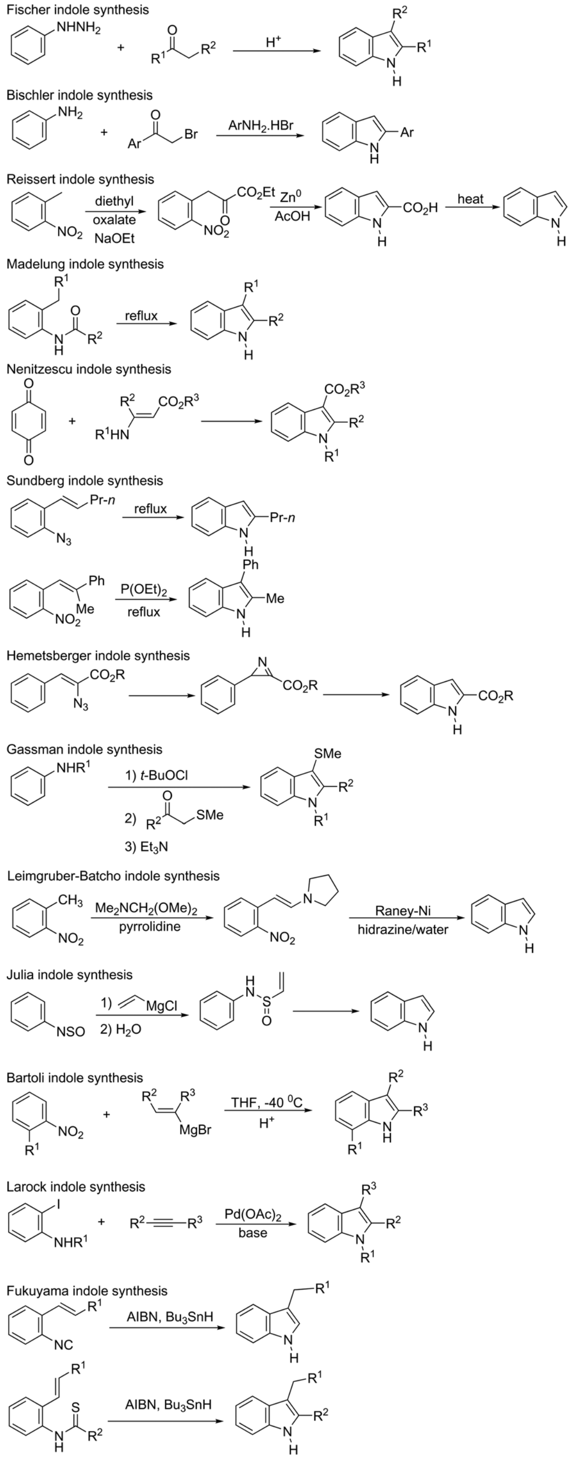


**José Sebastião Santos Neto**

*José Neto completed his graduation in Chemistry at the Federal University of Santa Maria (UFSM) in 2010. He obtained his MSc (2012) and Ph.D. (2016) degrees at the UFSM under the supervision of Prof. Gilson Zeni. After a postdoc period at the Federal University of Pelotas under the supervision of Prof. Diego Alves, he joined Prof. Antonio Luiz Braga's group at the Federal University of Santa Catarina, where he is a postdoctoral researcher. His research interests include organochalcogen studies with environmental synthetic methodologies and pharmacological applications.*

**Gilson Zeni**

*Gilson Zeni received his M.S. degree from the Federal University of Santa Maria-RS-Brazil, working under the direction of Prof. A. L. Braga, and his Ph.D. under the direction of Professor J. V. Comasseto (University of São Paulo). He did his postdoctoral studies at the Iowa State University-USA with Prof. R. C. Larock. He then moved to the Federal University of Santa Maria, where he is now a full professor. The synthesis and reactivity of organochalcogen compounds and the development of new synthetic methods for application of organochalcogen substrates in cyclization reactions are among his main current research interests.*



Scheme 1

are particularly attractive ones because of the wide variability in alkyne reactivity, substituent tolerance, chemoselectivity and ability to react with both nucleophiles and electrophiles. The cooperative action between alkynes and nitrogen compounds as substrates in transition metal-catalyzed cyclization reactions is a useful alternative to the synthesis of indoles. We believe that summarizing these methods would be very useful for chemists. Because many advances in the synthesis of these compounds have been published in the last few years, the purpose of this review was to highlight ten years of these achievements. In addition, the number of articles found in the literature on this topic is very large; therefore, to cover as many as possible we summarized the results in equations and tables, avoiding in some cases lengthy discussions. To facilitate the presentation, the review is organized in alphabetical order of the metal used for the cyclization reaction.

## 2. Transition-metal catalyzed synthesis of indoles

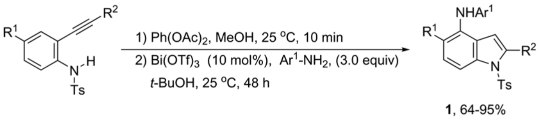
Transition metal-catalyzed activation of alkynes, followed by an intramolecular or intermolecular nucleophile addition, has become a powerful tool for the construction of the indole ring. Alkyne complexes containing bismuth, cobalt, copper, gold, indium, iridium, iron, manganese, mercury, nickel, palladium, platinum, rhenium, ruthenium, scandium, silver, titanium, tungsten, zinc, and zirconium have been employed as active catalysts for the synthesis of indole derivatives. In the next subsections, the utility of these reactions will be reviewed focusing on specific examples that appeared in the literature in the last ten years.

### 2.1. Bismuth-catalyzed synthesis of indoles

Bismuth salts have been shown to act as suitable catalysts for the cyclization reactions involving alkynes and nitrogen substrates for the preparation of indoles. Thus, the direct addition of NH from anilines across carbon–hydrogen of the 2-alkynylcyclohexadienimines was efficiently catalyzed by a $Bi(OTf)_3$/*t*-BuOH system, resulting in the formation of *N*-arylindoles **1** (Scheme 2).[34] The required starting 2-alkynylcyclohexadienimines were prepared by oxidative dearomatization reaction promoted by $PhI(OAc)_2$.

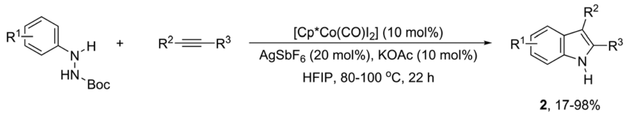
### 2.2. Cobalt-catalyzed synthesis of indoles

In contrast to palladium, copper, rhodium, and other transition-metal catalysts only a few reports on cobalt-catalyzed reactions of alkynes and nitrogen substrates for the preparation of indoles appeared in the literature in the last decade. In one of these reports, Boc-*N*-protected hydrazines were utilized as internal oxidizing directing groups for cobalt(III)-catalyzed annulation reaction with symmetrical and unsymmetrical alkynes for the synthesis of unprotected indoles **2**



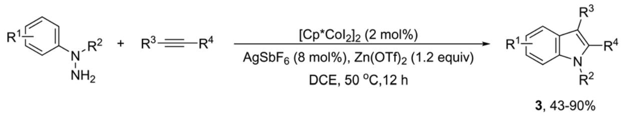
$R^1$ = 4-Me, 4-Et, 4-*n*-Bu; $R^2$ = H, $C_6H_5$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, *n*-Bu, *t*-Bu; $Ar^1$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 3,5-$(Me)_2$-$C_6H_3$, 4-*i*-Pr-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-pyridyl-$C_6H_4$.

Scheme 2



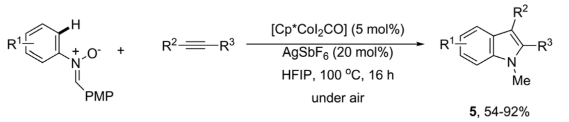
$R^1$ = H, 4-Br, 4-Cl, 4-F, 4-Me, 4-$C_6H_5$, 4-$F_3CO$, 4-NC; $R^2$ = $R^3$ = $C_6H_5$, 3-Me-$C_6H_4$, 3-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-F-$C_6H_4$, thienyl, *n*-$C_4H_9$; $R^2$ = $C_6H_5$ and $R^3$ = Me, Et, $EtO_2C$; $R^2$ = $MeO_2C$ and $R^3$ = *n*-$C_5H_{11}$.

Scheme 3



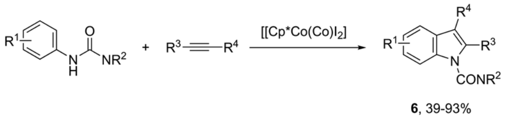
$R^1$ = 3-Br, 3-Cl, 4-Cl, 2-F, 4-F, 3-F, 2-Me, 3-Me, 4-Me, 3-MeO, 3-$MeO_2C$; $R^2$ = Me, Et, *i*-Pr, Ph, Bn; $R^3$ = $R^4$ = Et, *n*-Pr, *n*-Bu; $C_6H_5$; $R^3$ = $C_6H_5$ and $R^4$ = H, Me, Et, *n*-Pr, allyl.

Scheme 4



$R^1$ = H, 3-Me, 4-Me, 4-Br, 4-Cl, 4-F, 4-$EtO_2C$, 2-thienyl; $R^2$ = $R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$; $R^2$ = $EtO_2C$-$C_6H_4$ and $R^3$ = $C_6H_5$; $R^2$ = *n*-$C_5H_{11}$ and $R^3$ = 4-F-$C_6H_4$; $R^2$ = *n*-$C_4H_9$ and $R^3$ = 4-$O_2N$-$C_6H_4$; $R^2$ = $C_6H_5$ and $R^3$ = $O_2N$-$C_6H_4$.

Scheme 6



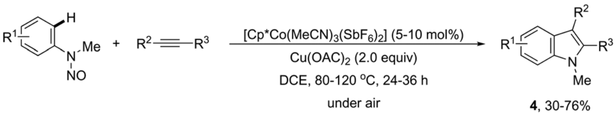
$R^1$ = H, 4-Br, 4-F, 4-$MeO_2C$, 2-Me, 3-Me, 3-$MeO_2C$, 2-MeO, 3,4-$(Me)_2$; $R^2$ = Me, pyrrolidine; $R^3$ = $R^4$ = $C_6H_5$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, thienyl; $R^4$ = $C_6H_5$ and $R^3$ = H, Me.

Scheme 7

(Scheme 3).[35] The authors developed a careful study to determine which hydrazine shows the best activity as a redox-neutral directing group, by comparing acetyl hydrazide, pivaloyl hydrazide, benzoyl hydrazide, and ethyl hydrazinecarboxylate, and Boc-phenylhydrazine led to the formation of products with best yields and selectivity. The Co(III)-catalyzed carbon–hydrogen functionalization/cyclization reactions can be also applied to 1-substituted-arylhydrazines and internal or terminal alkynes for the preparation of indoles **3** (Scheme 4).[36] The results indicated that a *meta*-substituent in the arylhydrazine and a branched chain in the alkynes governed the reaction regioselectivity.

The *N*-nitrosoanilines have also been reported as directing groups in the cationic cobalt(III) catalyzed intermolecular cyclization of alkynes for the regioselective preparation of *N*-substituted indoles **4** (Scheme 5).[37] A versatile cationic cobalt(III) catalyst using nitrones, as a nitrogen source, was also used in combination with internal alkynes for the preparation of 2,3-substituted indoles **5** (Scheme 6).[38] The authors carried out a comprehensive mechanistic study and concluded that this redox-neutral carbon–hydrogen/nitrogen–oxygen cyclization proceeds through carbon–hydrogen activation by carboxylate assistance.

*N*-Arylureas reacted with internal alkynes in a Cp*Co(III)-catalyzed oxidative annulation to afford indoles **6** (Scheme 7).[39] The authors observed that the presence of acetamides directly bonded to the nitrogen atom was crucial as directing groups. The methodology was very efficient for unsymmetrical internal alkynes giving the desired indoles with high regioselectivity.

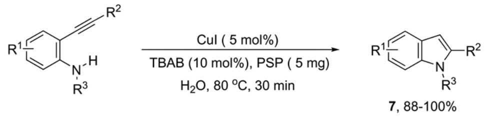


$R^1$ = H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-I, 4-Ph, 2-Me, 3-Me, 4-Me, 4-*t*-Bu, 4-$F_3CO$, 4-$F_3C$, 4-$MeO_2C$, 4-NC, (3-Cl, 4-Me), (4-$B_3$, 3-Me), (4-F, 3-Cl), 3,4-$(Cl_2)$; $R^2$ = $R^3$ = *n*-$C_5H_{11}$, $C_6H_5$, thienyl, $EtO_2C$; $R^2$ = $C_6H_5$ and $R^3$ = Me, allyl, *c*-$C_3H_5$.

Scheme 5

## 2.3. Copper-catalyzed synthesis of indoles

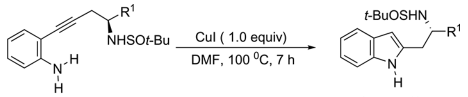
Copper salts constitute one of the most useful and powerful catalysts in organic synthesis, especially for carbon–carbon and carbon–heteroatom bond formation. This usefulness is particularly highlighted because of their lower costs, good accessibility and compatibility with a wide range of functional groups. However, at the beginning of their use, the reactions were conducted with equivalent amounts of copper salts, at high temperature, and with long reaction times. Over the past few years, great advancements have been made in copper-catalyzed reactions which include the use of a number of ligands such as aliphatic diamines, 1,10-phenanthroline, amino acids and their derivatives, and others.[40–42] These important outcomes permit the use of milder reaction conditions such as catalytic amounts of copper salts, lower temperature, and short reaction times. Several N-heterocyclic systems have been obtained through copper catalyzed intramolecular and intermolecular cyclization reactions.[43] A range of synthetic approaches involving alkynes in carbon–nitrogen bond formation, catalyzed by copper salts, has been applied for the generation of indoles. In one of these, a CuI-polystyrene-supported pyrrole-2-carbohydrazide catalytic system, in water, was applied for the cyclization of *N*-(2-ethynylphenyl)-sulfonamides for the preparation of indoles **7** (Scheme 8).[44] The catalytic system was successfully reused and recycled up to seven times, without any significant loss of activity. In another approach, the treatment of *ortho*-alkynylanilines with copper iodide, in DMF, at 100 °C, led to the 2-(2-aminoalkyl)indoles **8** (Scheme 9).[45] Although the authors observed from the TLC analyses a single spot corresponding to the products, they were obtained in low isolated yields after column chromatography, probably because of decomposition. When an imine is



**7**, 88-100%

$R^1$ = H, 4-Me, 3-MeO, 4-NC; $R^2$ = H, $C_6H_5$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-NC-$C_6H_4$, 4-*n*-Bu-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 4-*n*-Pr-$C_6H_4$, 4-*c*-Pr-$C_6H_4$; $R^3$ = Ts, Ms, $F_3COC$, MeOC.

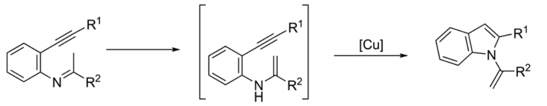
Scheme 8



**8**, 15-40%

$R^1$ = $Me_2CH$, $Me_2CHCH_2$, $PhCH_2$, $PhCH_2CH_2$, Ph.

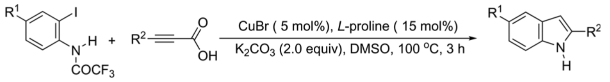
Scheme 9



**9** **10**, 42-88%

$R^1$ = H, $C_6H_5$, 2-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-$EtO_2C$-$C_6H_4$, 2-thienyl, *n*-$C_6H_{13}$, *c*-$C_3H_5$, *c*-$C_6H_{10}$, $HOCH_2(CH_2)_2$; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-$O_2N$-$C_6H_4$, 2-thienyl, 2-furyl, *c*-$C_6H_{11}$, *c*-$C_6H_{10}$.

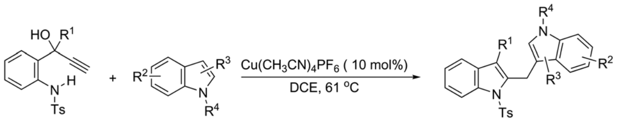
Scheme 10



**12**, 70-90%

$R^1$ = H, 4-$CH_3O_2C$, 4-NC, 4-Br; $R^2$ = $C_6H_5$, 3-Br-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 2-F-$C_6H_4$, 3,4-$(F)_2$-$C_6H_3$, (3-F,4-EtO)-$C_6H_3$, 4-$HO_2C$-$C_6H_4$, 3-$MeO_2C$-$C_6H_4$, 4-$MeO_2C$-$C_6H_4$, 4-$O_2N$-$C_6H_4$, 2-thienyl.

Scheme 12



**13**, 42-95%

$R^1$ = Me, *n*-Bu, *i*-Pr, Ph; $R^2$ = H, 2-Me, 3-Me, 4-Me, 4-MeO, 2-Cl, 4-Cl, 2-F, 3-F, 4-F; $R^3$ = H, 2-Me, 3-Me Ph, $NCCH_2$; $R^4$ = H, Me.

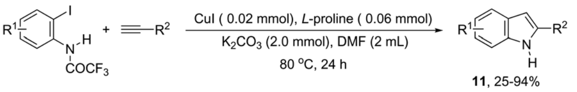
Scheme 13

incorporated into the aromatic ring at the *ortho*-position of the alkyne, such as *N*-(2-alkynylphenyl)imines, the *endo*-cyclic products, *N*-vinylindoles **10**, are formed (Scheme 10).[46] The authors suggested that the enamine **9** is the *N*-nucleophilic source, which is generated *via* tautomerization of the imine.

The synthesis of a number of indoles has been achieved by the copper-catalyzed domino Sonogashira coupling/cyclization reaction of *N*-substituted *ortho*-haloanilines with terminal alkynes. For example, the copper-catalyzed one-pot reaction of *ortho*-bromotrifluoroacetanilides with terminal alkynes, using CuI/L-proline as the catalytic system and $K_2CO_3$ as a base, in DMF, at 80 °C, gave 2-substituted indoles **11** (Scheme 11).[47] In an extension of this work, *ortho*-arylindoles **12** were prepared by copper catalyzed domino sp–sp$^2$ decarboxylative cross-coupling following cyclization reactions of arylpropiolic acids with *ortho*-iodotrifluoroacetanilides (Scheme 12).[48] Subsequently, analogous to these strategies, the reaction of *N*-substituted *ortho*-iodoanilines with terminal alkynes catalyzed by CuI, using DBU as a base, in EtOH, in the absence of a ligand, gave the corresponding indoles in good yields.[49] Even though the authors developed the work using copper as a catalyst, they concluded that a palladium contaminant as low as 100 ppb was the promoter of the reaction.

A copper-catalyzed tandem annulation/arylation has been developed for the synthesis of diindolylmethanes **13** from propargyl alcohols (Scheme 13).[50] The investigation of the reaction mechanism indicated that the formation of indoles **13** involves a key allyl cation intermediate, which is attacked by an indole nucleophile to form the product. The indole nucleophiles can be replaced by other carbon or oxygen nucleophiles such as 1,3-dimethoxybenzene and alcohols.

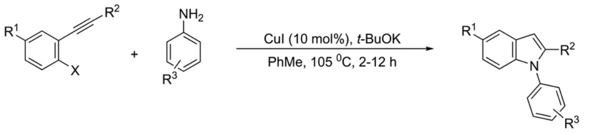
The domino *N*-arylation/hydroamination strategy has found many applications for the synthesis of functionalized indoles. This reaction occurs between *ortho*-alkynylhaloarenes and a nitrogen substrate in the presence of copper catalysts. In this case, the copper salt plays a dual role of both promoting the formation of the carbon–nitrogen bond and catalyzing the cyclization. These reactions were applied to the synthesis of several *N*-arylindoles **14** starting from *ortho*-alkynylbromoarenes (Scheme 14).[51] The reaction utilized anilines as an *N*-nucleophilic source and copper iodide as a catalyst in a ligand-free system. Other *N*-nucleophiles, such as amides, required the presence of a diamine as a ligand for the preparation of the corresponding *N*-acylindoles. The *N*-arylation/hydroamination described above was extended to construct the 1,2-disubstituted indoles **15** through Cu(II)-catalyzed domino coupling/cyclization reactions of *ortho*-alkynylanilines and boronic acids (Scheme 15).[52] This sequence was also applied



**11**, 25-94%

$R^1$ = H, 4-Et, 4-MeO, 5- MeO, 4-$O_2N$, 4-$MeO_2C$, 3-$MeO_2C$, 4-MesN, 4-MeBnN, 4-Cl; $R^2$ = $C_6H_5$, 4-$C_6$-$C_6H_4$, 4-$MeO_2C$-$C_6H_4$, 4-MeO-$C_6H_4$, 3-MeOC, *n*-$C_5H_{11}$, $BnOCH_2$, $THPOCH_2$.

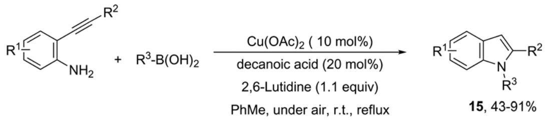
Scheme 11



**14**, 21-84%

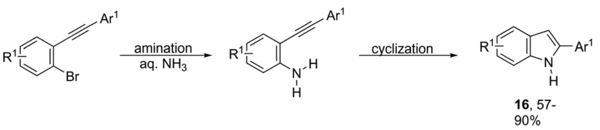
$R^1$ = H, $F_3C$; $R^2$ = *n*-$C_6H_{13}$, *n*-$C_4H_9$; $R^3$ = H, 4-Me, 3-MeO, 4-MeO, 4-Cl, (2-Cl, 4-MeO), (2-Cl, 5-MeO),1-naphthyl.

Scheme 14



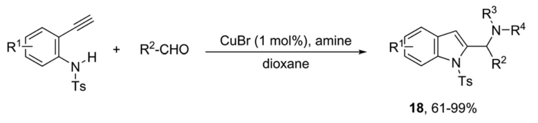
$R^1$ = H, 4-Me, 4-Cl, 4-NC; $R^2$ = $C_6H_5$, 2-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, c-$C_3H_5$, t-Bu; $R^3$ = $C_6H_5$, 2-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-n-Pr-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 3-MeO-$C_6H_4$, c-$C_3H_5$, n-$C_4H_9$, c-$C_6H_{11}$.

Scheme 15



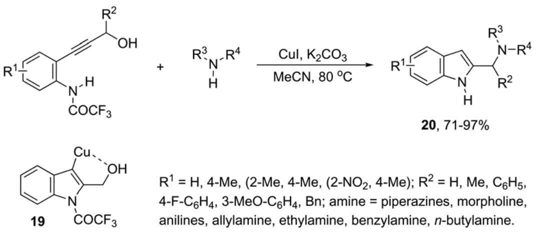
$R^1$ = H, 3-Me, 4-Me, 4-Cl, 4-F, 4-$O_2N$, 4-MeOC, 4-$F_3$CO, 4-$F_3$C; $Ar^1$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-$CF_3$-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeOC-$C_6H_4$, 3,5-(MeO)$_2$-$C_6H_3$, 1-naphthyl, 2-thienyl.

Scheme 16



$R^1$ = H, 3-$MeO_2C$, 3-$F_3C$, 4-Me; $R^2$ = H, n-Pr, $C_6H_5$, 4-$MeO_2C$-$C_6H_4$, 4-Me-$C_6H_4$, 2-Br-$C_6H_4$; amine = benzylamine, isopropylamine, ethylamine, piperidine, pyrrolidine, allylamine.

Scheme 18



$R^1$ = H, 4-Me, (2-Me, 4-Me, (2-$NO_2$, 4-Me); $R^2$ = H, Me, $C_6H_5$, 4-F-$C_6H_4$, 3-MeO-$C_6H_4$, Bn; amine = piperazines, morpholine, anilines, allylamine, ethylamine, benzylamine, n-butylamine.

Scheme 19

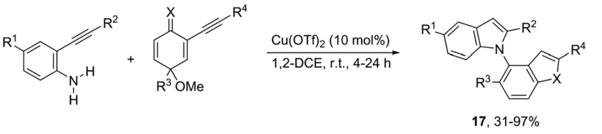
to the synthesis of free *N-H*-2-arylindoles **16**, which included copper(II)-catalyzed amination of *ortho*-bromoarylalkynes with aqueous ammonia (Scheme 16).[53] The advancement of the methodology was due to the convenience and atom economy of using aqueous ammonia.

*N*-Alkylation reaction employing 2-alkynyl cyclohexadienimines, as the alkylating agents, has been proven to be very effective at the construction of N-heteroarylated indoles **17** (Scheme 17).[54] The use of 2-alkynyl cyclohexadienones, as the alkylating agents, led to the formation of 1-(benzofuran-4-yl)-1*H*-indoles. The optimization of the reaction conditions revealed that higher yields of indoles were obtained using Cu(OTf)$_2$ in 1,2-dichloroethane as the catalytic system.

Copper-catalyzed domino three-component coupling-cyclization of *ortho*-alkynylanilines with secondary amines and aldehydes can also yield indoles. In the former case, cyclic or acyclic secondary amines, aldehydes and *ortho*-alkynylanilines allowed the copper(I)-catalyzed formation of 2-(aminomethyl) indoles **18** in high yields (Scheme 18).[55,56] The reaction involved the formation of two carbon–nitrogen bonds and one carbon–carbon bond producing water as the only waste. In addition, the copper-catalyzed cyclization of 3-(*ortho*-trifluoroacetamidophenyl)-1-propargyl alcohols, in the presence of primary or secondary amines, gave free *NH*-2-(aminomethyl) indoles **20** (Scheme 19).[57] The proposed key intermediate is a σ-indolyl copper **19**, which can undergo substitution of the hydroxyl group for the nucleophilic amino group, assisted by the coordination of oxygen to copper (Scheme 19).

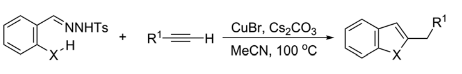
*ortho*-Amino-*N*-tosylhydrazones, which are prepared using the corresponding aldehydes, can be also applied to copper(I)-catalyzed cyclization with terminal alkynes to afford 2-substituted indoles **21** (Scheme 20).[58] In additional studies, the authors used *N*-tosylhydrazones and *ortho*-aminoarylalkynes in a reaction catalyzed by CuBr to form 2-substituted indoles **22** (Scheme 21).[59] The proposed mechanism consists of the *in situ* preparation of a diazo compound, followed by a copper acetylide attack on the diazo compound to give the copper carbine **23**. The migratory insertion of the carbenic carbon into the alkynyl group affords the propargyl cuprate intermediate **24**. The formation of an allene and an intramolecular cyclization promoted by the copper catalyst afford the desired indoles (Scheme 22).

The intramolecular cyclization between *ortho*-alkynylanilines and copper salts is an established method for the synthesis of 3-haloindoles. It has been demonstrated that through this methodology 3-chloro- and 3-bromoindole derivatives **25** can be prepared in good yields by the reaction of *ortho*-alkynyl-



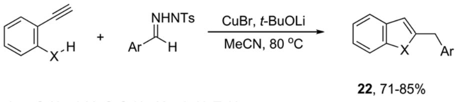
$R^1$ = H, Me, i-Pr, Cl, F; $R^2$ = H, $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, c-$C_3H_5$, t-$C_4H_9$, n-$C_4H_9$; $R^3$ = Me, $C_6H_5$, MeO, Cl; $R^4$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, c-$C_3H_5$, n-$C_4H_9$, t-$C_4H_9$; X = TsN, MsN, AcN, BzN, O.

Scheme 17



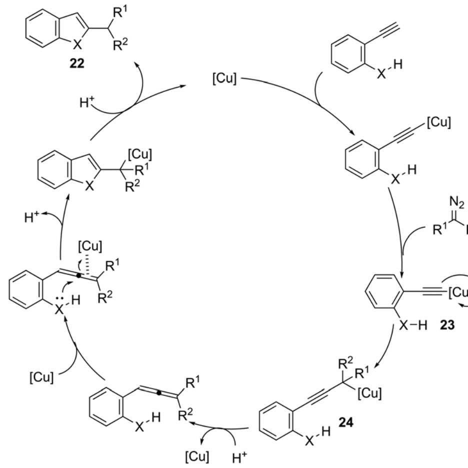
X = O, NH, AcN; $R^1$ = $C_6H_5$, 3-thienyl, $PhCH_2CH_2$.

Scheme 20

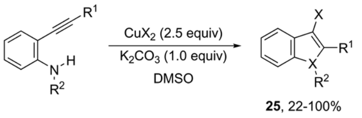


Ar = $C_6H_5$, 4-MeO-$C_6H_4$; X = AcN, TsN.

Scheme 21

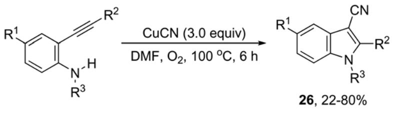


Scheme 22



$R^1$ = H, $C_6H_5$, n-$C_4H_9$, n-$C_6H_{13}$, $MeOCH_2$, $HOCH_2$, TMS;
$R^2$ = H, Ts, Ms, Ac; X = Cl, Br.

Scheme 23

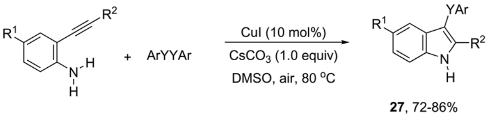


$R^1$ = H, 4-MeO, 4-NC; $R^2$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-F-$C_6H_4$, n-$C_5H_{11}$;
$R^3$ = H, Ts.

Scheme 24

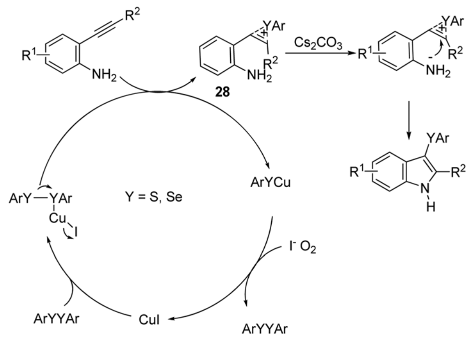
anilines with cupric halide in dimethyl sulfoxide (Scheme 23).[60] The authors determined that $CuBr_2$ instead of $Br_2$ promotes the bromocyclization reaction and that the inactive Cu(0), formed in the reaction, can be oxidized by $CuX_2$ to produce CuX, which activates the alkynes. By using CuCN as a promoter, *N*-protected *ortho*-alkynylanilines gave 3-cyanoindoles **26** *via* a sequential cyclization–cyanation reaction (Scheme 24).[61] In the proposed mechanism, the molecular oxygen promotes the oxidation of a Cu(I)–alkyne complex intermediate to the corresponding Cu(II) or Cu(III). It has been reported that the use of camphorsulfonic acid (CSA), as an additive, was effective in increasing the yield of 3-cyanoindoles.[62]

The copper catalyzed tandem cyclization of *ortho*-alkynylanilines with dichalcogenides provided an expedient approach for the synthesis of 3-chalcogenindoles **27** (Scheme 25).[63] The results indicated that the copper catalyst promotes the chalcogen–chalcogen bond cleavage to form an electrophilic chalcogen species, which activates the carbon–carbon triple bond of the *ortho*-alkynylanilines *via* chalcogenonium cation **28**. The nitrogen intramolecular attack on the cation **28** produces the corresponding 3-chalcogen-indoles (Scheme 26).



$R^1$ = H, 4-Cl; $R^2$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-MeO-$C_6H_4$; Ar = $C_6H_5$, 4-Me-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$; Y = S, Se

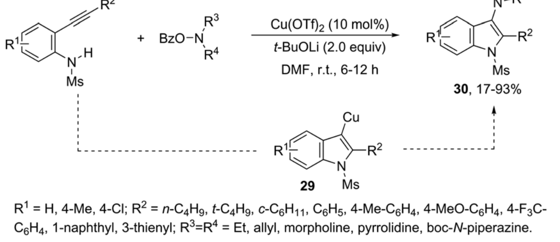
Scheme 25



Scheme 26

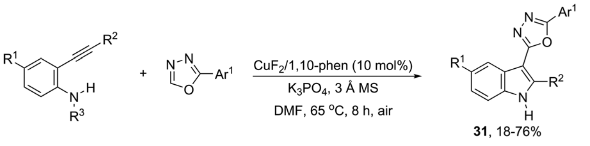
This tandem reaction was also attempted by using *O*-benzoyl hydroxylamines to capture the copper intermediate. Thus, the copper catalyzed cyclization of *ortho*-alkynylanilines produced the indolyl copper intermediate **29**, which reacted with *O*-benzoyl hydroxylamines to give 3-aminoindoles **30** (Scheme 27).[64] The investigation of the mechanism carried out by the authors indicated that a nonradical electrophilic amination of the heteroarylcopper species and a carbon–nitrogen bond-forming step were involved. Following the same reaction sequence, C3-azolylindoles **31** were synthesized from copper-promoted annulative direct coupling of *ortho*-alkynylanilines with 1,3,4-oxadiazoles (Scheme 28).[65] The authors suggested that the carbon–carbon triple bond of anilines is activated by an oxadiazoyl copper intermediate **32**, which promotes the annulative aminocupration leading to the product after reductive elimination (Scheme 29).

Another approach to obtain 3-substituted indole derivatives employed a visible-light-induced copper-catalyzed process for carbon–hydrogen annulation of arylamines with terminal



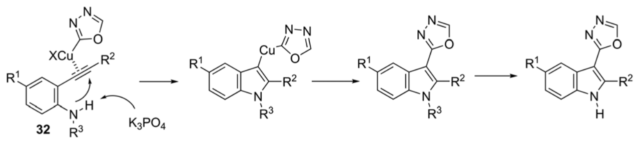
$R^1$ = H, 4-Me, 4-Cl; $R^2$ = n-$C_4H_9$, t-$C_4H_9$, c-$C_6H_{11}$, $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 1-naphthyl, 3-thienyl; $R^3$=$R^4$ = Et, allyl, morpholine, pyrrolidine, boc-*N*-piperazine.

Scheme 27

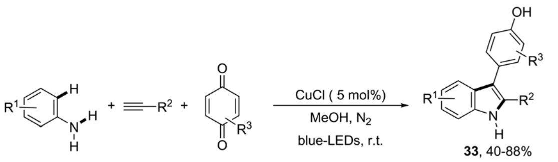


$R^1$ = H, 4-Me, 4-Cl; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 1-naphthyl, *t*-$C_4H_9$; $R^3$ = 2-F-$C_6H_4CO$, 2-$F_3C$-$C_6H_4CO$, $MeO_2S$; $Ar^1$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-Cl-$C_6H_4$, 1-naphthyl, $PhCH_2CH_2$.

Scheme 28



Scheme 29

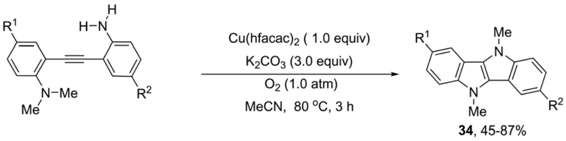


$R^1$ = H, naphthyl, anthracenyl, 4-$MeO_2C$, 5-NC, 4-phenyacetylene; $R^2$ = 4-*t*-Bu-$C_6H_4$, 4-Me-$C_6H_4$, 3-HO-$C_6H_4$, 4-HO-$C_6H_4$, 3-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-NC-$C_6H_4$, 4-$NCCH_2$-$C_6H_4$, 4-$MeCO_2CH_2$-$C_6H_4$, 4-MeNHCO-$C_6H_4$, 3-$O_2N$-$C_6H_4$, 4-Ph-$C_6H_4$, *n*-$C_6H_{13}$, *c*-$C_6H_{11}$; $R^3$ = 2-Me, 2,5 $(Me)_2$, 2-Cl.

Scheme 30

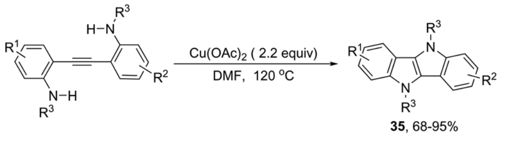
alkynes and benzoquinone. Thus, the visible-light irradiation of aniline derivatives with alkynes in the presence of benzoquinone using a mixture of $CH_3CN/CH_3OH$ (1 : 1 v/v) as the solvent and CuCl (5 mol%) as the catalyst, at room temperature, gave 3-*para*-hydroxyphenyl substituted indoles **33** (Scheme 30).[66]

The intramolecular oxidative diamination of bis-(2-aminophenyl)acetylenes promoted by a $Cu(hfacac)_2/O_2$ oxidation system was used for the preparation of 5,10-dihydroindolo[3,2-*b*]indoles **34** (Scheme 31).[67] The presence of both *N*,*N*-dimethylamine and primary amine groups in the bis-(2-aminophenyl) acetylenes was crucial for the success of the cyclization. The key step of the annulation process was the intermolecular *N*-methyl transfer from the nitrogen atom of *N*,*N*-dimethylamine to the primary amine. Subsequently, the cascade reaction annulation of diarylalkyne sulfonamides catalyzed by $Cu(OAc)_2$, in the absence of an oxidant, led to the formation of 5,10-dihydroindolo[3,2-*b*]indoles **35** (Scheme 32).[68] The authors stated that the process involves two sequential cyclizations with two carbon–nitrogen bond formation processes, in which $Cu(OAc)_2$ works as a catalyst in the first step and as an oxidant in the second step.



$R^1$ = H, *t*-Bu, Me, $MeO_2C$, Br, Cl, F; $R^2$ = Me, F, $MeO_2C$.

Scheme 31

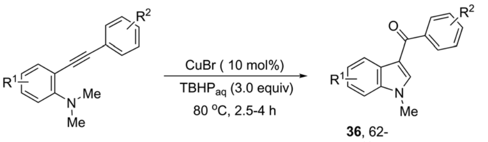


$R^1$ = H, 4-Br, 4-Cl, 4-F, 4-Me, 4-MeO, 2,5$(Me)_2$; $R^2$ = H, 4-Cl, 4-MeO; $R^3$ = Me, Ts, $PhSO_2$, 4-Cl-$C_6H_4SO_2$.

Scheme 32

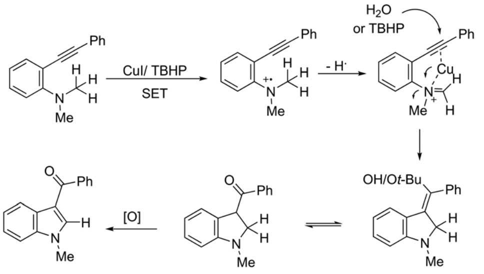
*ortho*-Alkynyl *N*,*N*-dimethylamines have been also utilized for the functionalization of the 3-position of the indole ring for the preparation of 3-aroylindoles **36**, *via* a copper catalyzed tandem process (Scheme 33).[69] In this cyclization, one carbon–carbon bond and one carbon–oxygen bond are formed while two $sp^3$ carbon–hydrogen bonds are cleaved. The reaction involves an $sp^3$ carbon–hydrogen bond activation of the methyl group bonded to nitrogen, followed by an intramolecular nucleophilic attack of water on the alkyne, which promotes the cyclization onto iminium carbon to give, after oxidation, the product (Scheme 34). The copper-catalyzed annulation of nitrosoarenes and alkynes, followed by deoxygenation, was also employed to obtain 3-substituted indoles **37** (Scheme 35).[70] It was proposed that the *in situ* formation of the Cu(I) species, by the reaction of CuI(I) with Cu(0), is responsible for deoxygenation of the *N*-hydroxyindole intermediate returning the CuI(II) species to the cycle.

The 3-acylated indole derivatives **38** have been prepared by the conjugate addition of *N*-formyl-2-haloanilines to acetylenic sulfones, ketones, and esters, followed by a copper-catalyzed

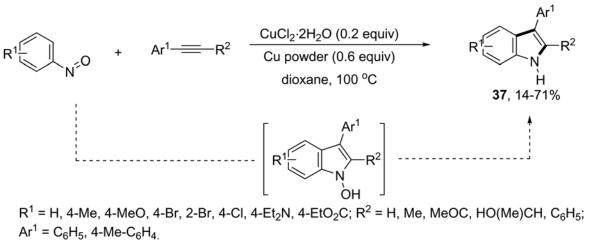


$R^1$ = H, 4-Me, 3,4 $(Me)_2$, 4-Br; $R^2$ = H, 4-Me, 4-*t*-Bu, 4-$O_2N$.

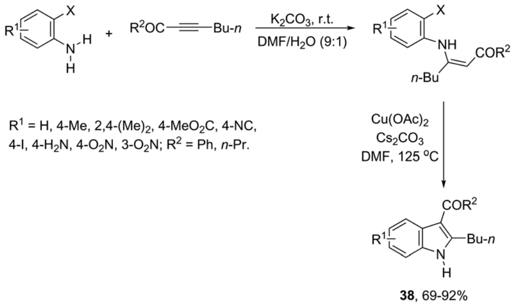
Scheme 33



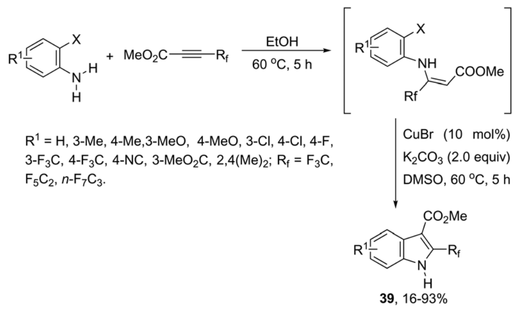
Scheme 34



Scheme 35

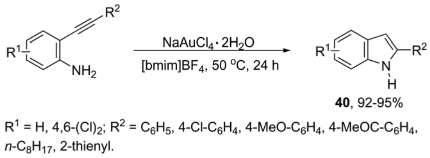


Scheme 36



Scheme 37

intramolecular C-arylation (Scheme 36).[71] The C-arylation step was achieved by employing copper(II) acetate as the catalyst in the complete absence of ligands, without the need to protect from air or water. Mechanistic studies carried out by the authors indicated that the formate ion, produced by the base-catalyzed hydrolysis of DMF, reduces copper(II) to the active copper(I) species and recycles any copper(II) that is produced in the reaction, preventing the deactivation of the catalyst. A similar strategy has been also successfully employed in the synthesis of 2-(perfluoroalkyl)indoles **39** (Scheme 37).[72] The reaction was carried out by the initial Michael addition of *ortho*-haloanilines to methyl perfluoroalkynoates giving *N*-(*ortho*-haloaryl)enamines, which afforded the corresponding indoles *via* a copper-catalyzed annulation reaction.



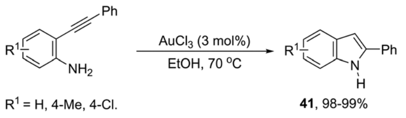
Scheme 38

### 2.4. Gold-catalyzed synthesis of indoles

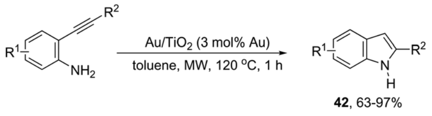
Gold-catalyzed reactions have attracted attention because of their useful applications in organic synthesis. In particular, gold salts have been extensively used as catalysts for reactions with a series of unsaturated precursors, such as alkynes, alkenes, and allenes.[73] The reactions of gold(I) and gold(III) salts with alkynes produce reactive complexes, which afford products with high selectivity, in most cases in a single step. Particularly, the gold activation of carbon–carbon bonds of alkynes towards attack by nitrogen nucleophiles is one of the most important methods to prepare indoles *via* carbon–nitrogen bond formation. The methodologies involving the preparation of indoles *via* hydroamination, cycloaddition, annulation, and cycloisomerization, among other reactions with alkynes, catalyzed by gold salts, will be shown below. Thus, several types of intramolecular gold-activated alkynes were easily reduced with simultaneous carbon–nitrogen bond formation affording indoles. For example, *ortho*-alkynylanilines when treated with $NaAuCl_4 \cdot H_2O$, using $[bmim]BF_4$ as the reaction medium, afforded 2-substituted indoles **40** in high yields (Scheme 38).[74] The catalytic system could be recycled using $n\text{-}Bu_4NAuCl_4$. In addition, 2,3-disubstituted indoles could also be prepared by the reaction of *ortho*-alkynylanilines and 3-butenone in a one pot annulation–alkylation sequence or *via* an aza-Michael addition–annulation–alkylation process, which afforded the 1,2,3-trisubstituted indoles.

In protic solvents, $AuCl_3$ catalyzed the cyclization of *ortho*-alkynylanilines to generate 2-substituted indoles **41** (Scheme 39).[75] When carried out using ethanol as the solvent at 70 °C, the reaction was very fast without needing to protect the amino group. Under the same reaction conditions, 2-amine-3-alkynylpyridines led to substituted pyrrolopyridines in good yields.

The catalytic activity of cationic gold could be hampered in the presence of basic amines. The cationic gold has much stronger affinity towards basic amines than towards the activation of carbon–carbon bonds of the alkyne substrates; thus the corresponding catalytic cycle could be inactivated. However, gold nanoparticles supported on titanium dioxide were found to be a highly efficient catalytic system for the intramolecular hydroamination of *ortho*-alkynylanilines to afford the corresponding indole derivatives **42** (Scheme 40).[76] The reaction conditions required low catalyst loading



Scheme 39



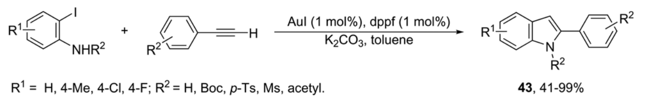
$R^1$ = H, 4-Cl, 5-Cl, 4-F, 5-F, 4-Me; $R^2$ = $n$-$C_4H_9$, $C_6H_5$, 4-F-$C_6H_4$, 2-Me-$C_6H_4$, 4-MeO-$C_6H_4$.

Scheme 40

(0.2 mol% Au) and toluene as the solvent under microwave heating. The catalytic system was reused through five straight runs without loss of catalytic activity.

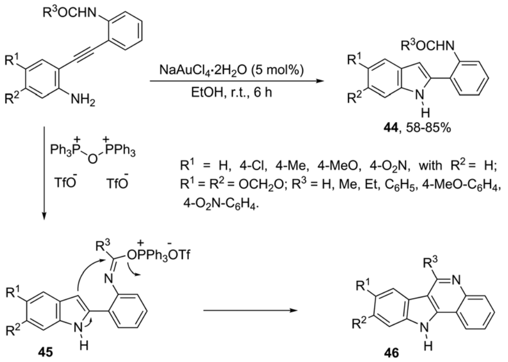
To avoid the previous preparation of *ortho*-alkynylanilines, one strategy is the use of a cross-coupling–cyclization reaction sequence of terminal alkynes with *ortho*-haloanilines. Thus, the gold(I) iodide catalyzed Sonogashira reactions of terminal alkynes with *ortho*-iodoanilines, in the presence of dppf as a ligand and toluene as a solvent, generated the corresponding 2-substituted indoles **43** in good to excellent yields (Scheme 41).[77] The reaction conditions worked well with aromatic terminal alkynes and *ortho*-iodoanilines; however, moderate yields were obtained with aliphatic terminal alkynes, whereas *ortho*-bromoanilines did not give the desired indoles. *N*-Substituted *ortho*-iodoanilines, such as *N*-Boc, *N*-*p*-Ts, *N*-Ms and *N*-acetyl *ortho*-iodoanilines, could also react with phenylacetylene, giving the coupling–cyclization products in good yields.

The catalyst $NaAuCl_4 \cdot 2H_2O$ promoted a chemoselective cyclization of aryl alkynes having two nitrogen nucleophiles in their structure with similar reactivities. Aryl alkynes having both amine and amide groups as nucleophiles, located in the *ortho*-position to the carbon–carbon triple bond, could undergo a competitive cyclization reaction to give 1*H*-indole or *N*-acetyl-indoles, respectively. However, the reaction of *N*-(2-((2-aminophenyl)ethynyl)phenyl)acetamide with $NaAuCl_4 \cdot 2H_2O$, in ethanol as the solvent, at room temperature, led to the exclusive formation of *N*-[2-(1*H*-indol-2-yl)phenyl]acetamides **44** (Scheme 42).[78] Alkynes containing alkylamide, formamide, benzamide, and carbamate groups were also transformed into the corresponding 1*H*-indole derivatives. The authors showed that treating *N*-[2-(1*H*-indol-2-yl)phenyl]acetamides **46** with bis-(triphenyl)oxodiphosphonium trifluoromethanesulfonate (Hendrickson reagent) gave 1*H*-indolo[3,2-*c*]quinolones, which were obtained *via in situ* preparation of amidate **45** (Scheme 42).



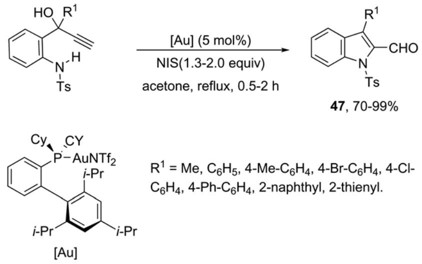
$R^1$ = H, 4-Me, 4-Cl, 4-F; $R^2$ = H, Boc, $p$-Ts, Ms, acetyl.

Scheme 41



$R^1$ = H, 4-Cl, 4-Me, 4-MeO, 4-$O_2N$, with $R^2$ = H; $R^1$ = $R^2$ = $OCH_2O$; $R^3$ = H, Me, Et, $C_6H_5$, 4-MeO-$C_6H_4$, 4-$O_2N$-$C_6H_4$.

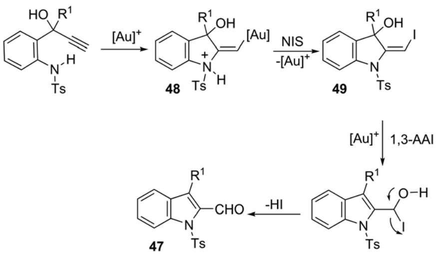
Scheme 42



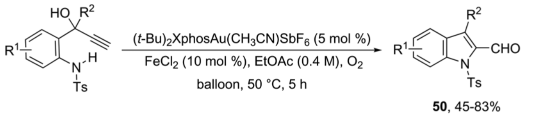
$R^1$ = Me, $C_6H_5$, 4-Me-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Ph-$C_6H_4$, 2-naphthyl, 2-thienyl.

Scheme 43

The 1*H*-indole-2-carbaldehydes **47** were efficiently prepared by gold(I)-catalyzed cycloisomerization of 1-(2-(tosylamino)phenyl)propynols in the presence of *N*-iodosuccinimide (Scheme 43).[79] The reaction conditions tolerated a wide variety of substrates, even with a bulky group at the propargyl position, affording the corresponding products from 70 to 99% yields. The reaction was highly regioselective occurring *via* an exclusive 5-*exo-dig* mode. Regarding the reaction mechanism, the authors' hypothesis is that the alkyne moiety is activated by the gold(I) catalyst, which promotes the intramolecular nucleophilic attack of aniline giving a vinyl gold intermediate **48**, followed by an iododeauration promoted by NIS to give the (*E*)-2-(iodomethylene)indolin-3-ol adducts **49**. The successive 1,3-allylic alcohol isomerization and formylation reaction give the 1*H*-indole-2-carbaldehydes **47** (Scheme 44). One of the major drawbacks of these cyclization reactions is the deauration step that could lead to the formation of by-products and a decrease in the yields. However, the cooperative use of gold and iron catalysts, in the presence of one atom of oxygen, was very efficient at promoting the cyclization of 1-(2-(tosylamino)phenyl)propynols to Ts*N*-indole-2-carbaldehydes **50** in good



Scheme 44



$R^1$ = H, 4-Cl; $R^2$ = Me, n-$C_5H_{11}$, $C_6H_5$, 4-Me-$C_6H_4$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$.

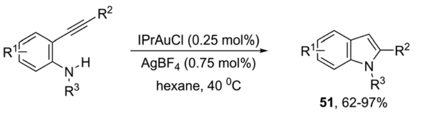
Scheme 45

yields (Scheme 45).[80] The success of the cyclization is credited to the presence of oxygen radicals that react with the vinyl–gold intermediate forming a new reactive species, helping in the gold catalyst turnover.

N-Heterocyclic carbenes (NHC) have been used as ligands in gold complexes for the successful synthesis of indole derivatives. Thus, the cyclization of *ortho*-alkynylanilines catalyzed by (IPr)AuCl afforded the 2-substituted indoles **51** (Scheme 46).[81] The gold(I) salt stabilized with an NHC bulky carbene was found to be more efficient than other potential catalysts, such as $NaAuCl_4{\cdot}2H_2O$, $AuCl_3$, and AuCl. The authors also reported that the counter anions had a strong effect on the efficiency of the catalyst, whereas $BF_4$ proved to be much more effective than Cl, TsO, and $NTf_2$.

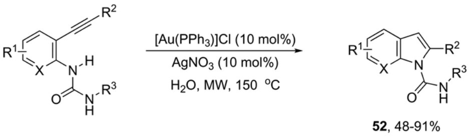
*ortho*-Alkynylureas were also successfully used for the synthesis of indole-1-carboxamides **52** (Scheme 47).[82] The reaction of *N′*-substituted *N*-(2-alkynylphenyl)ureas, catalyzed by $[Au(PPh_3)]Cl/Ag_2CO_3$, in water under microwave irradiation, gave indole-1-carboxamides **52**. The authors stated that three different products could be formed *via* a 5-*endo*, 6-*exo*, 7-*endo*-cyclization mode; however, the reaction was highly selective, giving only indole derivatives, formed *via* 5-*endo-dig* cyclization (Scheme 48). The substrate scope of this reaction was studied and it indicated that the reaction conditions were tolerant to a variety of functional groups such as *N′*-aryl, alkyl, and heterocyclic groups on the *ortho*-alkynylureas.

*N*-(*ortho*-Alkynyl)aryl-*N′*-substituted trifluoroacetamidines were also applied as the nucleophilic nitrogen source for the gold-catalyzed intramolecular hydroamination reactions. When *ortho*-alkynylarylamidines were treated with $NaAuCl_4{\cdot}2H_2O$ as the catalyst, in toluene as the solvent, at room temperature, a 5-*endo-dig* cyclization proceeded to give the corresponding indoles **53** (Scheme 49).[83] The authors demonstrated that the same substrate, when treated with $K_2CO_3$ as a base, gave the quinazolines in a 6-*exo-dig* process.



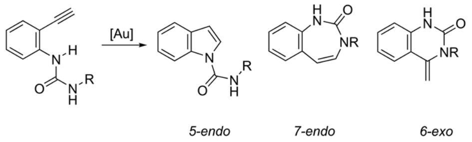
$R^1$ = H, 4-Me, 4-Br; $R^2$ = n-$C_4H_9$, $C_6H_5$, TMS, $BnOCH_2CH_2$, $R^3$ = H, Me, Bn.

Scheme 46

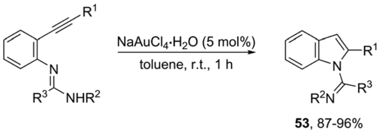


$R^1$ = H, 5-Cl, 4-F, 5-Me, 5-$F_3C$; $R^2$ = H, $C_6H_5$, $Cl(CH_2)_2CH_2$; $R^3$ = pyridyl, naphthyl, allyl, benzyl, n-$C_8H_{17}$, c-$C_6H_{11}$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-NC-$C_6H_4$, 2-MeO-$C_6H_4$, 3-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, 2-$F_3C$-$C_6H_4$.

Scheme 47



Scheme 48

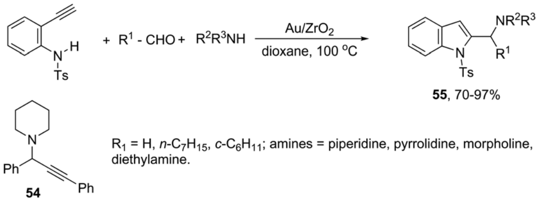


$R^1$ = H, $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$; $R^2$ = H, allyl, Bn, Me, c-$C_6H_{11}$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-$O_2N$-$C_6H_4$; $R^3$ = $F_3C$, $F_2BrC$.

Scheme 49

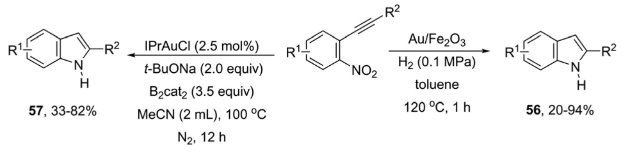
A three-component version of the gold(III)-catalyzed cyclization reaction employing aldehydes, piperidines, and alkynes was described for the preparation of indoles. The reaction carried out with phenylacetylene as the alkyne, under gold supported on nanocrystalline $ZrO_2$, gave the propargyl amines **54** (Scheme 50). The use of terminal *ortho*-alkynylanilines instead of phenylacetylene, under the same reaction conditions, afforded the 2-(aminomethyl)indole derivatives **55** in high yields with no formation of propargylamines (Scheme 50).[84]

*ortho*-Alkynylnitroarenes can be reduced to amino derivatives, which are then cyclized under gold catalysis to yield 2-substituted indoles. The major challenge of these reactions is the reduction of the nitro group without reaching other functional groups of the starting material. The reduction of *ortho*-alkynylnitroarenes, using hydrogenation conditions, under gold nanoparticles supported on $Fe_2O_3$, led to the formation of 2-substituted indoles **56** (Scheme 51).[85] It has also been reported that the synthesis of 2-substituted indoles **57**, *via* a diboron/base promoted a tandem reductive cyclization of *ortho*-alkynylnitroarenes, under 1,3-bis-(2,6-diisopropylphenyl)



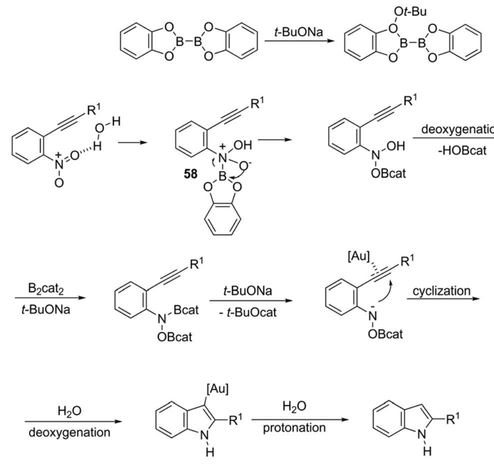
$R_1$ = H, n-$C_7H_{15}$, c-$C_6H_{11}$; amines = piperidine, pyrrolidine, morpholine, diethylamine.

Scheme 50



$R^1$ = H, 4-Me, 5-Me, 5-Cl, 5-F; $R^2$ = c-$C_3H_5$, t-$C_4H_9$, c-$C_6H_{11}$, n-$C_6H_{13}$, $C_6H_5$, 4-Me-$C_6H_4$, 2-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$C_5H_{11}O$-$C_6H_4$, $Me_3Si$.

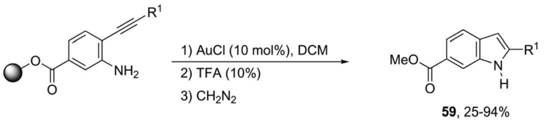
Scheme 51



Scheme 52

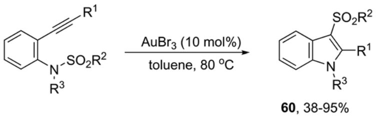
imidazol-2-ylidene gold(I)chloride (IPrAuCl) catalysis conditions (Scheme 62). In this last methodology, the reductive cyclization was proposed to occur *via* an initial attack of a nucleophilic boronic species on the nitro group, affording the nitroso intermediate **58**, *via* debromation/deoxygenation processes. Intermediate **58** is converted to borate-nitroso anions, which are cyclized with the help of IPrAuCl (Scheme 52).

The cyclization of immobilized *ortho*-alkynylanilines with a gold catalyst is particularly attractive because of the advantage of easy purification. The use of *ortho*-alkynylanilines immobilized in Wang resin in the reaction with AuCl was the method of choice for the preparation of resin-bound indoles, which after reaction with 10% TFA in DCM followed by methylation with diazomethane gave the resin-free indole **59** (Scheme 53).[86] The reaction conditions developed were applicable to a series of *ortho*-alkynylanilines, giving the corresponding indoles in 25–94% yields. The authors demonstrated that ortho-alkynylanilines having an aromatic substituent at the alkyne gave the indoles in better yields than those with an alkyl chain.



$R^1$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, n-$C_3H_7$, n-$C_5H_{11}$, $Cl(CH_2)_2CH_2$.

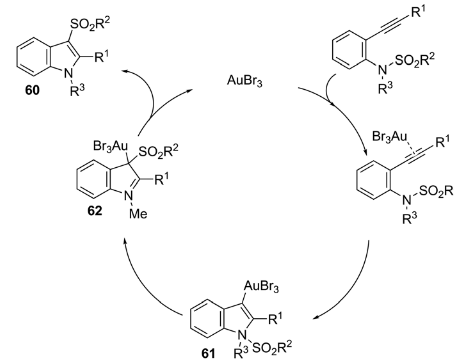
Scheme 53



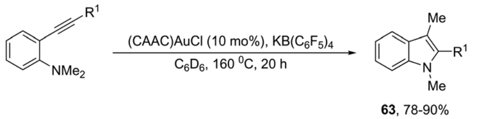
$R^1$ = H, n-$C_3H_7$, t-$C_4H_9$, c-$C_6H_{11}$, $EtO_2C$, $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$; $R^2$ = Me, $C_6H_5$, 4-MeO-$C_6H_4$, 4-MeOC-$C_6H_4$; $R^3$ = Me, i-$C_3H_7$, Bn.

Scheme 54

The gold-catalyzed cyclization of *ortho*-alkynylanilines, having a migrating group on the nitrogen atom, provides a successful route for preparation of 3-substituted indoles. This method for the synthesis of 3-sulfonylindoles **60** has been well investigated using different *ortho*-alkynyl-*N*-sulfonylanilines in the presence of a catalytic amount of $AuBr_3$ (Scheme 54).[87] The authors performed additional crossover experiments, which revealed that the migration of the sulfonyl group occurs in an intramolecular instead of intermolecular manner. Further experimental results led the authors to propose that the cyclization occurs through a nucleophilic attack of the nitrogen atom on the gold-active alkyne, leading to the cyclized intermediate **61**. The sulfonyl group intramolecularly migrates to the 3-position of the indole affording the intermediate **62**, which gives the 3-sulfonylindole **60**, after the elimination of $AuBr_3$ (Scheme 55). The strategies based on the methylamination reaction of 2-alkynyl-*N*,*N′*-dimethyl-benzenamines, in the presence of a 1 : 1 mixture of (CAAC)AuCl/KB$(C_6F_5)_4$ (10 mol%), were used in the preparation of 2,3-disubstituted indoles **63** (Scheme 56).[88] In this rearrangement, a methyl group bonded to nitrogen migrates to the 3-position of the indole ring. However, in the case of the *N*-ethyl substituted benzenamines, only the cleavage of the relatively weak carbon–



Scheme 55



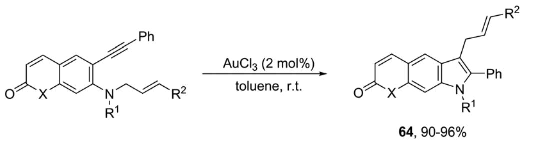
$R^1$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, n-$C_4H_9$.

Scheme 56

nitrogen bond was observed with loss of ethylene, and the 3-substituted indoles were not formed.

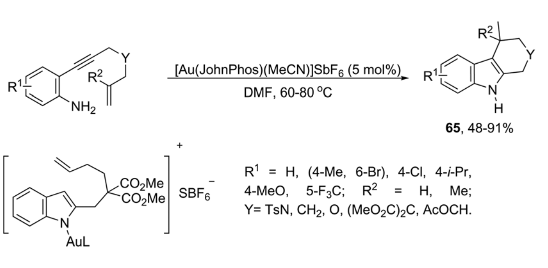
The intramolecular migration of alkenes has also been found to give 2,3-fused indole derivatives. The reaction of *N*-(allyl(methyl)-*ortho*-alkynylanilines) with a catalytic amount of $AuCl_3$, in toluene, at room temperature, afforded the pyranoindolones **64** *via* a cyclization/3,3 allyl migration sequence (Scheme 57).[89] The 2,3-fused indole derivatives **65** were prepared in high yields by reacting *ortho*-alkynylanilines having an unsaturated chain bonded to the alkyne, using $[Au(JohnPhos)(MeCN)]SbF_6$ as the catalyst (Scheme 58).[90] It was determined that the indole ring formed in the first reaction step reacts with the gold catalyst to form gold stable non-catalytic intermediates **66**. The intermediate **66** was isolated and the structure was proven by single crystal X-ray diffraction.

Aldehydes can be also used in combination with amines for the intramolecular functionalization of imines in the gold-catalyzed cyclization of 2-(4-aminobutynyl)anilines. The combination of catalytic amounts of AuIPrCl and $AgSbF_6$ was found to be the most efficient catalytic system, which promoted the formation of 1-aryl-*N*-tosyl-2,3,4,5-tetrahydropyrido [4,3-*b*] indole derivatives **67** in moderate to good yields (Scheme 59).[91] Further studies determined that the Au(I) species activates the alkyne *via* π-coordination with the carbon–carbon triple bond and Ag(I), facilitating the second step of the cyclization. Alternatively, the gold-catalyzed reaction of 2-[(2-aminophenyl)ethynyl]phenylamine derivatives with aldehydes is an efficient strategy used to prepare 1*H*-indolo-[3,2-*c*]quinolones.[92]



$R^1$ = Me, Et; $R^2$ = H, Me; X= C, O, N.

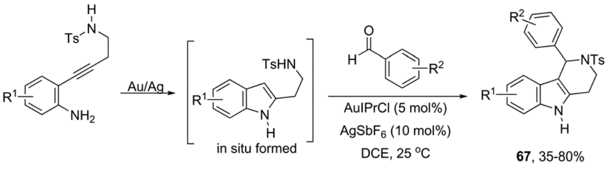
Scheme 57



$R^1$ = H, (4-Me, 6-Br), 4-Cl, 4-*i*-Pr, 4-MeO, 5-$F_3C$; $R^2$ = H, Me; Y= TsN, $CH_2$, O, $(MeO_2C)_2C$, AcOCH.

**66a**, [L = (JohnPhos)MeCN)], 90%
**66b**, [L = IPr], 95%

Scheme 58



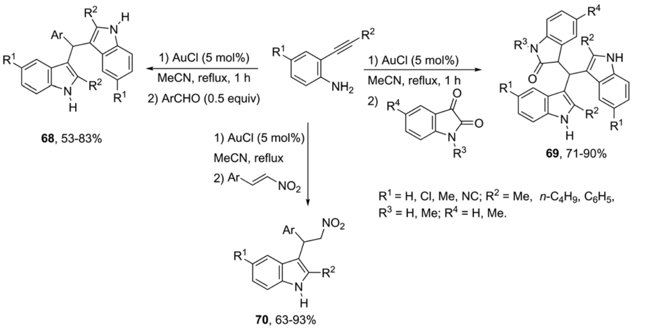
$R^1$ = H, MeO; $R^2$ = 2-Br, 4-Br, 4-Cl, 2-F, 4-F, 2-Me, 4-Me, 4-$O_2N$, 3,4-$(MeO)_2$, 3,5-$(MeO)_2$.

Scheme 59

The intermolecular version for gold-catalyzed cyclization/functionalization of the 3-position of *ortho*-alkynylanilines was also developed for the synthesis of 3-substituted indoles. For example, starting from *ortho*-alkynylanilines, three different classes of 3-substituted indoles were obtained, applying the same reaction conditions, just by changing the electrophile source.[93] The reaction of *ortho*-(phenylethynyl)aniline with aldehydes, catalyzed by 5 mol% AuCl in acetonitrile, under reflux, gave the bis-(indolyl)methanes **68**. The electrophilic source exchange for isatin instead of aldehydes led to di(indolyl)indolin-2-ones **69**, while the use of nitroalkenes as electrophiles gave 2-indolyl-1-nitroalkanes **70** *via* a cycloaddition/Michael addition sequence (Scheme 60).

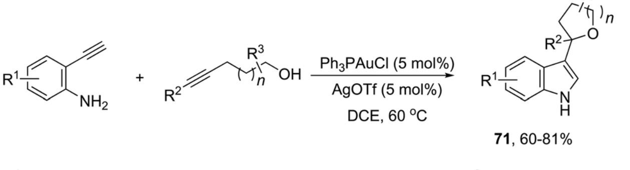
The gold(I)-catalyzed cyclization of *ortho*-alkynylanilines in the presence of alkynols provided an attractive route to a one-pot synthesis of 2-tetrahydrofuranyl indoles **71** (Scheme 61).[94] The studies carried out to determine the optimal reaction conditions indicated that $Ph_3PAuCl$ in combination with AgOTf was the best choice to promote the cyclization.

The nitrene precursors derived from an azido group, located in the *ortho*-azidoarylalkynes, were successfully utilized as electrophilic centers, for the general synthesis of 3-substituted indoles **72** (Scheme 62).[95] When substituted *ortho*-azidoarylalkynes was used as a nucleophile, a mixture of regioisomers was obtained. The reaction conditions dramatically



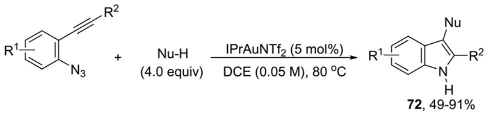
$R^1$ = H, Cl, Me, NC; $R^2$ = Me, *n*-$C_4H_9$, $C_6H_5$, $R^3$ = H, Me; $R^4$ = H, Me.

Scheme 60



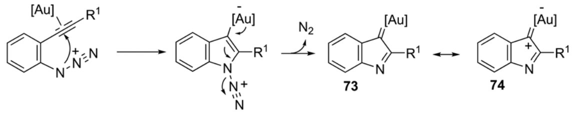
$R^1$ = H, 4-Me, 4-Cl, 4-F, 4-$F_3C$, 4-$O_2N$, 4-NC, 4-$NCCH_2$, 4-$MeO_2C$, $R^2$ = H, Me, Et, *n*-$C_6H_{13}$, 4-Me-$C_6H_4$; $R^3$ = *c*-$C_6H_{11}$, *c*-$C_5H_9$; *n* = 1, 2.

Scheme 61



$R^1$ = H, 4,6-(Me)$_2$, 3,2-(Cl)$_2$; $R^2$ = H, n-$C_4H_9$, t-$C_4H_9$, c-$C_3H_5$, c-$C_5H_9$, c-$C_6H_{11}$, 4-MeO-$C_6H_4$; Nu-H= aryl, n-BuOH, allyl alcohol.

Scheme 62



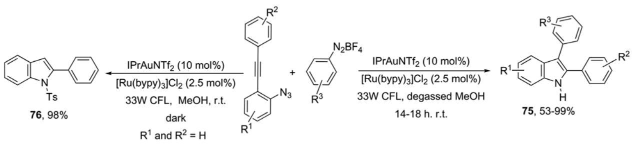
Scheme 63

influenced the distribution of products, whereas high temperature (80 °C), using 1,2-dichloroethane as the solvent and IPrAuNTf$_2$ as the catalyst, led to the best yield and ratio of regioisomers. The reaction is believed to proceed *via* gold carbene **73** and its cationic resonance form **74**, which could act as an electrophilic source (Scheme 63).

In addition to the *ortho*-azidoarylalkynes, the introduction of an aryl group at the 3-position of indoles was recently carried out through the reaction of *N*-Ts-*ortho*-alkynylanilines with phenyldiazonium catalyzed by dual Au/Ru catalysts under irradiation of a 33 W compact fluorescent light (CFL) bulb (Scheme 64).[96] Under these experimental conditions, the 3-arylindole products **75** competed with protodeauration product **76**. The chlorine anion present in the catalyst and the use of photoredox catalysis were essential for the formation of 3-arylindoles instead of 3-hydrogenated indoles. A conceptually similar approach employed heterogeneous gold nanoparticles to catalyze the cyclization of *ortho*-alkynylanilines in the preparation of 3,3′-bisindolyl products *via* domino cycloisomerization/oxidative homocoupling.[97]

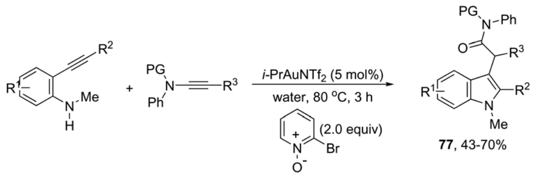
The use of gold-catalyzed tandem cycloisomerization/functionalization reaction of *ortho*-alkynylanilines and ynamides has also been explored to access functionalized 2-(1*H*-indol-3-yl)acetamides **77** (Scheme 65).[98] The reaction was carried out in water and the IPrAuNTf$_2$ catalyst promoted the cyclization of *ortho*-alkynylanilines and the intermolecular oxidation of ynamides.

An alternative gold-catalyzed system constituted by a carbophilic gold cation and a trifluoroacetate anion allowed the formation of 3-borylated indoles **78** (Scheme 66).[99] The reaction proceeds *via* formation of carbon–boron and carbon–nitrogen bonds in a single step from catalytic aminoboration of carbon–carbon triple bonds by boron–nitrogen σ bonds. Primary anilines led to the formation of 3-unsubstituted indoles *via* protodeauration promoted by N–H. Secondary anilines such as HNBn, HNTs, and HNMbs provided the product in very similar yields. The use of catecholborane, for the *in situ* formation of boron–nitrogen σ bonds, failed in the formation of 3-borylated indoles; however, the reaction starting from *ortho*-alkynylanilines and β-chlorocatecholborane gave the requisite boron–nitrogen intermediate, which afforded the products in good yields. The presence of sodium trifluoro acetate was also decisive for the success of the reaction, reactivating the catalyst, which was inhibited by the *in situ* formed Et$_3$NHCl.



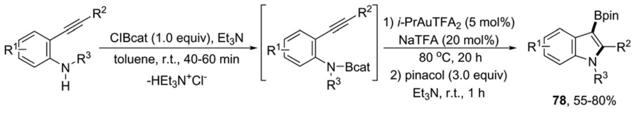
$R^1$ = H, 4-Cl, 4-F, 4-Me; $R^2$ = H, 4-Br, 4-Cl, 4-F, 4-Me, 4-MeO, 3-MeO, 2-naphthyl, 2-thienyl, 4-$C_6H_5$, $R^3$ = H, 4-F, 4-$EtO_2C$.

Scheme 64



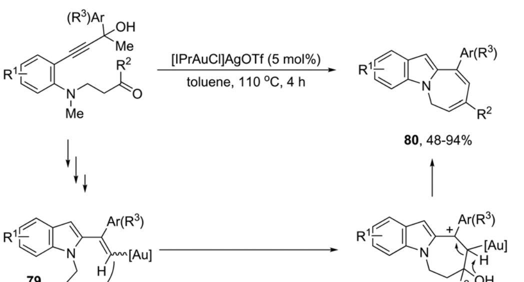
$R^1$ = H, 5-Cl, 4-Me; $R^2$ = n-$C_4H_9$, n-$C_5H_{11}$, Cl$(CH_2)_2CH_2$, $N_3(CH_2)_2CH_2$, naphthyl$(CH_2)_2CH_2$, BocO$(CH_2)_2CH_2$, AcO$(CH_2)_2$; $R^3$ = $C_6H_5$, 4-Cl-$C_6H_3$, 4-Me-$C_6H_4$.

Scheme 65



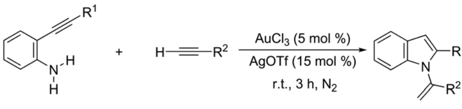
Scheme 66

The gold-catalyzed cyclization of *ortho*-alkynylanilines, having a reactive group bonded to the aniline nitrogen, is a versatile process for the N1–C2 connection to give fused indoles. Under optimal reaction conditions, [Au(IPr)Cl]/AgOTf, toluene and under reflux, the azepino[1,2-*a*]indoles **80** were obtained from 3-(2-aminoaryl)propynols (Scheme 67).[100] The possible mechanism to explain this reaction was hypothesized based on a control experiment, which indicated the initial formation of vinyl–gold intermediates **79** through a gold-triggered



$R^1$ = H, 4-F, 4-Me; $R^2$ = Me, Et, $C_6H_5$, 4-Cl-$C_6H_4$; Ar($R^3$) = $C_6H_5$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-$O_2N$-$C_6H_4$, Me, Et, i-Pr.

Scheme 67



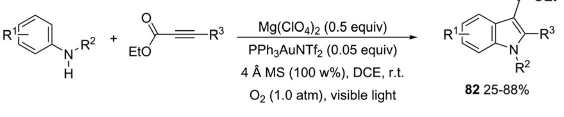
**81**, 17-82%

$R^1$ = $C_6H_5$, n-$C_3H_7$, n-$C_4H_9$, cyclohexenyl; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-F-$C_6H_4$, 4-MeO-$C_6H_4$, naphthyl, cyclohexenyl, n-$C_3H_7$, n-$C_4H_9$.

Scheme 68

5-*endo-dig* hydroamination/dehydration sequence. The intramolecular condensation of **79** with the ketone group would produce **80** after dehydration/1,3-proton-transfer/protodeauration sequence.

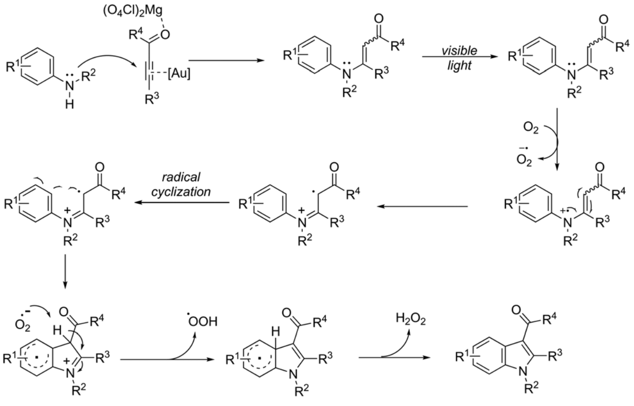
The sequential intermolecular hydroamination/cyclization reaction of anilines with alkynes was also used for the synthesis of various substituted indoles. An interesting intermolecular hydroamination sequence has been developed as an efficient route to the synthesis of *N*-vinylindoles **81**, starting from *ortho*-alkynylanilines and terminal alkynes (Scheme 68).[101] The process involves an efficient double hydroamination reaction catalyzed by gold(III) in the absence of a solvent. The authors determined that the first reaction step occurs *via* an intermolecular hydroamination, which is followed by intramolecular amination.



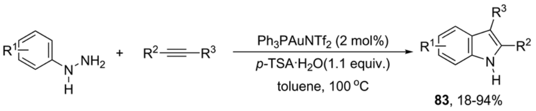
**82** 25-88%

$R^1$ = 4-$O_2N$, 4-$MeO_2S$, 4-NC, 4-$MeO_2C$, 4-OHC, 4-MeOC, 4-$Me_2CHO$, 4- PhOC, 4-MeOC; $R^2$ = H, Me, $MeCH_2$, $PhCH_2$; $R^3$ = 4-Me-$C_6H_4$, 2-MeO-$C_6H_4$, 3-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-NC-$C_6H_4$, thienyl, naphthyl.

Scheme 69



Scheme 70



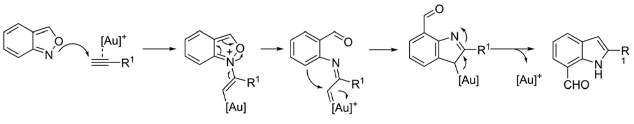
**83**, 18-94%

$R^1$ = 4-Me, 4-Cl, 4-Br, 4-F, 5-OMe, 6-I; $R^2$ = n-$C_3H_7$, n-$C_5H_{11}$, $PhCH_2$, $HOCH_2$, $HO(CH_2)_2CH_2$, $HO_2CCH_2CH_2$, $BnOCH_2CH_2$, $MeO_2CCH_2CH_2$, $HO_2CH_2$; $R^3$ = H, $CH_3CH_2$, $CH_3$, n-$C_3H_7$, n-$C_6H_{13}$, $C_6H_5$.

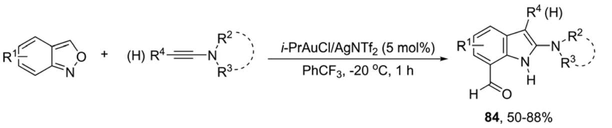
Scheme 71

An attractive method for the generation of 2,3-functionalized indoles is the gold-catalyzed hydroamination and visible-light-enabled photoredox cross-dehydrogenative coupling of anilines and internal alkynes.[102] The cyclization of anilines with arylpropiolates in the presence of 5 mol% of catalyst $PPh_3AuNTf_2$, 100 wt% of activated powdered 4 Å molecular sieves, and $Mg(ClO_4)_2$ in DCE, under a balloon oxygen atmosphere, and at room temperature, gave the indoles **82** (Scheme 69). The authors reported that the presence of the oxygen atmosphere and the use of $Mg(ClO_4)_2$ as a Lewis acid were essential to obtain good yields. The gold catalyst and a Lewis acid are fundamental for complexation with propiolate oxygen, increasing the reactivity of the triple bond towards the nitrogen nucleophilic attack (Scheme 70). A complementary method involving hydrohydrazination/indolization tandem reaction of alkynes and arylhydrazines has been developed to synthesize 2,3-disubstituted indoles **83** (Scheme 71).[103] The reaction was not sensitive to moisture and required very low $Ph_3PAuNTf_2$ loading (2 mol%) in combination with *p*-TSA·$H_2O$ to obtain the indoles. The authors proposed two different mechanisms, which depend on the substrates; with the alkynes having OH/COOH groups in their structure, a hydroalkoxylation/hydrocarboxylation sequence forms exocyclic enol ethers/lactones that react with hydrazines to produce indoles. However, the absence of OH/COOH groups in the alkynes leads to hydration to generate ketones that react with arylhydrazines to give the desired indoles.

A conceptually similar approach utilized anthranil both as a source of nitrogen and for *ortho*-aryl carbon–hydrogen insertion in the preparation of unprotected 7-acylindoles (Scheme 72).[104] The reaction of anthranil with alkynes catalyzed by gold gave an electrophilic α-imino gold carbenoid intermediate, which afforded the desired indoles *via* an intramolecular *ortho*-aryl carbon–hydrogen insertion (Scheme 73). The control experiments showed that the highest yields of 7-acylindoles **84** were obtained when IPrAuCl/$AgNTf_2$ was used



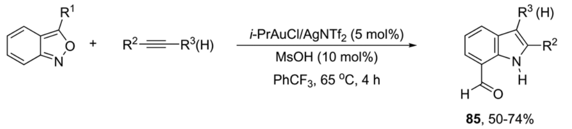
Scheme 72



**84**, 50-88%

$R^1$ = 3-t-$C_4H_9$, 3-MeO, 3-Cl, 3-Br, 3-AcO; $R^2$ = H, Me, $C_6H_5$, allyl; $R^3$ = Ms, Ts, t-$C_4H_9$, Bn; $R^4$ = n-$C_4H_9$, i-$C_3H_7$, Bn.

Scheme 73



**85**, 50-74%

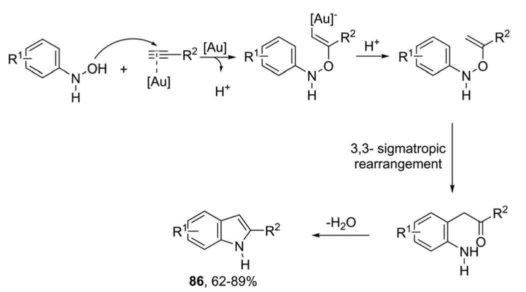
R$^1$ = H, styryl; R$^2$ = c-C$_3$H$_5$, c-C$_5$H$_9$, sec-C$_4$H$_9$, n-C$_6$H$_{12}$, C$_6$H$_5$; R$^3$ = H, C$_6$H$_5$.

Scheme 74

as the catalyst in PhCF$_3$ at −20 °C. Under these reaction conditions, polarized terminal and non-terminal alkynes, ynamides and various substituted anthranils could be used as substrates in the cyclization. In the case of non-polarized alkynes, just a slight adjustment of the reaction conditions, such as raising the temperature, extending the reaction time and adding 10 mol% MsOH, to facilitate the deauration process, led to the desired indoles **85** (Scheme 74).

*N*-Arylhydroxylamines have been used as nitrogen donors in gold-catalyzed preparation of 2-alkylindoles. This reaction effectively combined the *N*-arylhydroxylamines with aliphatic terminal alkynes giving access to *o*-alkenyl-*N*-arylhydroxylamines, which underwent sequential 3,3-rearrangements and cyclodehydrations to afford 2-alkylindoles **86** (Scheme 75).[105] The reaction was best catalyzed by (ArO)$_3$PAuNTf$_2$ (Ar = 2,4-di-*tert*-butylphenyl) in DCE. The authors reported the high regioselectivity towards 2-alkylindoles in the complete absence of 3-alkylindoles. This regioselectivity was attributed to the Markovnikov additions of hydroxamic acids to the gold-activated terminal alkynes. The reaction conditions were general for terminal alkyl alkynes with limitations to aryl terminal alkynes and internal alkynes, and the corresponding indoles were obtained in poor yields. Alternatively, AuCl(P(*t*-Bu)$_2$(*ortho*-biphenyl) catalyzed reactions of propargyl ethers with *N*-hydroxyanilines yielded ethyl 2-(1*H*-indolyl) derivatives **87** (Scheme 76).[106] The authors studied the *N*- *versus o*-attack chemoselectivity and concluded that for propargyl ethers and their benzoate derivatives the *o*-attack occurred selectively, whereas for 1,6-enynes the *N*-attack proceeded exclusively.

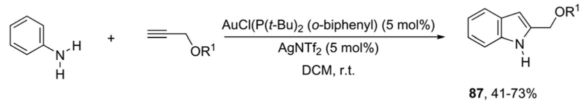
The cycloaddition reaction has been extensively applied to generation of heterocycles. For the indole synthesis a gold(I)-catalyzed intermolecular formal [4 + 2] reaction between 1,3-diynes and pyrroles has been developed. This reaction involved the intermolecular hydroarylation of 1,3-diynes with pyrroles, followed by an intramolecular hydroarylation to afford the 4,7-disubstituted indoles **88** (Scheme 77).[107] A gold-catalyzed cycloisomerization/[3 + 2] cycloaddition sequence, with diynes having an ynamide propargyl ester or carbonate group, has been developed for the preparation of 3-acyloxy-1,4-dihydrocyclopenta[*b*]indoles **89** (Scheme 78).[108] Control experiments indicated that the formation of indoles **89** proceeds through a competitive 1,2-OAc migration, followed by [3 + 2] cycloaddition of the vinyl gold-carbenoid intermediate **90** with the alkyne (Scheme 79).



**86**, 62-89%

R$^1$ = H, 4-Me, 4-Br, 4-F, 3,5-(Cl)$_2$-C$_6$H$_3$, 4-MeO$_2$C; R$^2$ = n-C$_{10}$H$_{21}$, c-C$_3$H$_5$, c-C$_5$H$_9$, c-C$_6$H$_{11}$, PhCH$_2$CH$_2$, BnOCH$_2$CH$_2$, THPOCH$_2$CH$_2$, PhthNH(CH$_2$)$_2$CH$_2$, Cl(CH$_2$)$_3$CH$_2$, HO$_2$C(CH$_2$)$_3$CH$_2$.

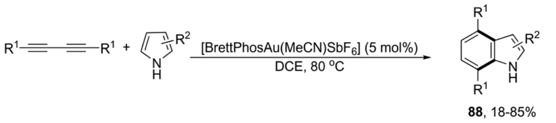
Scheme 75



**87**, 41-73%

R$^1$ = PhCH$_2$, PhO$_2$C, CH=CHCH$_2$CH$_2$.

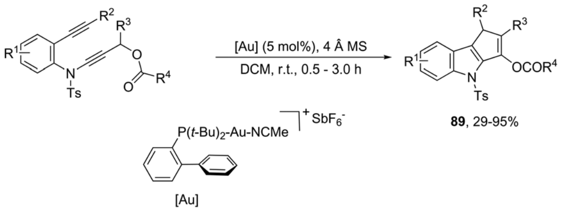
Scheme 76



**88**, 18-85%

R$^1$ = n-C$_4$H$_9$, C$_6$H$_5$, 2-Me-C$_6$H$_4$, 3-Me-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-CN-C$_6$H$_4$, 4-MeO$_2$C-C$_6$H$_4$, 2-thienyl, 3-thienyl, Cy; R$^2$ = H, 1-Me, 2-Me, 3-Me, CH=CHCH$_2$CH$_2$.

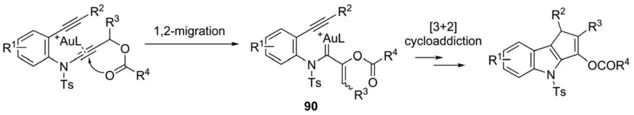
Scheme 77



**89**, 29-95%

R$^1$ = H, 4-Me, 4-Cl, 4-F; R$^2$ = C$_6$H$_5$, 4-Cl-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 2-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 2-thienyl; R$^3$ = Me, Et, i-C$_3$H$_8$, n-C$_4$H$_9$, C$_6$H$_5$; R$^4$ = Me, t-C$_4$H$_9$, C$_6$H$_5$, MeO, AcO, 4-Br-C$_6$H$_4$.

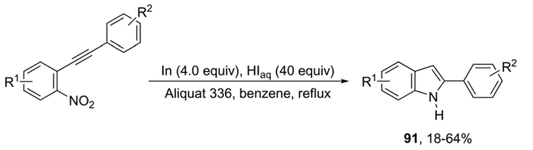
Scheme 78



Scheme 79

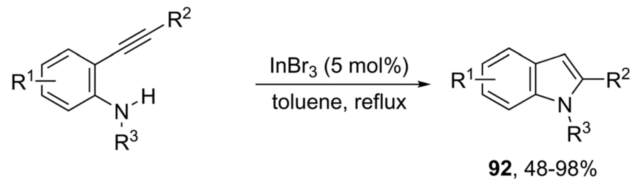
## 2.5. Indium-catalyzed synthesis of indoles

Indium-mediated cyclization reaction of alkynes with a nitrogen source was also utilized to prepare indole derivatives. When *ortho*-alkynylnitroarenes were reacted with indium and aqueous HI, under reflux of benzene, 2-arylindoles **91** were obtained in good yields (Scheme 80).[109] The reaction carried out in the presence of indium(III) chloride, in a mixture of THF



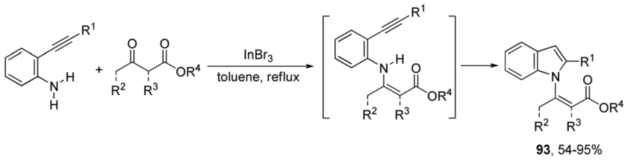
$R^1$ = H, 4-Me, 4-Cl, 3-Cl, 4-F; $R^2$ = H, 3-Me, 4-Me, 4-$F_3C$.

Scheme 80



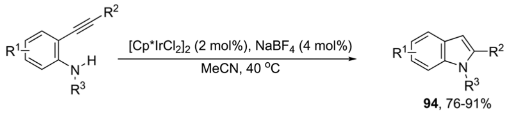
$R^1$ = H, 4-Me, 3,4-$(Me)_2$, 4-$O_2N$, 4-NC, 4-F; $R^2$ = $C_6H_5$, 4-*n*-Bu-$C_6H_4$, *n*-$C_6H_{13}$, *t*-$C_4H_9$, $HO(CH_2)_4$, 2-pyridyl; $R^3$ = H, Bn, MeOC, $EtO_2C$.

Scheme 81



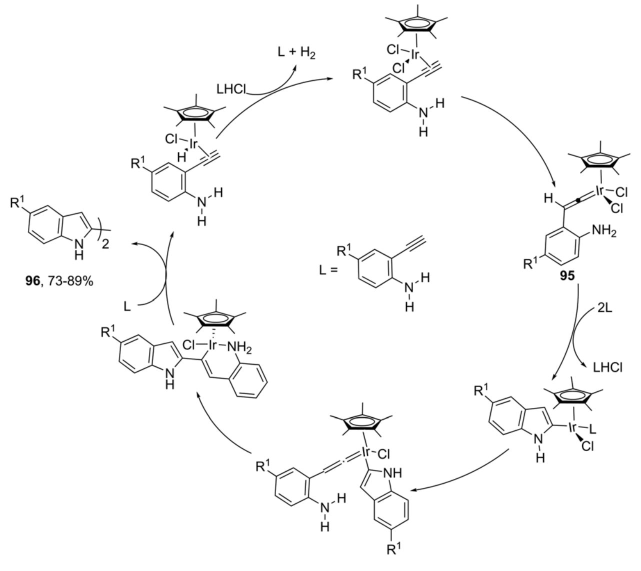
$R^1$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, *n*-$C_4H_9$, *c*-$C_6H_{11}$, *c*-$C_6H_9$; $R^2$ = H, Me; $R^3$ = H, Me; $R^4$ = Me, Bn, *i*-Pr, *t*-Bu, allyl.

Scheme 82



$R^1$ = H, 4-Me, 4-*t*-Bu, 4-Cl, 4-$O_2N$, 4-$MeO_2C$, 4-$EtO_2C$; $R^2$ = $C_6H_5$, 4-*n*-Bu-$C_6H_4$, 4-Cl-$C_6H_4$, *n*-Bu, $Me_3Si$; $R^3$ = H, Me, Bn, $MeO_2S$.

Scheme 83



$R^1$ = H, Me, *t*-Bu, Br, Cl, $O_2N$, NC, $MeO_2C$, $EtO_2C$.

Scheme 84

and $H_2O$ as the solvent, formed only *ortho*-alkynylanilines. However, when *ortho*-alkynylanilines having an alkyl or aryl group on the alkyne were treated with indium(III) bromide in toluene under reflux, the 2-susbtituted indoles **92** were obtained from 48 to 98% yields (Scheme 81).[110] In contrast, the *ortho*-alkynylanilines with a trimethylsilyl group or with no substituent group on the terminal alkyne gave polysubstituted quinoline derivatives *via* indium-promoted intermolecular dimerization.

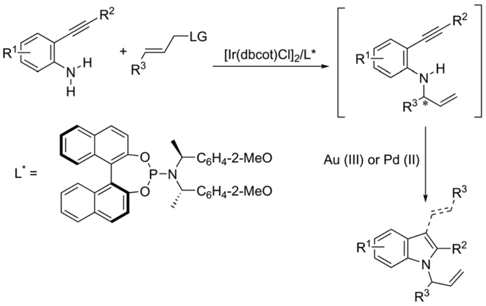
β-(*N*-Indolyl)-α,β-unsaturated esters **93** are readily accessible by tandem β-enamino ester formation, followed by cyclization with *ortho*-alkynylanilines catalyzed by indium(III) bromide (Scheme 82).[111] It was observed that indium(III) bromide catalyzed the intermolecular amination with a subsequent intramolecular cyclization and promoted the formation of the β-enamino esters instead of intramolecular cyclization. The experimental results also indicated that the cyclization proceeded exclusively *via* a 5-*endo*-*dig* mode in place of 6-*exo*-*dig* mode.

### 2.6. Iridium-catalyzed synthesis of indoles

Indoles can also be synthesized from *ortho*-nitrogen substituted aryl alkynes under iridium-catalyzed cyclization reaction. The synthesis of 2-substituted indoles **94** *via* $[Cp^*IrCl_2]_2$-catalysed cyclization of internal *ortho*-alkynylanilines has been developed (Scheme 83).[112] If hydrogen-substituted alkynes were used as substrates, 2,2′-biindoles **96** were obtained in good yields (Scheme 84).[113] The mechanistic studies indicated that the reaction proceeds *via* formation of a (vinylidene) iridium intermediate **95** and an intramolecular hydroamination, followed by the insertion reaction.

The asymmetric synthesis of functionalized *N*-allylindoles **97** was achieved by the iridium-catalyzed asymmetric allylic amination reaction with *ortho*-alkynylanilines, followed by cyclization reactions (Scheme 85).[114] An interesting secondary $sp^3$ carbon–hydrogen bond activation of *N*-benzylureas and an *N*-allyl urea, initiated by a cationic Ir(I)–JOSIPHOS catalyst, led to the preparation of 2,3-disubstituted indoles **98** (Scheme 86).[115] The use of urea as a directing group, the secondary $sp^3$ carbon–hydrogen bond cleavage and an intramolecular alkyne insertion were a key for the formation of indoles in good yields.

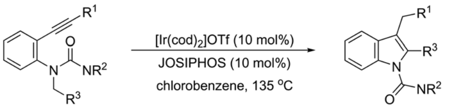
A concise route based on visible-light induced intramolecular oxidative cyclization of *N*,*N*-dibenzyl *ortho*-alkynylanilines, using an iridium complex as a photocatalyst, was developed for the synthesis of 3-acylindoles **99** (Scheme 87).[116] The reaction proceeds *via* addition of an $sp^3$ carbon–radical alpha-amino group to the carbon–carbon triple bond of the alkyne, followed by a carbon–oxygen bond formation. When



**97**, 44-95 %; ee = 92-99 %

$R^1$ = H, 4-Me, 4-Cl; $R^2$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 2-thienyl, $PhCH_2CH_2$; c-$C_6H_{11}$; $R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 3-$F_3C$-$C_6H_4$, Et, c-$C_3H_5$.

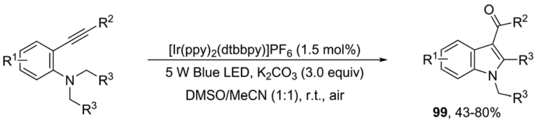
Scheme 85



**98**, 48-80%

$R^1$ = n-Bu, TMS, $C_6H_5$; $R^2$ = Et, c-$C_5H_9$, c-$C_6H_{11}$; $R^3$ = $C_6H_5$, 4-Br-$C_6H_4$, 4-NC-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-MeO-$C_6H_4$, allyl.

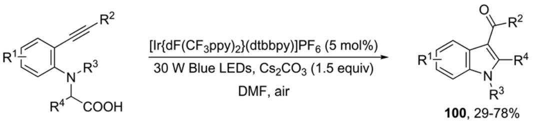
Scheme 86



**99**, 43-80%

$R^1$ = H, Me; $R^2$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 2-thienyl, n-$C_4H_9$; $R^3$ = $C_6H_5$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-t-Bu-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$.

Scheme 87



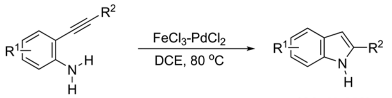
**100**, 29-78%

$R^1$ = H, 4-Me, 3-Cl, 4-F; $R^2$ = $C_6H_5$, 4-Et-$C_6H_4$, 4-t-Bu-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-MeO-$C_6H_4$, 2-thienyl, 3-thieny; $R^3$ = H, Me, Et, Ac; $R^4$ = H, Me.

Scheme 88

*ortho*-alkynylanilines having a carboxylic acid as a substituent were treated with the iridium complex as the photocatalyst, the 3-acylindoles **100** were obtained in yields ranging from 29 to 78% (Scheme 88).[117] The control experiments, carried out by the authors, indicated that the oxygen atom of the ketonic carbonyl group comes from the atmosphere rather than carboxylic acid.

## 2.7. Iron-catalyzed synthesis of indoles



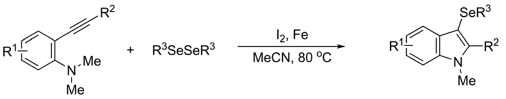
**101**, 40-88%

$R^1$ = H, 5-Cl, 5-$O_2N$, 4-Me; $R^2$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-$O_2N$-$C_6H_4$, $EtO_2C$, thienyl.

Scheme 89

In recent years, the necessity for the development of environmentally benign protocols for the synthesis of heterocycles using green, mild, and relatively cheaper methods has grown significantly.[118] Therefore, iron salts have appeared as a versatile alternative due to their low price and toxicity.[119] The use of catalytic amounts of iron salts has been applied to promote the carbon–heteroatom (C–N, C–O, and C–S) bond formation.[120] Catalytic and stoichiometric amounts of iron reagents also appear as a useful alternative to promote cyclization type reactions.[121] Indoles have also been synthesized by several methods using catalytic or stoichiometric amounts of iron salts as discussed below. The catalytic combination between $FeCl_3$ and $PdCl_2$ was successfully used for the synthesis of 2-substituted indoles **101** (Scheme 89).[122] In this reaction, iron(III) presented a dual activity as a cooxidant and a Lewis acid to promote the cyclization.

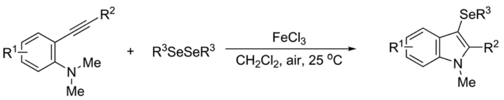
*N*-Methyl-3-chalcogeno-indoles **102** were prepared by iron–iodine-mediated electrophilic annulation reactions of *ortho*-alkynylaniline derivatives using diorganyl disulfides or diorganyl diselenides as a chalcogen source (Scheme 90).[123] In this reaction, the function of iron was to form a complex with nitrogen and the alkyne enabling cyclization, whereas iodine was used to promote the *in situ* preparation of the chalcogen electrophilic species, responsible for the activation of the triple bond and functionalization of the 3-position of the indole. We developed an approach for the synthesis of 3-organoselenyl-(*N*-methyl)indoles **103** *via* cyclization of *ortho*-alkynylanilines using a cooperative action between iron(III) chloride and diorganyl dichalcogenides in the complete absence of a halogen source (Scheme 91).[124] The main advantage of this method-



**102**, 32-95%

$R^1$ = H, 4-Me, 4-F; $R^2$ = $C_6H_5$, 2-Me-$C_6H_4$, 4-Me-$C_6H_4$, 2-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, 3-$F_3C$-$C_6H_4$, 4-$O_2N$-$C_6H_4$, n-$C_6H_{13}$, t-$C_4H_9$; $R^3$ = $C_6H_5$, 4-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 4-$O_2N$-$C_6H_4$, (2-$O_2N$, 4-Cl)-$C_6H_3$, pirydyl, Me, Et, c-$C_6H_{11}$; Y = S, Se.

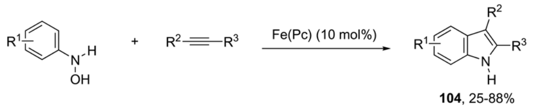
Scheme 90



**103**, 36-81%

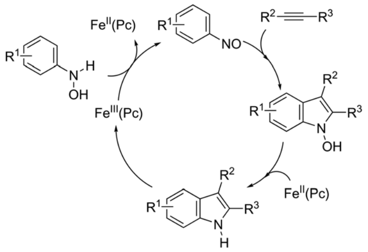
$R^1$ = H, 4-Me, 4-Cl; $R^2$ = $C_6H_5$, 2-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 2-Cl-$C_6H_4$, naphthyl, n-$C_4H_9$, n-$C_6H_{13}$; $R^3$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 3-$F_3C$-$C_6H_4$, 4-Me-$C_6H_4$, naphthyl, n-$C_4H_9$.

Scheme 91



$R^1$ = H, 2-Me, 3-Me, 4-Me, 4-NC, 3-Cl, 4-Cl, 3-$F_3C$; $R^2$ = H and $R^3$ = $C_6H_5$, 4-MeO-$C_6H_4$, 3,4-$(MeO)_2$-$C_6H_3$, pyridyl; $R^2$ = $R^3$ = *c*-octyne.

Scheme 92



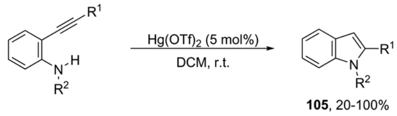
Scheme 93

ology is the incorporation of both portions of diorganyl diselenides (2 RSe) in the final product, which makes it a more useful and valuable method in terms of atom economy.

The iron-catalyzed annulation reactions of aryl hydroxylamines with terminal and internal alkynes provide another useful route to synthesize 3-arylindole derivatives **104** (Scheme 92).[125] The best results were obtained with 10 mol% iron(II) phthalocyanine [Fe(Pc)] under toluene reflux. The proposed catalytic mechanism involved the initial oxidation of hydroxylamines by a Fe(III)(Pc) species to give the arylnitroso intermediate, which reacts with alkynes in a cyclocondensation reaction affording *N*-hydroxyindole. The catalytic cycle is completed by reducing the *N*-hydroxyindole to the corresponding indole with Fe(II)(Pc) (Scheme 93).

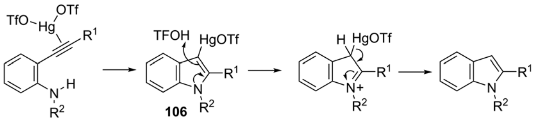
## 2.8. Mercury-catalyzed synthesis of indoles

Until now, limited methods for indole synthesis *via* mercury-promoted cyclization reactions of alkynes with a nitrogen substrate have been developed. In 2007, it was reported that mercuric triflate-catalyzed cycloisomerization reaction of *ortho*-alkynylanilines afforded indole derivatives **105** (Scheme 94).[126] The results support the hypothesis that an activation of the carbon–carbon triple bond by $Hg(OTf)_2$ *via* a π-complexation of the alkyne, followed by a nucleophilic attack of nitrogen, leads to the indol 3-mercury intermediate and TfOH. Protonation and demercuration of **106** give the indole and regenerate the catalyst $Hg(OTf)_2$ (Scheme 95). Very recently, it has been demonstrated that $Hg(OTf)_2$ catalyzed the cyclization of *ortho*-nitroalkynes to produce the corresponding indoles **109** in good yields *via* a regioselective 6-*endo-dig* process (Scheme 96).[127] The structures of mercury–carbenes **107** and **108** have been proposed as the key intermediates in the reaction mechanism.

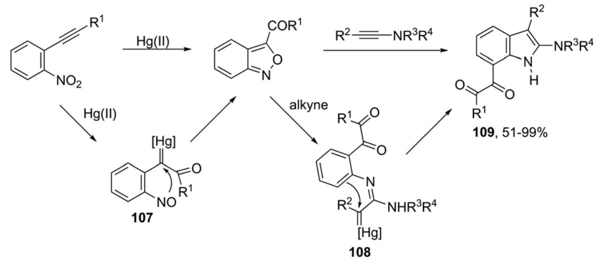


$R^1$ = H, *i*-Pr, *n*-$C_4H_9$, *t*-Bu, $HO(CH_2)_4$, $TsO(CH_2)_4$, $AcO(CH_2)_4$, $TBSO(CH_2)_4$, $C_6H_5$, 4-MeO-$C_6H_4$, 4-$O_2N$-$C_6H_4$; $R^2$ = H, Ts, Ac, 2-$O_2N$-$C_6H_3O_2S$, 4-$O_2N$-$C_6H_3O_2S$.

Scheme 94



Scheme 95



$R^1$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 2-MeO-$C_6H_4$, 2-NC-$C_6H_4$, *n*-$C_5H_{11}$, *t*-Bu; $R^2$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 2-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, naphthyl; $R^3$ = Me, allyl, propargyl, *n*-$C_4H_9$, Bn; $R^4$ = Ms, Ts.

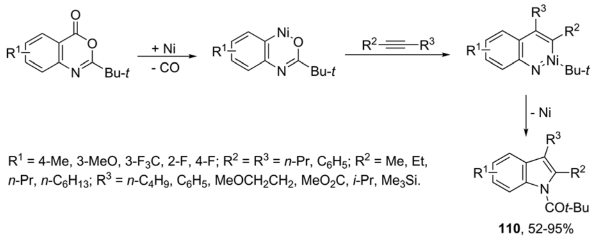
Scheme 96

## 2.9. Nickel-catalyzed synthesis of indoles

The nickel-catalyzed (6-3 + 2) cycloaddition reaction of anthranilic acid derivatives and alkynes gave indoles **110** (Scheme 97).[128] The cyclization was carried out with catalytic amounts of $Ni(cod)_2$ and xylene, under reflux. The mechanism of the reaction is believed to proceed *via* oxidative addition of an ester to a Ni(0) complex, decarbonylation, alkyne insertion, 1,3-acyl migration, and reductive elimination.

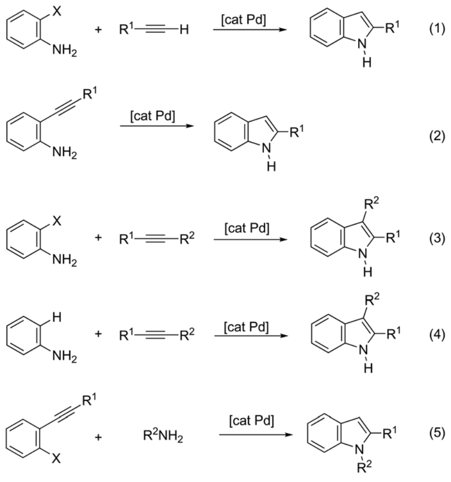
## 2.10. Palladium-catalyzed synthesis of indoles

The palladium-catalyzed cyclization of alkynes is one of the most convenient methods for the preparation of indoles.[129–138] Extensive efforts have been made in developing new methods for the synthesis of indoles by inter- or intramolecular palladium-catalyzed cyclization on functionalized alkynes. The



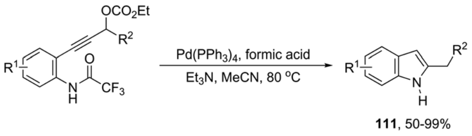
$R^1$ = 4-Me, 3-MeO, 3-$F_3C$, 2-F, 4-F; $R^2$ = $R^3$ = *n*-Pr, $C_6H_5$; $R^2$ = Me, Et, *n*-Pr, *n*-$C_6H_{13}$; $R^3$ = *n*-$C_4H_9$, $C_6H_5$, $MeOCH_2CH_2$, $MeO_2C$, *i*-Pr, $Me_3Si$.

Scheme 97



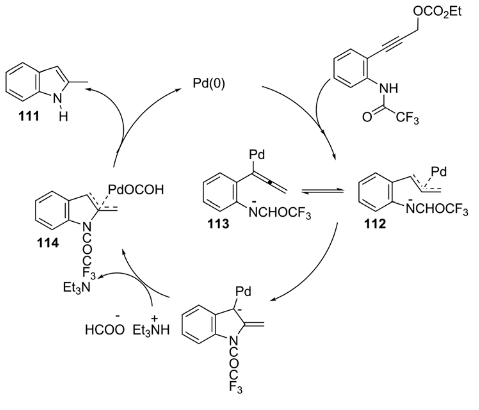
Scheme 98

principal synthetic strategies for this purpose are based on the nitrogen nucleophilic addition to the active carbon–carbon triple bond. The nitrogen atom can be a portion of the starting material or introduced in a key position of the molecule that leads to a subsequent cyclization reaction. In cases in which the nitrogen atom is a part of the molecule, the cyclization reactions may occur *via*: (i) palladium cross-coupling of 2-haloanilines and terminal alkynes or palladium-catalyzed cyclization of 2-alquinilanilines (Scheme 98, eqn (1) and (2)), or (ii) palladium-catalyzed annulation of 2-haloanilines and disubstituted alkynes (Scheme 98, eqn (3)), and palladium-catalyzed C–H activation of anilines, followed by inter- or intramolecular cyclization with alkynes (Scheme 98, eqn (4)). When the nitrogen atom is not present on the structure of the starting material, the palladium-catalyzed *N*-arylation/hydroamination sequence has been widely used to generate functionalized indoles (Scheme 98, eqn (5)). Next, the utility of these methodologies is addressed in terms of such specific examples that appear in the literature.



$R^1$ = H, 4-Cl, 4, 6-(Me)$_2$, 4-Me, (4-Me, 6-O$_2$N), (4-Me, 6-Cl), (4-F, 6-Me), (4-Cl, 6-F$_3$C), 4-MeCO, 4-MeO$_2$C; $R^2$ = H, C$_6$H$_5$, 3-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-F-C$_6$H$_4$

Scheme 99

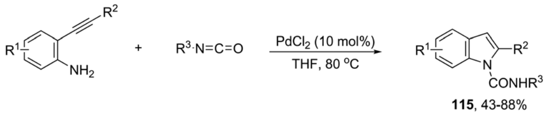


Scheme 100

**2.10.1. Palladium-catalyzed cyclization of *ortho*-alkynylanilines.** Propargyl carbonates have been used as substrates in palladium-catalyzed reductive cyclization reactions to access NH free 3-unsubstituted 2-alkylindoles **111** (Scheme 99).[139] Under palladium-catalyzed conditions, the 3-(*ortho*-trifluoroacetamidophenyl)-1-propargyl carbonates were transformed into the π-propargyl palladium intermediate **112** and σ-allenyl palladium complex **113**, which gave the carbene **114**, *via* an intramolecular nucleophilic attack of the nitrogen atom at the central carbon of the allenyl/propargyl palladium complex. The transformation of the carbene **114** into a π-allylpalladium complex gave the alkylindoles **111** *via* a concerted decarboxylation and hydride transfer sequence (Scheme 100).

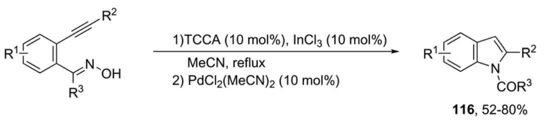
The ligand-free PdCl$_2$ catalyst was active for the cyclization of 2-alkynyl urea affording indole-1-carboxamide derivatives **115** (Scheme 101).[140] The 2-alkynyl urea was prepared *in situ* through reactions of 2-alkynylanilines with isocyanates. The main advantage of this protocol is the use of a simple experimental procedure (PdCl$_2$ (10 mol%), THF and 80 °C) giving the indoles in 43–88% yields *via* an exclusive 5-*endo-dig* cyclization mode.

The reaction of 1-(2-alkynylphenyl)ketoximes with a palladium catalyst using cyanuric chloride and InCl$_3$ as cocatalysts can afford the corresponding indole derivatives **116** (Scheme 102).[141] The 2-alkynylanilide required as a starting material was initially formed *via* a Beckmann rearrangement of 1-(2-alkynylphenyl)-ketoxime. Thus, the intramolecular cyclization occurred in the presence of two catalytic systems to generate the indole derivatives. The authors also described that the simple addition of CuCl$_2$ (2.0 equiv.) to the reaction medium led to the 3-chloroindoles **117** *via* a multicatalytic



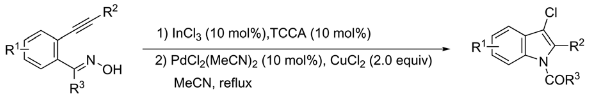
$R^1$ = H, 4-F$_3$C, 4-Me; $R^2$ = C$_6$H$_5$, 4-MeO-C$_6$H$_4$, *c*-C$_3$H$_5$; $R^3$ = C$_6$H$_5$, 4-MeO-C$_6$H$_4$, 4-F-C$_6$H$_4$

Scheme 101



$R^1$ = H, 5-Cl, 5-CH$_3$; $R^2$ = C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, *c*-C$_3$H$_5$, *n*-C$_4$H$_9$, Me$_3$Si; $R^3$ = Me, Et, Ph

Scheme 102



**117**, 61-70%

$R^1$ = H, 5-Cl, 5-$CH_3$; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, *c*-$C_3H_5$, *n*-$C_4H_9$, $Me_3Si$; $R^3$ = Me, Et, Ph

Scheme 103

one-pot Beckmann rearrangement/intramolecular cyclization/halogenation process (Scheme 103).

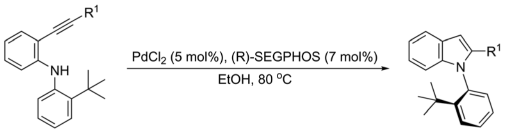
The asymmetric palladium-catalyzed reaction of 2-(*t*-butyl)-*N*-(2-ethynylphenyl)anilines has led to an enantioselective 5-*exo*-aminocyclization forming the nitrogen–carbon axially chiral indoles **118** in up to 83% *ee* (Scheme 104).[142,143] The authors suggested that the enantioselectivity was strongly influenced by the bulkiness of the *ortho*-substituents and the electron density on the arylethynyl group due to the dynamic axial chirality generated by the twisting of the aryl substituent (Scheme 105).

A versatile one-pot multi-step synthetic methodology, combining solid-supported heterogeneous and homogeneous palladium salts, was applied as a catalytic system in the synthesis of indoles **119** (Scheme 106).[144] The sequence started with Sonogashira coupling of 2-iodoaniline with trimethylsilylacetylene giving the 2-[(trimethyl)ethynyl]aniline. The second step involved desilylation, affording the ethynylaniline. Then, Sonogashira coupling with an aromatic iodide, followed by cyclization gave the indole derivatives in yields ranging from 11 to 59% for the four-step reactions (Scheme 106).

A variety of nitro- or amino-indoles have been selectively synthesized *via* tandem Sonogashira coupling/heteroannulation reaction of 2-halonitroanilines and terminal alkynes. The selective product formation was achieved by controlling the solvent; by choosing DMA as the solvent, nitro-indole derivatives **120** were exclusively obtained; whereas the use of DMF gave selectively the amino-indole derivatives **121** (Scheme 107).[145] It was suggested that in the reaction using DMF, as the solvent, an ammonium formate derivative was *in situ* formed, which could act as a source of hydrogen becoming, in association with palladium salt, a reducing system.

The palladium-catalyzed, one-pot, two-step reaction of ynamides with *ortho*-iodoanilines led to 2-aminoindoles **122** (Scheme 108).[146] After the Sonogashira reaction took place, the spontaneous intramolecular hydroamination of the triple bond afforded the 2-aminoindoles from 26% to 87% yields.

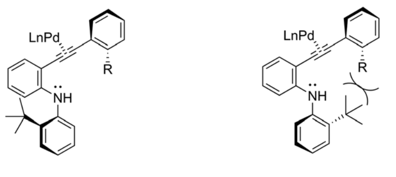
When *ortho*-iodoanilines are subjected to palladium-catalyzed cross-coupling with (trimethylsilyl)acetylene plus a solution of $K_2CO_3$ in aqueous MeOH, the 2-(hetero)aryl indoles **123** were isolated in good yields instead of the 2-alkynylanilines (Scheme 109).[147] The power of the methodology is the use of 10% Pd/C–CuI/$PPh_3$ to achieve the sequential (i) C–C coupling, followed by (ii) C–Si bond cleavage and subsequent (iii) C–C and (iv) C–N bond forming reactions in a single pot.



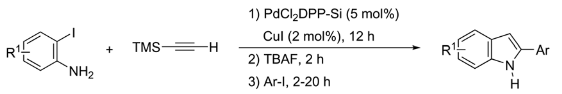
**118**, 18-83%

$R^1$ = *n*-$C_4H_9$, *n*-$C_6H_{11}$, $C_6H_5$, 2-Me-$C_6H_4$, 2-*i*-Pr-$C_6H_4$, 2-Cl-$C_6H_4$, 2-Br-$C_6H_4$, 4-$O_2N$-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$

Scheme 104



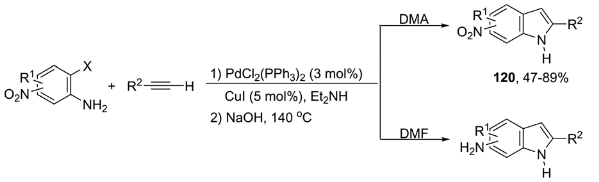
Scheme 105



**119**, 11-59%

$R^1$ = Cl, CN, $NO_2$, $MeO_2C$; Ar = phenyl, 2-naphthyl, 2-pyridyl, 2-thienyl, 3-F-$C_6H_4$, 4-Br-$C_6H_4$.

Scheme 106

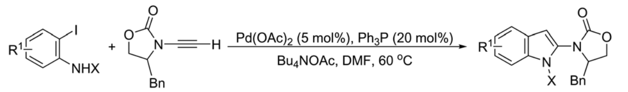


**120**, 47-89%

**121**, 30-66%

$R^1$ = 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$; $R^2$ = Ph, *c*-$C_6H_9$, *n*-$C_4H_9$, *n*-$C_5H_{11}$, 4-F,3-Me-$C_6H_3$, 3-Cl-$C_6H_4$

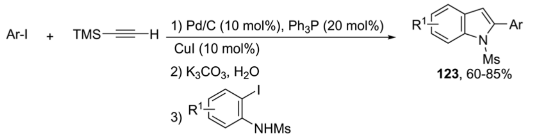
Scheme 107



**122**, 26-87%

$R^1$ = Cl, $F_3C$, NC, CO, Me, $O_2N$; X = H, Boc, $EtO_2C$

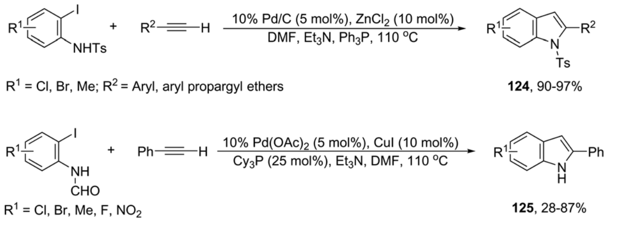
Scheme 108



**123**, 60-85%

Ar = 3-Cl-$C_6H_4$, 3-$F_3C$-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-HO-$C_6H_4$, 3-$H_2N$-$C_6H_4$, 3-$EtO_2C$-$C_6H_4$; $R^2$ = 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$

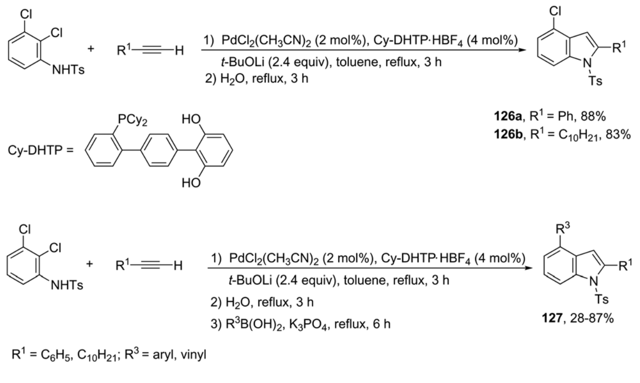
Scheme 109



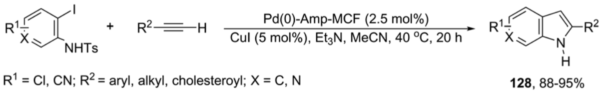
Scheme 110

Zinc chloride can also serve as a co-catalyst in place of copper(I) iodide in the palladium-cross coupling/cyclization reaction of *N*-tosyl-2-iodoanilines with terminal alkynes for the synthesis of 2-substituted indoles.[148] In this study, when 2-iodoanilines reacted with terminal alkynes, at 110 °C, in the presence of 10% Pd/C, moist $ZnCl_2$, $Et_3N$ and $PPh_3$, using DMF as the solvent, the indole derivatives **124** were obtained in high yields (Scheme 110). The authors reported that the reactions carried out under anhydrous conditions gave only the Sonogashira products in the complete absence of a cyclized product. It was suggested that the presence of $HO^-$, liberated from moist $ZnCl_2$, allows an *in situ* generation of zinc acetylide, which accelerates the cross-coupling/cyclization sequence. In order to obtain *N*-unsubstituted indoles, some studies were carried out utilizing *N*-formamide-2-iodoanilines instead of *N*-tosyl-2-iodoanilines. In this case, when *N*-(2-iodoaryl)formamides were reacted with terminal alkynes under palladium cross-coupling/cyclization, indoles **125** were formed through an intramolecular cascade carbon–carbon/carbon–nitrogen bond formation (Scheme 110).[149]

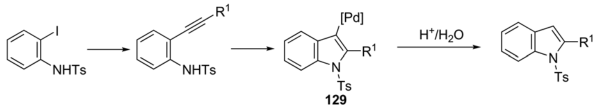
In an effort to prepare 4-chloroindoles **126**, the reaction of 2,3-dichloroaniline derivatives with terminal alkynes, catalyzed by palladium and dicyclohexyl-(dihydroxyterphenyl)phosphine (Cy-DHTP), allowed the Sonogashira coupling, followed by the cyclization reaction at the *ortho*-position. The addition of boronic acid to the above conditions resulted in the synthesis of 2,4-disubstituted indoles **127** *via* a one-pot Sonogashira cross-coupling/cyclization/Suzuki–Miyaura sequence (Scheme 111).[150]



Scheme 111



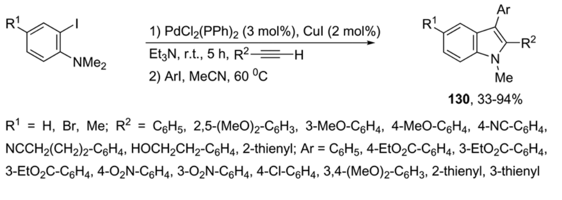
Scheme 112



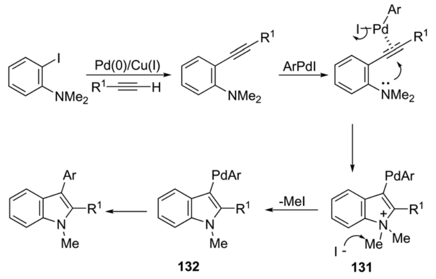
Scheme 113

The palladium nanoparticles supported on a siliceous mesocellular foam (Pd(0)-AmP-MCF) were used as the catalytic system in the reaction of *ortho*-iodoanilines with terminal alkynes, which gave the indoles **128** (Scheme 112).[151] This transformation was influenced by the presence of a small amount of water (1 equiv.). The authors suggested that the presence of water improved the yields of the indoles by increasing the rate of hydrolysis of the vinyl palladium intermediate **129**, formed in the cyclization process (Scheme 113).

**2.10.2. Palladium-catalyzed cascade reactions of alkynes *via* an aminopalladation/reductive elimination process.** Palladium-catalyzed cascade reactions are a rapidly growing area of modern organic chemistry because their timesaving, high efficiency and atom economy. These reactions can be efficiently applied to the formation of π-alkyne–sigma-arylpalladium complexes having a proximal nitrogen nucleophile that can undergo a new carbon–nitrogen bond formation, giving consequently indoles. Extensive efforts have been also made in recent years in developing synthesis of indoles *via* aminopalladation/reductive elimination reactions. In 2009, Larock reported the results on the microwave-assisted, one-pot, three-component coupling reaction for the synthesis of indoles **130** (Scheme 114).[152] The reaction was carried out in two steps under standard Sonogashira coupling conditions from 2-iodoanilines and terminal alkynes, followed by the addition of an aryl iodide (Scheme 114). Larock proposed a reaction mechanism for the one-pot synthesis of indoles, which is illustrated in Scheme 115. The oxidative addition of the aryl iodide to Pd(0) affords an ArPdI species, which activates the alkyne triple bond of the *N*,*N*-dialkyl-2-(1-alkynyl)aniline formed in the first step *via* a Sonogashira coupling. The intramolecular *trans*-aminopalladation gives the indolium anion **131** that loses a methyl group *via* $S_N2$ displacement by the *in situ* generated iodide anion, leading to the indole-containing Pd(II) inter-



Scheme 114



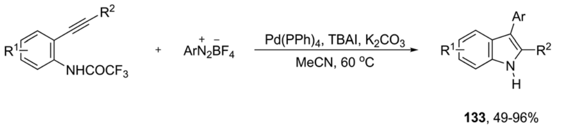
Scheme 115

mediate **132**. The reductive elimination generates the indole (Scheme 115).

The palladium-catalyzed reaction of arenediazonium tetrafluoroborates and 2-alkynyltrifluoroacetanilides afforded free *N-H*-2,3-disubstituted indoles **133** (Scheme 116).[153] The reaction is believed to proceed through a domino process that starts with the reaction of iododediazoniation with TBAI to the *in situ* formation of the aryl iodide. The reaction tolerates a variety of useful substituents, both in the starting alkyne and the arenediazonium salt, including halo substituents, and nitro, cyano, keto, ester, ether, methoxy and methyl groups.

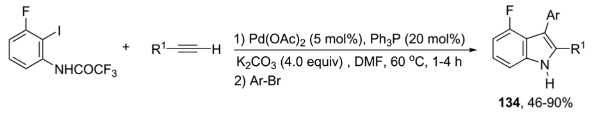
The aminopalladation/reductive elimination sequential reaction, developed by Cacchi and co-workers, has also been employed as a useful strategy for the regioselective construction of 3-aryl-4-fluoro-2-substituted-1*H*-indoles **134** from *ortho*-alkynyltrifluoroacetanilides (Scheme 117).[154] The authors showed that although the use of an inorganic base, such as $K_2CO_3$ or $Cs_2CO_3$, gave good results in the formation of indoles, the cyclization worked better with $Et_3N$ as a base in a microwave-irradiated process.

The scope of the aminopalladation/reductive elimination sequential reaction described by Cacchi can be extended to 2-bromoanilides instead of the corresponding iodides in the preparation of 2,3-disubstituted indoles **135** (Scheme 118).[155] However, the major difficulty found in this reaction was the low reactivity of bromides, which led to the formation of a hydroamidation product without the incorporation of the aryl group at the 2-position of the indole ring. This problem was solved by the authors through a complete study of the best reaction conditions, which involved important parameters such as the base, solvent, temperature, and ligand.



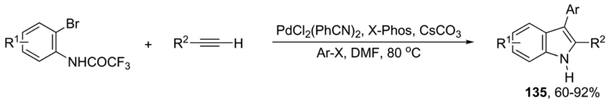
$R^1$ = H, 4-Cl, 4-F, 4-Me, 4-MeCO; $R^2$ = *n*-$C_5H_{11}$, $C_6H_5$, 2-Br-$C_6H_4$, 4-MeO-$C_6H_4$, 4-MeOC-$C_6H_4$, 2-Me-$C_6H_4$, 4-MeOC-$C_6H_4$, 2-Me,4-MeO-$C_6H_3$; Ar = $C_6H_5$, 4-MeO-$C_6H_4$, 4-MeOC-$C_6H_4$, 4-Me-$C_6H_4$, 3-$F_3C$-$C_6H_4$, 4-Cl-$C_6H_4$, 2-Me,4-MeO-$C_6H_3$, 4-CN-$C_6H_4$, 3-F-$C_6H_4$, 3-$O_2N$-$C_6H_4$, 4-MeOC-$C_6H_4$

Scheme 116



$R^1$ = $C_6H_5$, 4-MeO-$C_6H_4$, *n*-$C_4H_9$, *n*-$C_6H_{13}$, 3-thienyl; Ar = 2-$O_2N$-$C_6H_4$, 4-MeO-$C_6H_4$, 3-Me-$C_6H_4$, 4-NC-$C_6H_4$

Scheme 117



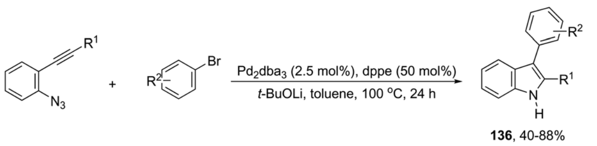
$R^1$ = $C_6H_5$, 4-$MeO_2C$-$C_6H_4$, 4-NC-$C_6H_4$; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, *c*-$C_6H_{11}$; Ar = $C_6H_5$, 4-MeO-$C_6H_4$, 4-$MeO_2C$-$C_6H_4$; X = Cl, Br.

Scheme 118

A series of 2-aryl indoles **136** has been prepared using 2-alkynyl arylazides and aryl bromides under catalysis of $Pd_2dba_3$, dppe as a ligand and *t*-BuOLi as a base in toluene at 100 °C (Scheme 119).[156] In this cyclization, the nitrogen nucleophile is generated *in situ* from azides by a Staudinger reaction.[157] The authors proposed two possible pathways, which are illustrated in Scheme 130. In the first one, the iminophosphorane **137** is formed *in situ* from 2-alkynyl arylazide by a Staudinger reaction. Then, the 5-*endo*-*dig* cyclized intermediate **138** is generated through the nitrogen nucleophilic attack on the activated triple arylpalladium(II). The reductive elimination of intermediate **138**, followed by hydrolysis, gives the product. The second mechanism proposed involves the palladium(II) carbene species **139** formed from intermediate **138**, which after a migratory insertion, isomerization and protonation sequence affords the indole (Scheme 120).

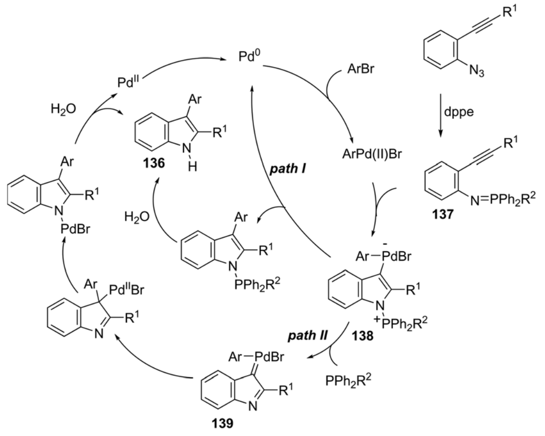
Another type of aminopalladation/reductive elimination reaction involved the regioselective palladium-catalyzed 5-*endo*-*dig* ring-closing reaction of 2-alkynylarylcarbamates with diaryliodonium salts to give 2,3-disubstituted indoles **140** (Scheme 121).[158] In this reaction, diaryliodonium salts react with palladium to form a palladium(II) intermediate that acts by activating the carbon–carbon triple bond and as an arylating agent.

Very recently, Cacchi described the preparation of 2-(aminomethyl)-3-arylindoles **141** *via* palladium-catalyzed reaction of 3-(*ortho*-trifluoroacetamidoaryl)-1-propargyl alcohols, amines, and aryl iodides through a simple procedure that allows for the formation of two carbon–nitrogen bonds and a carbon–carbon bond in a one-pot reaction (Scheme 122).[159] The experi-

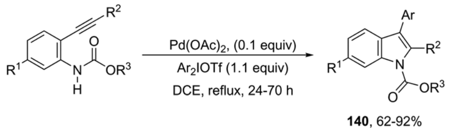


$R^1$ = *n*-$C_4H_9$, *c*-$C_3H_5$, $C_6H_5$, 4-Me-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-F-$C_6H_4$; $R^2$ = 2-Br, 4-Br, 4-Cl, 4-F, 4-MeO, 4-$CH_3$, 4-*t*-Bu, 4-TMS, 3-$CF_3$, 4-$F_3C$, 3-MeO, 2-CN

Scheme 119

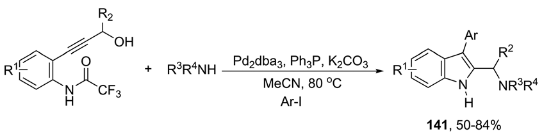


Scheme 120



$R^1$ = H, Me, F; $R^2$ = *n*-Bu, $C_6H_5$, 4-Me-$C_6H_4$; $R^3$ = Et, Me, *t*-Bu; Ar = $C_6H_5$, 4-Me-$C_6H_4$, 4-F-$C_6H_4$.

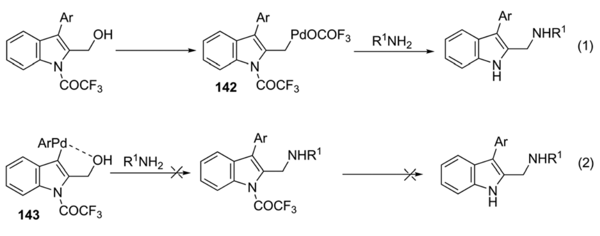
Scheme 121



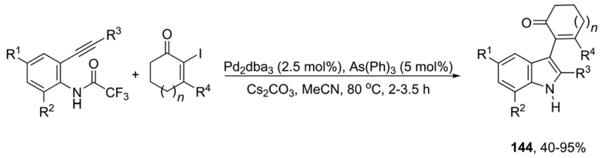
$R^1$ = H, 4-Me, 4-MeCO; $R^2$ = Me, $C_6H_5$; $R^3$,$R^4$ = ethyl, butyl, alkyl, benzyl, aryl piperazinyl; Ar = 4-MeO-$C_6H_4$, 3-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 3-F-$C_6H_4$, 3-$F_3C$-$C_6H_4$, 4-MeCO-$C_6H_4$.

Scheme 122

mental evidence obtained by the authors supported the hypothesis that a trifluoroacetyl ester is formed in the reaction medium and that a palladium intermediate **142** is directly involved in the formation of indoles (Scheme 123, eqn (1)). The results of these experiments led the authors to discard the formation of indoles *via* a direct nucleophilic substitution of the amino nucleophile for the hydroxyl group assisted by the coordination of oxygen to palladium species **143** (Scheme 123, eqn (2)).



Scheme 123



$R^1$ = H, F, $O_2N$; $R^2$ = H, F, CN, $R^3$ = $C_6H_5$, 3-$MeO_2C$-$C_6H_4$, 4-MeO-$C_6H_4$, 2-Br-$C_6H_4$, 2-thienyl, *n*-$C_4H_9$; $R^4$ = H, $CH_3$; *n* = 0,1, 2.

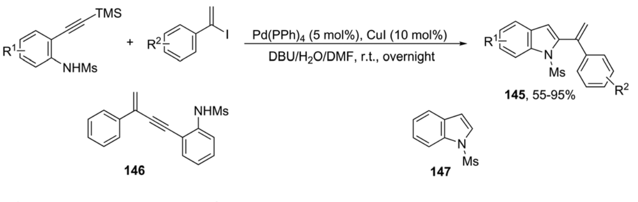
Scheme 124

Instead of aryl halides, vinyl halides are also suitable electrophiles for the sequential aminopalladation/reductive elimination of palladium(0) to afford indoles. Alfa-iodoenones at different ring sizes were efficiently used as electrophiles in the palladium-catalyzed cyclization of 2-alkynyltrifluoroacetanilides to afford 2,3-disubstituted indoles **144** (Scheme 124).[160] Various experimental conditions were tested by the authors for the cyclization, and the best results were obtained with $Pd_2(dba)_3$ as a catalyst and $AsPh_3$ as a ligand; although, in the absence of the ligand, $Pd_2(dba)_3$ was also effective.

The 1-phenylvinyl iodides have also been used for the one-pot conversion of *N*-protected *ortho*-alkynylanilines to 2-(1-phenylvinyl)indoles **145** (Scheme 125).[161] A mixture of unsubstituted enynes **146** and indoles **147** was obtained and the ratio between them can be greatly dependent on the substituent on the aniline nitrogen atom. Unprotected anilines gave no trace of products, *N*-tosylanilide and trifluoromethyl acetanilide gave a mixture of enynes **146** and indoles **147** and the best result was obtained with *N*-mesylanilide, which gave the desired indole **145** in 73% yield together with small amounts of unsubstituted indoles **147**. Under $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), and DBU (12 equiv.) and using a mixture of DMF and water as the solvent, the *N*-mesyl *ortho*-alkynylanilines were transformed into the corresponding 2-(1-phenylvinyl) indoles **145** from moderate to good yields.

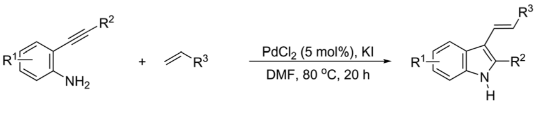
The aminopalladation reactions with the concomitant oxidative coupling have also been reported by using alkenes instead of halide derivatives. The palladium-catalyzed cascade reaction of 2-alkynylaniline and functionalized alkenes led to structurally diverse 3-alkenylindoles **148** (Scheme 126).[162] The cyclization reactions follow the regioselective 5-*endo*-*dig*-mode, whereas the subsequent Heck-type coupling with alkenes occurs stereoselectively with exclusive formation of the E isomers.

Using palladium-catalyzed reactions of arenediazonium tetrafluoroborates with *N*-allyl-2-alkynyl anilines, Cacchi has



$R^1$= H, 3-MeO, 4-MeO, 4-$F_3C$, 4-F; $R^2$ = 2,3,4-MeO-$C_6H_2$, 2-F,3-MeO-$C_6H_3$, 2,3-Cl-$C_6H_3$, 4-F-$C_6H_4$, 4-Br-$C_6H_4$.

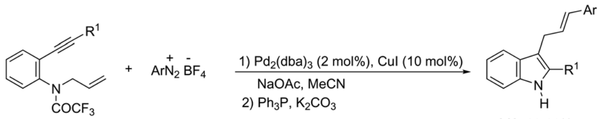
Scheme 125



**148**, 32-95%

$R^1$ = $MeO_2C$, Me; $R^2$ = H, n-$C_6H_{13}$, 4-$MeC_6H_4$, 4-$EtO_2C$-$C_6H_4$, TMS, $HO(CH_2)_3CH_2$;
$R^3$ = $CO_2Et$, $CO_2Me$, CN, $SO_2Me$

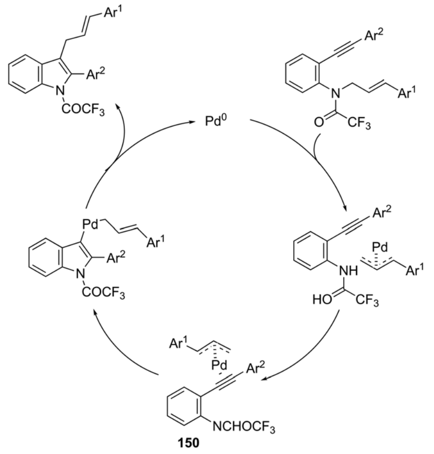
Scheme 126



**149**, 69-88%

$R^1$= H, 4-MeCO, 2-Cl, 4-Cl, 4-MeO; Ar = $C_6H_5$, 4-MeO-$C_6H_4$, 4-NC- $C_6H_4$

Scheme 127

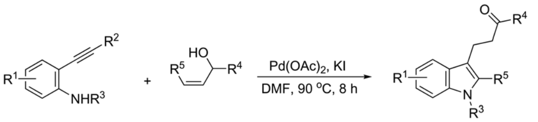


Scheme 128

obtained 2-alkenyl indoles **149** *via* an intramolecular amino-cyclization/oxidative Heck-coupling sequence (Scheme 127).[163] The reaction can be efficiently carried out *via* a simple one-pot, two-step procedure just by the addition of $PPh_3$ and $K_2CO_3$ to the crude mixture and heating at 100 °C. Although the cyclization follows a mechanism similar to that shown in Scheme 128, it should be highlighted that the central step is the formation of π-allylpalladium species **150**, which activates the carbon–carbon triple bond and introduces the functionality at the 3-position of the indoles.

Instead of simple alkenes, allylic alcohols were efficiently used in palladium-catalyzed oxidative cyclization of 2-alkynyl anilines in the synthesis of β-indole ketones **151** (Scheme 129).[164] The effectiveness of the cyclization depends on the catalyst species ($Pd(OAc)_2$) and the presence of oxygen for the regeneration of palladium(II) active species.

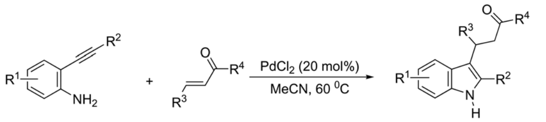
A series of 2,3-disubstituted indoles **152** have been prepared by cascade reaction of *N*-unprotected-2-alkynylanilines with electron-deficient alkenes using palladium as a catalyst



**151**, 72-90%

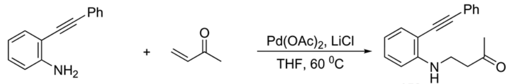
$R^1$ = 4-$CH_3$, 4-$F_3C$, 4-$MeO_2C$, 4-NC; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 2-F-$C_6H_4$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 4-$O_2N$-$C_6H_4$, n-$C_4H_9$, $NC(CH_2)_2CH_2$; $R^3$ = H, Me; $R^4$ = Ar; $R^5$ = H, Me.

Scheme 129



**152**, 40-97%

$R^1$ = H, Me, 2,4 $(Me)_2$, Cl, $O_2N$; $R^2$ = c-$C_3H_5$, c-$C_5H_9$, c-$C_6H_{11}$, n-$C_4H_9$, n-$C_7H_{15}$, $(MeO_2C)_2CHCH_2$, $HO(CH_2)_3CH_2$, i-$C_3H_7$, $C_6H_5$, $R^3$ = H, Me, $C_6H_5$; $R^4$ = Me, Et, MeO, $C_6H_5$.

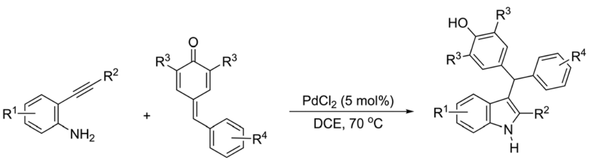


**153**

Scheme 130

(Scheme 130).[165] The authors observed that the product distribution was affected by the nature of the palladium catalyst. The use of $PdCl_2$ in acetonitrile at 60 °C resulted in the formation of 2,3-disubstituted indole derivatives **152**, whereas the catalytic system formed by $Pd(OAc)_2$/LiCl in THF at 60 °C produced *N*-alkylated-2-alkynylaniline derivatives **153**.

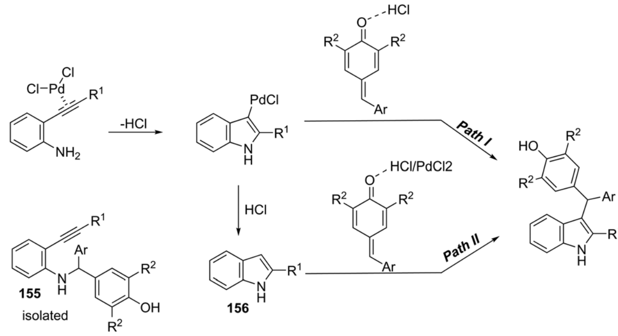
The synthesis of highly substituted unsymmetrical diarylindolylmethane derivatives **154** has been developed through palladium-catalyzed annulation of *ortho*-alkynylanilines, followed by 1,6-conjugate addition to *para*-quinones (Scheme 131).[166] Various substituted *ortho*-alkynylanilines and *para*-quinones were used in the cyclization, giving the unsymmetrical diarylindolylmethanes in excellent yields. The careful monitoring of the reaction revealed that the amine addition product **155** was also formed in considerable amounts; however, it is not an intermediate of the reactions. The formation of **155** is reversible and its concentration gradually decreased with the formation of indoles **154**. The authors suggested that the 2-arylindole **156** is a key intermediate and its formation is the rate-determining step of the cyclization (Scheme 132).



**154**, 59-98%

$R^1$ = H, Cl, F, NC; $R^2$ = c-$C_3H_5$, c-$C_5H_9$, $C_6H_5$, 4-Me-$C_6H_4$, 4-t-Bu-$C_6H_4$, 2,4,5-$(Me_3)_3$-$C_6H_2$, 6-(Me)-4-naphthyl-$C_6H_3$, 2-Me-4-MeO-$C_6H_3$, 4-$Me_2N$-$C_6H_4$, 4-Br-$C_6H_4$, 4-Ph-$C_6H_4$, 4-NC-$C_6H_4$; $R^3$ = Me, i-Pr, t-Bu; $R^4$ = H, Et, t-Bu, 2-F, 4-$F_3C$, naphthyl, alkynyl.

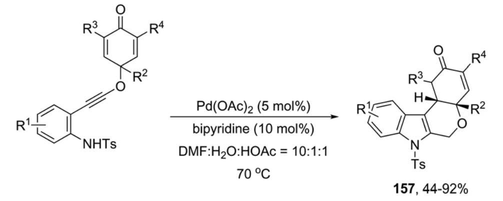
Scheme 131



Scheme 132

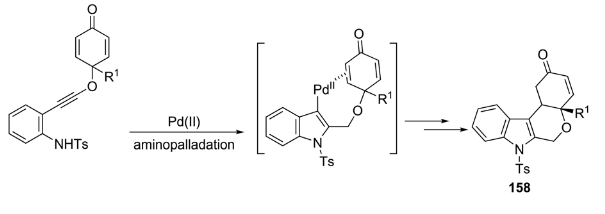
The $Pd(OAc)_2$, bipyridine and DNF/$H_2O$/AcOH catalytic system is active for the intramolecular cyclization of aniline-tethered alkynyl cyclohexadienones in the preparation of cyclohexenone-fused tetrahydropyrano[3,4-*b*]indoles **157** (Scheme 133).[167] The authors suggested that the intramolecular cascade reaction would be initiated by aminopalladation of alkynes and quenched by the addition to the intramolecular cyclohexenone. The asymmetric version of this tandem cyclization was also described by using a chiral bipyridine ligand, which gave the chiral cyclohexanone fused tetrahydropyrano[3,4-*b*]indoles **158** in good yields with excellent enantioselectivities (93–96% ee) (Scheme 134).

The addition of a halide source to palladium-catalyzed annulation of an *ortho*-alkynylaryl containing nitrogen nucleophile has been a methodology used for the synthesis of 3-haloindoles. For example, Li and co-workers reported that in the presence of $PdX_2$ and $CuX_2$ (X = Cl, Br), the annulation reactions of 2-ethynylbenzeneamines gave the 2-substituted 3-haloindoles **159** (Scheme 135).[168] More recently, Li and Zhang discovered that in the presence of $PdX_2$ (X = Br, Cl) and halide sources, the 2-alkynyl aryl azides were also suitable substrates for halopalladation cyclization reactions to afford the corresponding 2-substituted 3-haloindoles **160** (Scheme 136).[169]



$R^1$ = H, 4-Br, 4-Cl, 4-F, 4-MeO, 4-TBSOCH$_2$, 4-C$_6$H$_5$, 4-F$_3$C, 4-Me, 3-Me; $R^2$ = Et, *i*-Pr, *t*-Bu, Ph, Bn, Cy, Me; $R^3$,$R^4$ = H, Me.

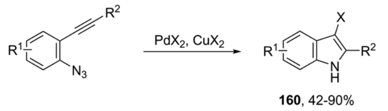
Scheme 133



Scheme 134

$R^1$ = H, 3,4-(F)$_2$, 3,5-(Cl)$_2$, 3-O$_2$N; $R^2$ = *t*-Bu, *n*-C$_8$H$_{17}$, C$_6$H$_5$, AcOCH$_2$CH$_2$; X = Cl, Br.

Scheme 135

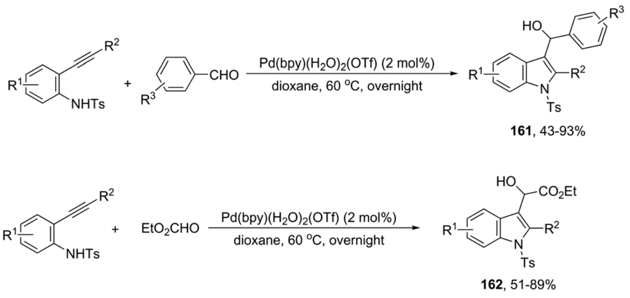


$R^1$ = H, 3,5-(Cl)$_2$, 3-O$_2$N; $R^2$ = C$_6$H$_5$, 2-Me-C$_6$H$_4$, 4-O$_2$N-C$_6$H$_4$, 2-thienyl; X = Cl, Br

Scheme 136

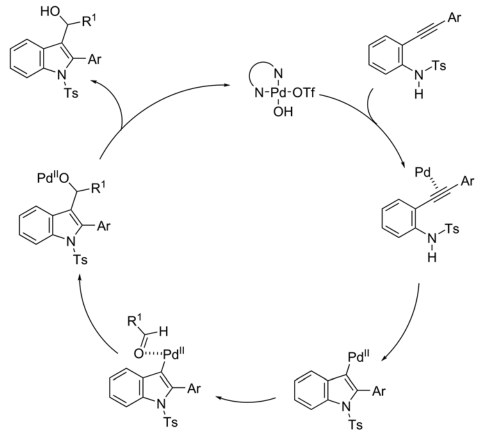
The intermolecular version of the sequence of carbon–nitrogen and carbon–carbon bond formation has been described in the course of the reaction of *N*-tosyl-2-arylethynylanilines with aldehydes catalyzed by the palladium(II) species in the synthesis of substituted 3-hydroxymethylindoles **161** (Scheme 137).[170] The same reaction conditions were extended to ethyl glyoxylate, which afforded the alpha-hydroxyindolyl acetate **162** in good yield. According to the authors, a tandem reaction is started by an aminopalladation of 2-arylethynylanilines, followed by quenching of the carbon–palladium bond with a carbonyl group. This regenerates the active palladium(II) species without the necessity of a redox system (Scheme 138).

The intramolecular version of the sequence of carbon–nitrogen and carbon–carbon bond formation with the migration of the functional carbonyl group was also described. Thus, the reaction of *N*-acyl-2-alkynylanilines with $PdCl_2(CH_3CN)_2$ in $CH_3CN$ at 90 °C gave the 3-acyl-indoles **163**, resulting from the acyl migration (Scheme 139).[171] The reaction conditions also promoted the migration of pyruvoyl, amide and sulfonyl groups in comparable yields.

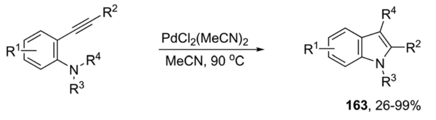


$R^1$ = H, 4-Me, 4-Cl, 4-F, 5-F; $R^2$ = C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-Br-C$_6$H$_4$, *n*-C$_6$H$_{13}$, CH$_3$OCH$_2$; $R^3$ = H, 3-O$_2$N, 4-O$_2$N, 5-Cl-4-O$_2$N, 4-CH$_3$OC, 4-NC.

Scheme 137



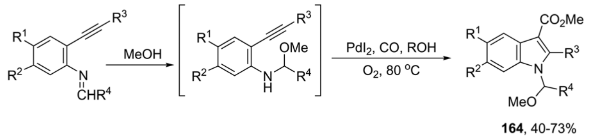
Scheme 138



$R^1$ = H, 4-Me, 4-MeO, 4-Cl, 4-Br, 4-F, 4-F$_3$C; $R^2$ = n-$C_4H_9$, c-$C_3H_5$, c-$C_6H_{11}$, t-Bu, Bn, $C_6H_5$, 4-MeO-$C_6H_4$, 3-F-$C_6H_4$, 3-thienyl, Cl$(CH_2)_2CH_2$, $MeO_2C(CH_2)CH_2$, AcO$(CH_2)_2CH_2$, BocNH$CH_2$; $R^3$ = Me, Et, Bn; $R^4$ = CHO, COR(CO)$_2$R, CONHR, $SO_2R$.

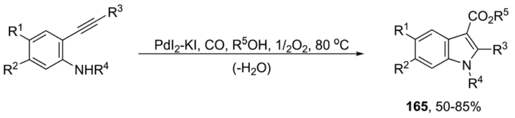
Scheme 139

The palladium-catalyzed oxidative carbonylation of 2-alkynylaniline imines and 2-alkynylaniline derivatives in the preparation of indole-3-carboxylic acid esters has also been reported. When imine derivatives were used as the starting material, the sequential reaction with an initial nucleophilic attack on carbon of the imine group, followed by a palladium-catalyzed oxidative nitrogen-cyclization–alkoxycarbonylation, occurred to form the [1-(alkoxyarylmethyl)indole]-3-carboxylic esters **164** (Scheme 140).[172] When 2-alkynylanilines were used as the starting material, in the reaction with CO, $O_2$, and an alcohol in the presence of the $PdI_2$/KI as the catalytic system, indole-3-carboxylic esters **165** were formed in good yields (Scheme 141).[173] In addition, on changing the alcohol to trimethyl orthoformate, 2-alkynylanilines gave 1-(dimethoxymethyl) indole-3-carboxylic esters *via N*-(dimethoxymethyl)-2-alkynylaniline derivatives as intermediates.



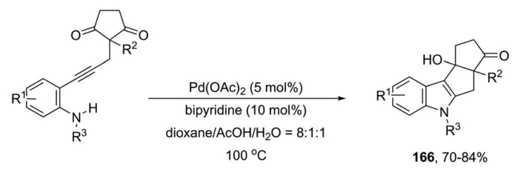
$R^1$ = H, Cl, $C_6H_5$, Me; $R^2$ = H, Me, $F_3C$; $R^3$ = n-Bu, $C_6H_5$, 4-Br-$C_6H_4$, 4-Me-$C_6H_4$, 3-thienyl; $R^4$ = Me, Et.

Scheme 140



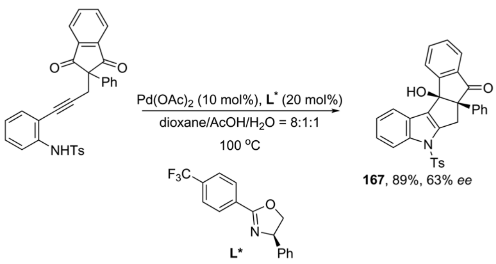
$R^1$ = H, Cl, Me; $R^2$ = H, $F_3C$, Me; $R^3$ = n-Bu, $C_6H_5$, 4-Br-$C_6H_4$, 4-Me-$C_6H_4$; $R^4$ = Bn, i-Bu; $R^5$ = Me, Et.

Scheme 141



$R^1$ = H, 4-Me, 5-Me, 4-Cl, 4-F, 4-$F_3C$, 4-MeO, 4-$MeO_2C$; $R^2$ = $CO_2Me$, CN, $CH_2OMe$; $R^3$ = Ts, Ms.

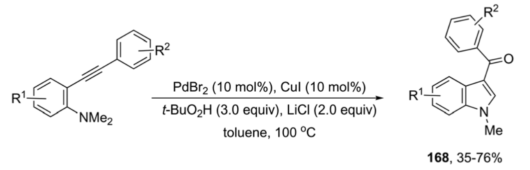
Scheme 142



Scheme 143

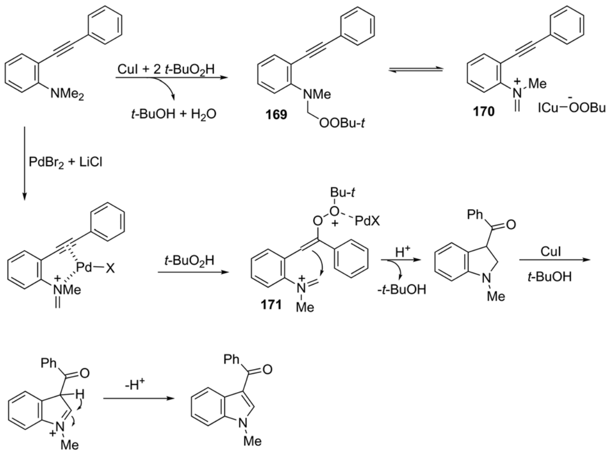
Ketones can be also used as electrophiles in the aminopalladation-initiated tandem cyclization. As reported, the Pd $(OAc)_2$ catalyst was effective at tandem cyclization of 2-alkynylanilines having a cyclopentanone to synthesize pentaleno[2,1-*b*] indoles **166** (Scheme 142).[174] This reaction involves the initial aminopalladation of the carbon–carbon triple bond, followed by quenching of the palladium intermediate by intramolecular addition to carbonyl groups. In the obtained tetracyclic indole framework **167**, two neighboring stereocenters were formed, with excellent diastereoselectivity in a single process by using an oxazole derivative as the ligand (Scheme 143).

Results from the palladium/copper cocatalyzed oxidative cyclization of 2-alkynylanilines showed that 3-acylindoles **168** were obtained in good yields by using $PdBr_2$ (10 mol%) and CuI (10 mol%) in the presence of *t*-butyl hydroperoxide (Scheme 144).[175] In this cyclization reaction, *t*-butyl hydroperoxide was used as either the oxidant or oxygen source to introduce the carbonyl functionality. Based on the results of control experiments the authors concluded that the ketone moiety did not originate from water and molecular oxygen. These results in association with ESI/MS analysis results indicated that the reaction followed the mechanism shown in Scheme 145. The 2-alkynylaniline reacts with two molecules of *t*-butyl hydroperoxide under copper catalysis to give the peroxide **169**, which is in equilibrium with the iminium intermediate **170**. The nucleophilic attack of *t*-butyl hydroperoxide on the activated carbon–carbon triple bond of **170** generates the intermediate



$R^1$ = 4-Me, 4-Cl; $R^2$ = H, 2-Cl, 3-Cl, 4-Cl, 3-F, 4-F, 3,4(Me)$_2$, 4-MeOC, 3-Me, 4-Me, 4-MeO, 4-*i*-Pr, 4-$O_2N$, 2-thienyl.

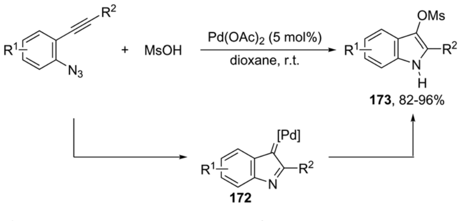
Scheme 144



Scheme 145

**171** that gives the 3-acylindoles after the intramolecular cyclization, oxidation, and deprotonation sequence.

In a recent study, 2-alkynyl arylazides and sulfonic acids were examined with regard to the synthesis of 1*H*-indole-3-sulfonates *via* palladium-catalyzed tandem reactions.[176] It was found that the desired products, 1*H*-indole-3-sulfonates **173**, were obtained in moderate to excellent yields when 2-alkynyl arylazides reacted under Pd(OAc)$_2$ at room temperature, followed by the addition of MsOH (Scheme 146). It was proposed that the formation of the intermediate **172** is responsible for the success of the reaction. The reaction conditions could be applied to 2-alkynyl arylazides with an aryl group containing pendant electron-donating and electron-withdrawing substituents or a hetero aryl group on the alkyne carbon. 2-Alkynyl arylazides bearing the aliphatic substituted groups on the alkyne carbon were also suitable substrates, giving the desired indoles in comparable yields; however, 2-alkynyl arylazides containing a terminal alkyne did not afford the products.

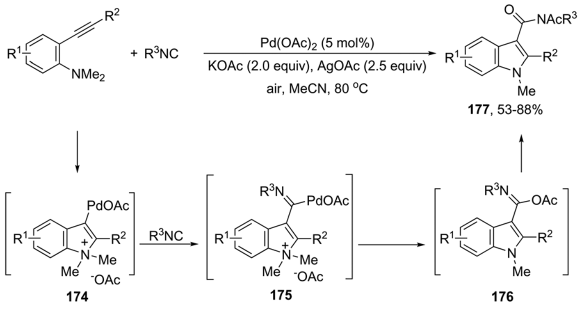


$R^1$ = H, 4-Cl, 5-Cl, 4,6-(Cl)$_2$, 4-$F_3C$, 4-Me; $R^2$= H, $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, $MeO_2C$-$C_6H_4$, *n*-$C_4H_9$, *n*-$C_5H_{11}$, *t*-Bu, *c*-$C_3H_5$, $BnOCH_2CH_2$, 3-thienyl.

Scheme 146

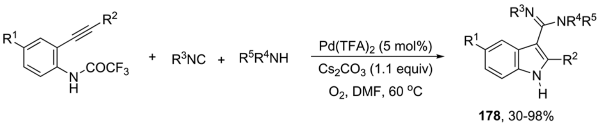
The application of isocyanides as electrophiles in the aminopalladation-initiated tandem cyclization was studied for the synthesis of 3-amidylindoles **176**[177] and 1*H*-indole-3-carboxamidines **177**.[178] In the former case, Pd(OAc)$_2$ and silver acetate catalyzed the reaction of *N*,*N*-dimethyl-2-alkynylanilines and isocyanides, leading to 3-amidylindoles **176** in moderate to good yields (Scheme 147). When Pd(TFA)$_2$ was used as the catalyst and silver acetate was switched to silver trifluoroacetate, *N*,*N*-dimethyl-2-alkynylanilines gave 3-cyanoindoles **177** (Scheme 147). In addition, the use of a trace amount of water under these reaction conditions led to the formation of 3-amidylindoles.[179] In the mechanism proposed, the authors hypothesized that silver acetate would act as an oxidant and a reactant and that **174–176** are the key intermediates in the formation of products (Scheme 147). In the latter case,[178] isocyanides, *ortho*-alkynyltrifluoroacetanilides and amines are involved in a three-component process for the synthesis of 2-substituted 1*H*-indole-3-carboxamidines **178** (Scheme 148). The reaction proceeds through intramolecular aminopalladation of alkynes activated by isocyanide-ligated palladium(II) species **179** (Scheme 149).

The same group has used diazoacetates to synthesize 3-alkylindole derivatives **180** *via* a carbene insertion.[180] In this cyclization reaction, *ortho*-alkynyltrifluoroacetanilides were activated by PdCl$_2$, starting an aminopalladation triggered carbene insertion reaction *via* intermediates **181–184** to give aryl-substituted methyl 2-(2-phenyl-1*H*-indol-3-yl)acetates **180** (Scheme 150). The use of alpha-diazoacetates could result in a



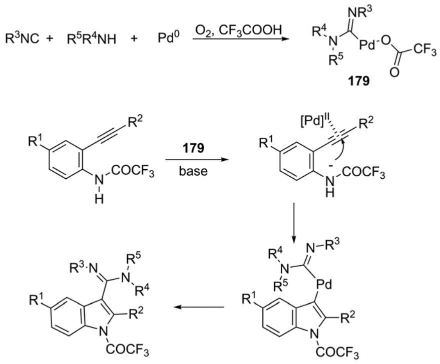
$R^1$ = F, Me, *i*-Pr; $R^2$ = $C_6H_5$, 4-Cl-$C_6H_4$, 2-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, *n*-$C_4H_9$, TMS, *c*-$C_3H_5$; $R^3$ = *n*-$C_4H_9$, *n*-$C_5H_{11}$, *t*-Bu, *c*-$C_6H_{11}$.

Scheme 147

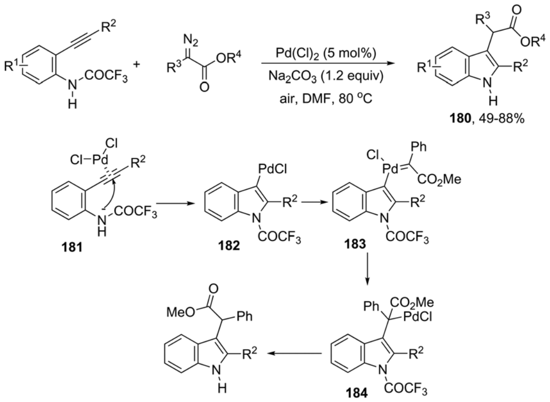


$R^1$ = 4-Cl, 4-Br, 4-F, 4-M; $R^2$ = $C_6H_5$, 2-Cl-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Ac-$C_6H_4$,*n*-$C_4H_9$, *c*-$C_6H_{11}$, *c*-$C_6H_9$, 2-thienyl; $R^3$ = *t*-Bu, n-$C_5H_{11}$, *c*-$C_6H_{11}$; $R^4$,$R^5$ = H, Me, Et, *n*-Bu, *c*-$C_5H_9$, $C_6H_5$.

Scheme 148

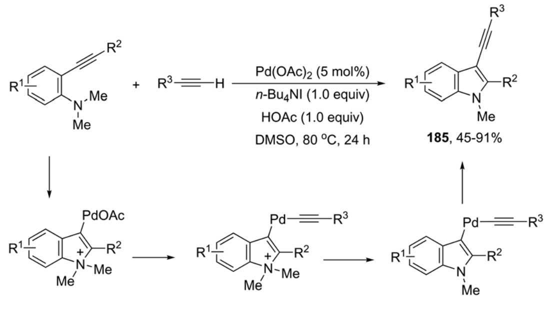


Scheme 149



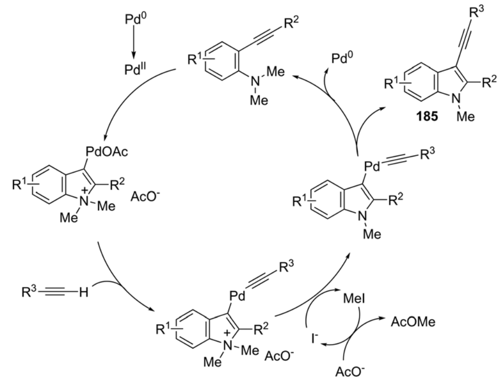
$R^1$ = $C_6H_5$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-Me-$C_6H_4$, 4-6-$(Me)_2$-$C_6H_4$; $R^2$ = $C_6H_5$, 4-Br-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, *c*-$C_6H_{10}$, 2-thienyl; $R^3$ = H, $C_6H_5$, 4-Cl-$C_6H_4$, 2-Br-$C_6H_4$, 4-MeO-$C_6H_4$, 3-MeO-$C_6H_4$; $R^4$= Me, Et.

Scheme 150



$R^1$= $C_6H_5$, 4-Me-$C_6H_4$; $R^2$= $C_6H_5$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, *n*-$C_6H_{13}$, $CN(CH_2)_2CH_2$,$Cl(CH_2)_2CH_2$; $R^3$= $C_6H_5$, 4-F-$C_6H_4$, 2-Me-$C_6H_4$, 2-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, *n*-$C_6H_{13}$, $CN(CH_2)_2CH_2$, $HO(CH_2)_2CH_2$, $BnO(CH_2)_2CH_2$.

Scheme 151

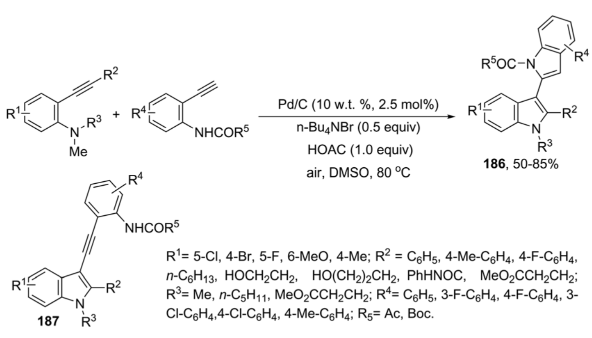


Scheme 152

competition between the carbon–carbon bond formation and nitrogen–hydrogen insertion. The authors thus postulated that the migratory insertion of the carbene into the sigma-indolylpalladium intermediate was favored over the nitrogen–hydrogen insertion.

Terminal alkynes are useful partners for the palladium-catalyzed oxidative cyclization of *ortho*-alkynylanilines, have been proven to be extremely useful for the synthesis of 3-alkynylindoles *via* carbon–carbon bond formation. In this regard, a range of 2,3-disubstituted 3-alkynylindoles **185** were prepared by palladium(II)-catalyzed domino reaction between *ortho*-alkynylanilines and terminal alkynes (Scheme 151).[181] The control experiments were carried out to determine the reaction mechanism, in which the authors identified as elementary steps the formation of a σ-alkynylpalladium(II) complex and aminopalladation of *ortho*-alkynylaniline, leading to a sigma-indolylpalladium(II) intermediate. In these experiments, they also found that the *N*-demethylation step occurs after the formation of the σ-alkynylpalladium intermediates (Scheme 152). Thus, the proposed mechanism for this transformation involves the aminopalladation of *ortho*-alkynylanilines, giving the σ-indolylpalladium intermediate. The coordination of the terminal alkyne with σ-indolylpalladium, followed by deprotonation, leads to σ-alkynylpalladium. The *N*-demethylation promoted by iodide affords 3-indolylpalladium intermediate and reductive elimination provides the 3-alkynylindoles **185** (Scheme 152).

In a similar manner to that of 3-alkynylindoles **185**, the 2,3′-bisindoles **186** were prepared by intermolecular cyclization using two *ortho*-alkynylanilines. The palladium-catalyzed conditions, consisting of Pd/C, *n*-$Bu_4NBr$, AcOH, and DMSO at 80 °C, were very effective at promoting the cyclization of *ortho*-alkynylanilines and 2-ethynylaniline to 2,3′-bisindole derivatives **186** (Scheme 153).[182] For the mechanism, the authors proposed two temporally separate catalytic cycles, in which the



$R^1$= 5-Cl, 4-Br, 5-F, 6-MeO, 4-Me; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-F-$C_6H_4$, *n*-$C_6H_{13}$, $HOCH_2CH_2$, $HO(CH_2)_2CH_2$, PhHNOC, $MeO_2CCH_2CH_2$; $R^3$= Me, *n*-$C_5H_{11}$, $MeO_2CCH_2CH_2$; $R^4$= $C_6H_5$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 3-Cl-$C_6H_4$,4-Cl-$C_6H_4$, 4-Me-$C_6H_4$; $R_5$= Ac, Boc.

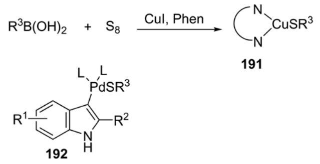
Scheme 153

formation of 3-alkynylindole **187** occurs first, followed by a second cyclization from **187** giving the bisindoles **186** (Scheme 153).

The palladium-catalyzed cyclization of *ortho*-alkynylanilines merged with cross-coupling with bis-(pinacolato)diboron was achieved upon treatment with $Pd_2(dba)_3$ and $Ph_3As$, affording indole 3-boronic esters **188** (Scheme 154).[183] The authors carried out control experiments to confirm that the borylation reaction is a process that occurs during cyclization rather than after indole formation.

An efficient one-pot protocol was developed for the synthesis of the 3-sulfenylindoles **189** from diorganyl disulfides and *ortho*-alkynylanilines (Scheme 155).[184] The results from this cyclization process, using $PdCl_2$ in DMSO at 80 °C, indicated that a molar ratio of 2 : 1 between *ortho*-alkynylanilines and diorganyl disulfides and excellent yields were obtained. This result is significant because it indicates that the two portions (RS) of organosulfur reagents were transferred to the substrate.

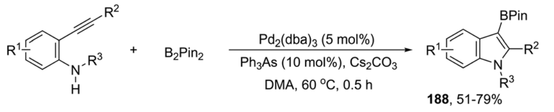
An important extension of this methodology was accomplished by the conversion of *ortho*-alkynylanilines to 3-sulfenylindoles **190** *via* three-component cyclization reaction involving sulfur and boronic acids catalyzed by $Pd(TFA)_2$ and CuI in ionic liquids (Scheme 156).[185] The innovation of this methodology was the preparation of 3-sulfenylindoles in excellent yields by a one-pot procedure avoiding the previous preparation of diorganyl disulfides. Several control experiments indicated that the sulfur moiety is introduced *via* a copper thiolate **191** generated *in situ* from elemental sulfur, CuI and boronic acid and that palladium complex **192** is the key intermediate for the success of this cyclization (Scheme 157).



Scheme 157

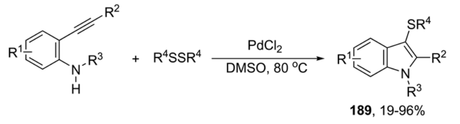
The exploration of the application of trifluoromethanesulfanylamide for the palladium-catalyzed cyclization/trifluoromethylthiolation of *ortho*-alkynylanilines was also described. The sequential cyclization and thiolation reactions between *ortho*-alkynylanilines with trifluoromethanesulfanylamide in the presence of $Pd(OAc)_2$ and bismuth(III) chloride allowed a straightforward synthesis of 3-((trifluoromethyl)thio)indole derivatives **193** in excellent yields (Scheme 158).[186] The presence of a quantitative amount of bismuth(III) chloride is essential for the success of this transformation because it participates in the formation of sulfur electrophilic species *via* an activation of trifluoromethanesulfanylamide. The transformation is believed to proceed *via* a palladium-catalyzed intramolecular cyclization of *N*,*N*-dimethyl-*ortho*-alkynylaniline giving the intermediate **194**. The removal of the methyl group from intermediate **194** by chloride anions from bismuth(III) chloride with concomitant trifluoromethanesulfanyl cation formation affords the 3-((trifluoromethyl) thio)indoles **193** (Scheme 159).

Another good example of a simple, but efficient, intramolecular migration of the sulfonyl group instead of allyl groups was described in the preparation of 3-sulfonyl indoles **195** (Scheme 160).[187] In this reaction, the authors studied the influence of different oxidation states of palladium salts in the migratory effect. It was found that the reaction of *N*-allyl-*N*-sul-



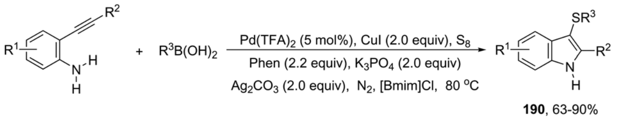
$R^1$= H, 5-Cl; $R^2$= $C_6H_5$, *n*-$C_4H_9$, $PhCH_2CH_2$, $BnOCH_2$; $R^3$=Ts, Ms.

Scheme 154



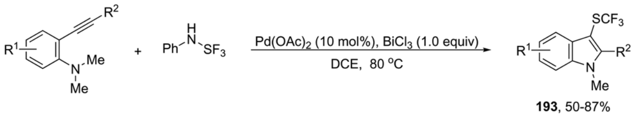
$R^1$ = H, 4-Cl, 4-Me; $R^2$ = $C_6H_5$, 2-Br-$C_6H_4$, 2-MeO-$C_6H_4$, 4-MeOC-$C_6H_4$, 2-thienyl, *n*-$C_6H_{13}$, *t*-Bu; $R^3$ = H, Me, Ac; $R^4$ = Me, $C_6H_5$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-Me$C_6H_4$, 4-MeO-$C_6H_4$, 2-$H_2N_2$-$C_6H_4$, 4-$O_2N$-$C_6H_4$.

Scheme 155



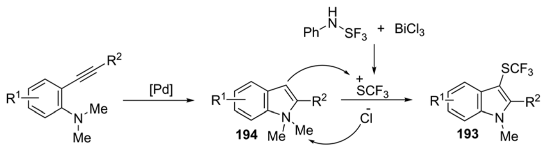
$R^1$ = H, 4-Me, 5-Me, 2,5(Me)$_2$, 4-MeO, 4-Cl, 5-Cl, 4,6-(Cl)$_2$, 4-Br, 4-$F_3C$, 4-$MeO_2C$; $R^2$ = 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-$O_2N$-$C_6H_4$, *n*-$C_3H_7$, *c*-$C_3H_5$, *n*-$C_4H_9$, *c*-$C_5H_9$, $C_5H_{11}$, *c*-$C_6H_{11}$, *c*-$C_5H_9CH_2$, *c*-$C_6H_{11}CH_2$, *c*-$C_6H_{10}$, 3-thienyl, $NC(CH_2)_2CH_2$; $R^3$ = 4-Cl-$C_6H_4$, 3,4-(Cl)$_2$-$C_6H_3$, 2-F-$C_6H_4$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 2-furyl.

Scheme 156

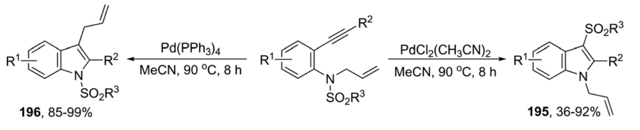


$R^1$ = H, 5-Cl, 5-F, 5-Me, 5-$EtO_2C$; $R^2$ = H, $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 2-MeO-$C_6H_4$, 4-$MeO_2C$-$C_6H_4$, *c*-$C_3H_5$, *n*-$C_4H_9$.

Scheme 158



Scheme 159



$R^1$ = 4-Cl, 4-F, 4-NC, 5-Br, 5-Me, 4-$F_3C$; $R^2$ = $C_6H_5$, c-$C_3H_5$, c-$C_6H_{11}$, n-$C_4H_9$, $AcO(CH_2)_2CH_2$, $Cl(CH_2)_2CH_2$; $R^3$ = Me, Et, $C_6H_5$.

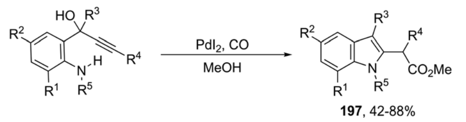
Scheme 160

fonyl-*ortho*-alkynylanilines with $Pd(PPh_3)_4$ led to the formation of 3-allylindoles **196**, with exclusive transference of the allyl group, whereas with $PdCl_2(CH_3CN)_2$ the sulfonyl group was selectively transferred, giving the 3-sulfonylindoles **195** (Scheme 160).

Moving the sequential aminopalladation reactions from functionalization of the 3-position to the 2-position of indoles, Gabriele and co-workers have described that 1-(2-aminoaryl) ynols, having a primary or secondary amino group, afforded indol-2-acetic esters **197** *via* a carbonylation reaction promoted by the $PdI_2$/KI catalytic system in the presence of CO, $O_2$ and MeOH (Scheme 161).[188] In addition, 1-(2-aminoaryl)ynols, having a primary amino group, gave quinoline-3-carboxylic esters, under oxidative conditions, *via* a 6-*endo-dig* cyclization.

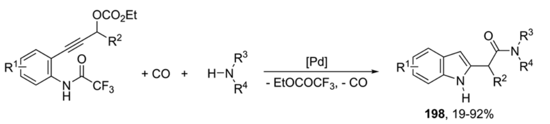
Cacchi and co-workers showed that the reaction of ethyl 3-(*ortho*-trifluoroacetamidoaryl)-1-propargyl carbonates with primary or secondary amines in the presence of $Pd_2(dba)_3$, dppf and carbon monoxide in THF at 80 °C afforded *NH*-indole 2-acetamides **198** (Scheme 162).[189] The authors found some limitations in the methodology when aniline and benzylamine were used as substrates, whereas the indole products were formed in trace amounts.

Cacchi and co-workers also demonstrated that $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ are effective at catalyzing the cyclization reaction of 3-(*ortho*-trifluoroacetamidoaryl)-1-propargyl alcohols and carbonate derivatives with amines to give 2-(aminomethyl) indoles **199** and **200**, respectively (Scheme 163).[190,191] This is a very useful procedure, which works well with primary and secondary amines, although primary amines give moderate yields.



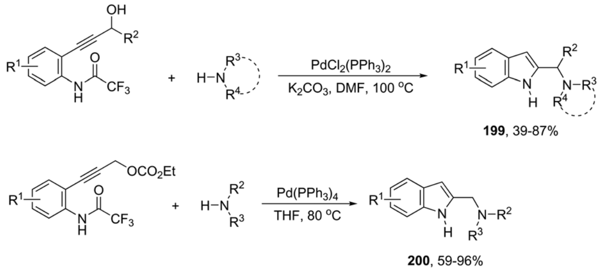
$R^1$ = H, MeO; $R^2$ = H, Cl; $R^3$ = Me, Ph; $R^4$= t-Bu, n-Bu, Ph,TMS; $R^5$ = H, Me.

Scheme 161



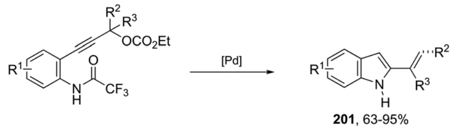
$R^1$ = 4-Cl, 4,5(F)$_2$, 4-$MeO_2C$; $R^2$ = H, Me, $C_6H_5$; amines= piperazine, morpholine, *tert*-butylamine, cyclohexylamine, pyrrolidine.

Scheme 162



$R^1$ = H, 4,6-(Me)$_2$, 4-F; $R^2$ = H, Me, $C_6H_5$; $R^3$ = H, alkyl; $R^4$ = alkyl.

Scheme 163



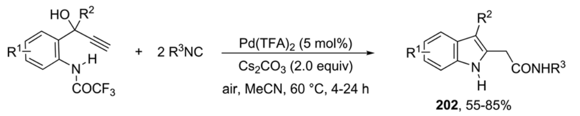
$R^1$ = H, 4,6-(Me)$_2$, 4-F; $R^2$ = H, Me, $C_6H_5$; $R^3$ = H, alkyl; $R^4$ = alkyl.

Scheme 164

The author justified that primary amines could cause competitive side reactions. When the palladium-catalyzed cyclization conditions were applied to ethyl 3-(*ortho*-trifluoroacetamidoaryl)-1-propargyl carbonates, bearing an alkyl substituent at the propargyl position, an elimination reaction occurred to form 2-vinylic indoles **201** instead of 2-(aminomethyl)indole derivatives (Scheme 164).

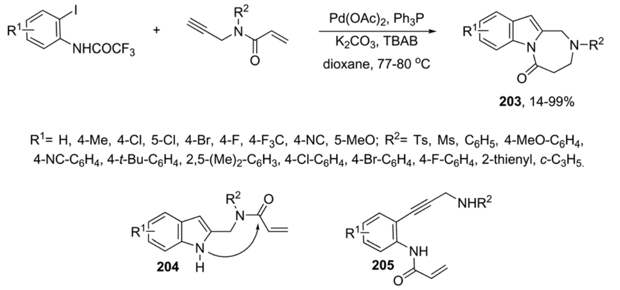
Results from the palladium-catalyzed cascade cyclization of (aminoaryl)propargyl alcohols and isocyanides showed that 2-indolylacetamides **202** were obtained in excellent yields, using $Pd(TFA)_2$ as the palladium source and MeCN as the solvent, under air atmosphere at 60 °C (Scheme 165).[192] Under these conditions, the intermolecular cycloaddition was successfully applied to a range of substrates, although hindered isopropyl isocyanide, phenyl isocyanide and internal alkynes were found to be unreactive, even after the prolonged reaction time and at elevated temperatures. The reaction is believed to proceed through a cascade that includes aminopalladation, isocyanide insertion, and 1,4-hydroxyl migration in which the two oxidation states of palladium promoted the activation and cyclization processes of each cycle without the use of oxidants.

For intermolecular functionalization of 2-position of indoles, an interesting study has recently been developed aiming at the synthesis of tetrahydro[1,4]diazepino[1,2-*a*]



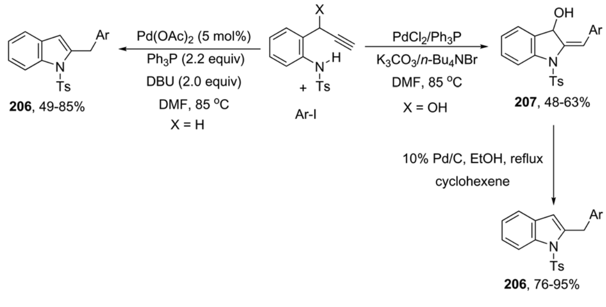
$R^1$= H, 4-Me, 5-Me, 4-Cl, 4-$O_2N$; $R^2$= $C_6H_5$, 2-F-$C_6H_4$, 4-F-$C_6H_4$, 2-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 2-MeO-$C_6H_4$; R3= t-Bu, t-$BuCH_2(Me)_2CH$.

Scheme 165



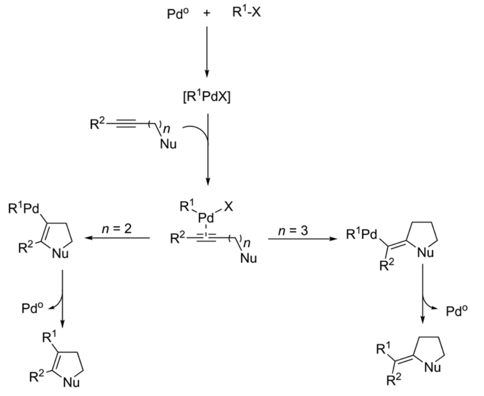
$R^1$= H, 4-Me, 4-Cl, 5-Cl, 4-Br, 4-F, 4-$F_3C$, 4-NC, 5-MeO; $R^2$= Ts, Ms, $C_6H_5$, 4-MeO-$C_6H_4$, 4-NC-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 2,5-$(Me)_2$-$C_6H_3$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 2-thienyl, *c*-$C_3H_5$.

Scheme 166

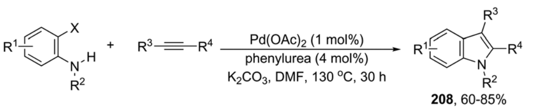


Ar = $C_6H_5$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-$MeO_2C$-$C_6H_4$, 4-$O_2N$-$C_6H_4$, 4-MeO-$C_6H_4$, 2-thienyl.

Scheme 167



Scheme 168



$R^1$ = H, 4-Me; $R^2$ = H, Me, Ac; $R^3$ = Me, Ph; $R^4$ = *n*-$C_3H_7$, $C_6H_5$, 2-MeO-$C_6H_4$; X= Br, Cl.

Scheme 169

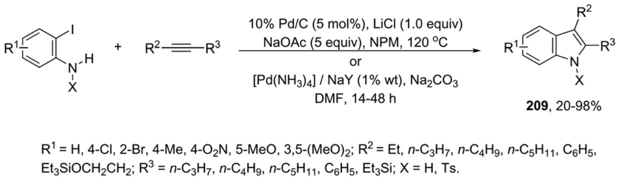
indoles **203** from 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamides and *N*-protected (prop-2-yn-1-yl)acrylamides (Scheme 166).[193] It was proposed that the cascade sequence, including the palladium-catalyzed Sonogashira coupling, indole cyclization, regio- and chemoselective *N*-acylation, and 1,4-Michael addition, is involved in obtaining the indole derivatives. The control experiments carried out by the authors indicated that indole **204** is the key intermediate for this cyclization. They discard the participation of intermediate **205**, formed *via* an intermolecular transamidation (Scheme 166).

The palladium-catalyzed cascade cyclization can be a useful alternative to other methods to access C2 functionalized indoles. For example, the (2-propynyl)anilines and (2-aminoaryl)propynols were applied as suitable substrates in the preparation of 2-arylmethylindoles. Chowdhury and coworkers found that in the presence of a palladium catalyst (2-propynyl)anilines and (2-aminoaryl)propynols demonstrated divergent reactivity. On the one hand, the reaction of (2-propynyl)anilines with aryl halides, catalyzed by $Pd(OAc)_2$, $PPh_3$ and DBU, led to the direct formation of 2-arylmethylindoles **206** in good yields in a single step (Scheme 167).[194] On the other hand, when (2-aminoaryl)propynols were used as substrates in the reaction with $PdCl_2$, $PPh_3$, $K_2CO_3$, and *n*-$Bu_4NBr$ in DMF, the products obtained were (arylmethylidene)indolinols **207**. The hydrogenolysis employing Pd/C and cyclohexene in refluxing ethanol afforded 2-arylmethylindoles **206** in a two-step reaction (Scheme 167).[195]

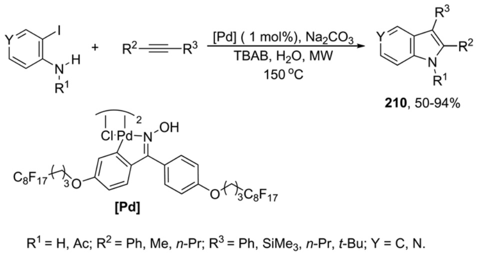
**2.10.3. Palladium-catalyzed annulation of internal alkynes.** The palladium-catalyzed annulation of internal alkynes by aryl halides, bearing a nucleophile at an appropriate distance, is a versatile way to generate a wide variety of heterocycles. When the nucleophile is a nitrogen atom located in the *ortho*-position of aryl halides, the substrates deliver the indole derivatives. This reaction normally involves the addition of aryl halides to a palladium(0) complex, with cleavage of the covalent carbon–halogen bond and oxidation of palladium(0) giving a sigma-organopalladium(II) halide complex. This palladium(II) species undergoes rapid insertion of a carbon–carbon bond of the alkynes to give the palladium(II) intermediate *via cis*-carbopalladation. The intramolecular nitrogen nucleophile attack induces the displacement of palladium(0), most likely by prior palladacycle formation and reductive elimination giving the indole (Scheme 168). This chemistry, originally developed by Larock,[31] has been an area of continuing expansion; for example a methodology using phosphine-free ligands to mediate palladium-catalyzed indolization of 2-bromoanilines with internal alkynes was developed.[196] Phenylurea was found to be an optional ligand, which together with $Pd(OAc)_2$ catalyzed the synthesis of 2,3-disubstituted indoles **208** in good yields with high regioselectivity (Scheme 169).

The use of a heterogeneous ligand and a salt-free procedure to prepare indoles was also described. In this reaction, *ortho*-haloanilines reacted with internal alkynes under Pd/C, $Na_2CO_3$, and DMF at 120 °C to afford the indole derivatives **209** (Scheme 170).[197–199] This catalytic system could be used under aerobic conditions, and successfully re-used at least for four cycles.

In an alternative method, indole derivatives **210** were efficiently prepared by palladium-catalyzed annulation of functionalized aryl iodides with internal alkynes in aqueous medium under microwave irradiation (Scheme 171).[200] Both



Scheme 170



Scheme 171

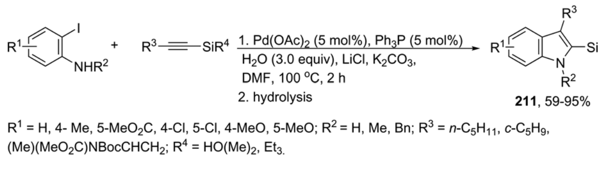
symmetrical and unsymmetrical internal alkynes bearing alkyl, aryl and silyl groups could be used as substrates for this cyclization. The annulation reactions exhibit excellent regioselectivity, where the most hindered group is located on the 2-position. The catalytic system was successfully recycled five times with a slight decrease in activity.

The alkynyldimethylsilyl *t*-butyl ethers reacted with *ortho*-iodoanilines, with excellent regioselectivity, to afford 2,3-disubstituted indoles **211** (Scheme 172).[201] The regioselectivity depends mainly upon the bulkier *t*-butoxysilyl ether substituent on the alkynes, whereas migratory insertion could occur to minimize the steric strain. In addition, the triethylsilyl propargyl glycine derivatives were coupled with *ortho*-iodoanilines, catalyzed by $Pd(OAc)_2$ and $PPh_3$, providing useful access to *N*-ethyl-D-tryptophans.[202]

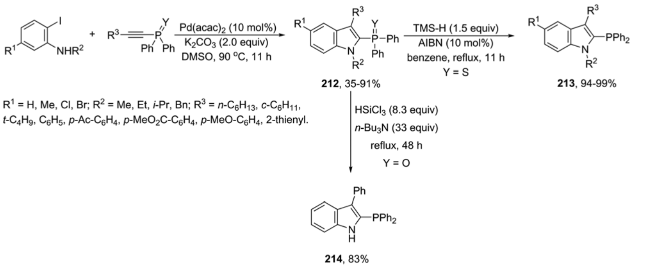
Palladium-catalyzed annulation of 1-alkynylphosphine sulfides with *ortho*-iodoanilines gave the corresponding 2-indolylphosphine sulfides **212**, which could be easily reduced to the corresponding trivalent phosphines **213** in the presence of tris-(trimethylsilyl) silane and a catalytic amount of AIBN. With the parent 1-alkynylphosphine oxides, the palladium-mediated cyclization gave, exclusively, the 2-indolylphosphine oxide derivatives, which were reduced to the trivalent phosphine **214** by treating with trichlorosilane and tributylamine (Scheme 173).[203]

The reaction of ethynyloxazolidinones with *ortho*-iodoanilines, under Larock's heteroannulation conditions, produced optically active 2-silyl-3-indolylglycine derivatives **215**, which can be induced to undergo a desilylation reaction resulting in 3-indolylglycine **216** (Scheme 174).[204] Treatment of ethynyloxazolidinones and *ortho*-iodo-*N*-Ts-anilines with $Pd(OAc)_2$, LiCl, $Na_2CO_3$, and DMF at 90 °C promoted the cyclization to give **215**. In contrast, the reaction with $Pd(OAc)_2$, $PPh_3$, $n$-$Bu_4Cl$, DIPEA, and DMF at 90 °C afforded **217**.

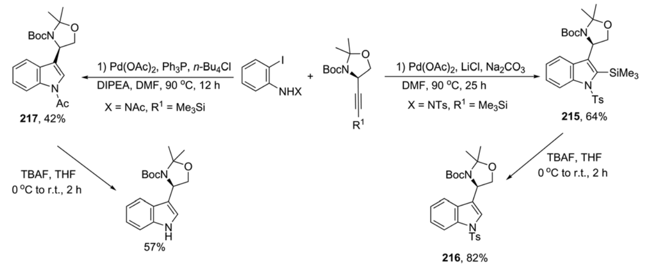
The generation of indoles *via* palladium-catalyzed three- or four-component coupling of aryl iodides, alkynes, and amines has also been described. In a one-pot protocol, the treatment of *N*-substituted-*ortho*-iodoanilines, alkynes and amines with $Pd(OAc)_2$, cyclopentadiene–phosphine, and *t*-BuOLi, led to the desired indole derivatives **218** (Scheme 175).[205] These conditions could be efficiently applied to a variety of *ortho*-iodoanilines, symmetric and unsymmetric alkynes, and cyclic and acyclic amines. The author argues that the cleavage of the $C(sp^3)$–N bond on the intermediate **219** is the key step for the formation of desired products. After this cleavage step, the reaction could follow two pathways as illustrated in Scheme 176. The same research group also described that the indole-containing alkyl iodides **220** were obtained in the absence of amines, where palladium promoted $C(sp^3)$–I bond



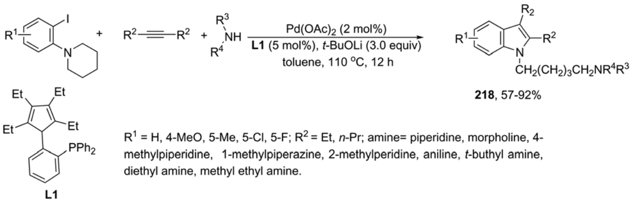
Scheme 172



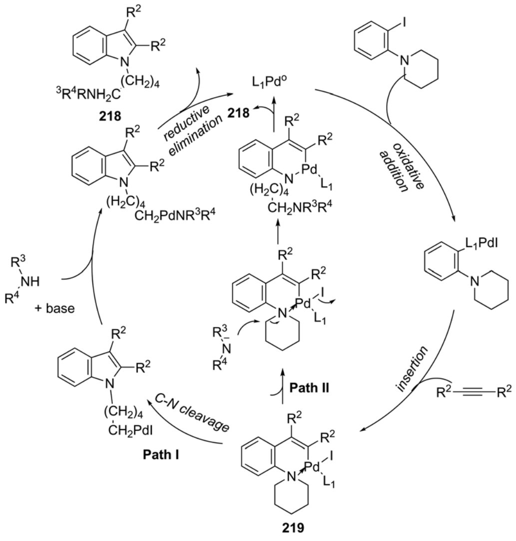
Scheme 173



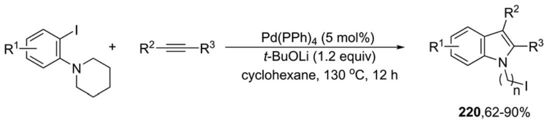
Scheme 174



Scheme 175



Scheme 176

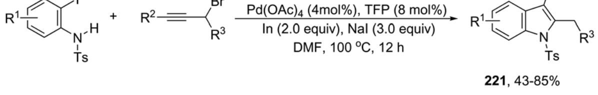


R$^1$ = H, 5-Me, 5-F; R$^2$ = Me, Et, *n*-Pr, C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$, 2-thienyl, 3-thienyl;
R$^3$ = Et, *n*-Pr, TMS, C$_6$H$_5$, 4-F-C$_6$H$_4$, 2-thienyl, n = 4, 5.

Scheme 177

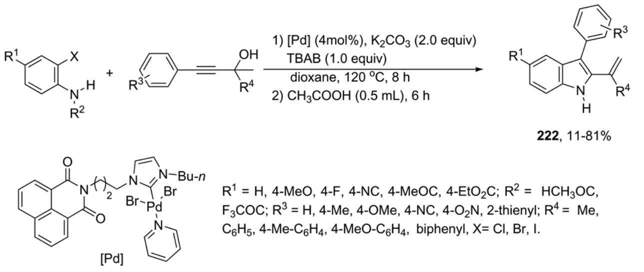
formation *via* reductive elimination instead of *syn*-β-hydride elimination (Scheme 177).[206] The authors observed that the use of Pd(π-allyl)Cp instead of Pd(OAc)$_2$ facilitated the C(sp$^3$)–I for the reductive elimination process.[207]

An important improvement in Larock's indole synthesis was accomplished by the application of propargyl bromides as alkyne sources. In this methodology, the palladium(0)-catalyzed one-pot reaction of *N*-Ts or *N*-Ms *ortho*-iodoanilines and propargyl bromides afforded indoles **221** (Scheme 178).[208] It was assumed that the reaction involves the carbon–carbon bond coupling forming allenes and azapalladation. The substituent group of the nitrogen atom greatly influenced the reaction. The *N*-Ts- and *N*-Ms-substituted *ortho*-iodoanilines gave the corresponding indoles in good yields; however, *N*-*p*-Ns-substituted 2-iodoaniline (*p*-Ns = 4-nitrobenzenesulfonyl) afforded a trace amount of indole products.



R$^1$ = H, 4-Cl, 4-Br, 4-F, 4-MeO, 5-Cl; R$^2$ = H, Me, *n*-Pr, *n*-Bu, allyl, cinnamyl, C$_6$H$_5$, 4-MeO-C$_6$H$_4$;
R$^3$ = H, Et.

Scheme 178



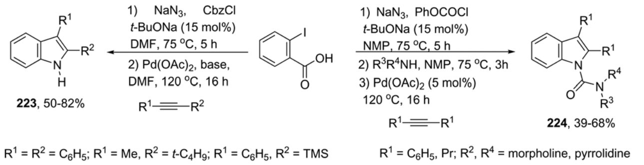
R$^1$ = H, 4-MeO, 4-F, 4-NC, 4-MeOC, 4-EtO$_2$C; R$^2$ = HCH$_3$OC, F$_3$COC; R$^3$ = H, 4-Me, 4-OMe, 4-NC, 4-O$_2$N, 2-thienyl; R$^4$ = Me, C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, biphenyl, X= Cl, Br, I.

Scheme 179

Expanding upon the use of alkynes in the Larock indole synthesis, very recently, the palladium(II)/N-heterocyclic naphthalimide carbene complex heteroannulation of tertiary propargyl alcohols with *ortho*-haloanilines, resulting in the formation of 2-alkenylindoles **222**, has been reported (Scheme 179).[209] A single regioisomer was obtained and this high regioselectivity was attributed to the coordination of the palladium catalyst to the propargyl hydroxyl moiety during the palladium insertion step. In addition, the authors concluded through experimental evidence that the *in situ* generation of HBr is the promotor of terminal double bond formation by a dehydration process. Moreover, the presence of naphthalimide units of the NHC was crucial for the success of the catalytic process.

*ortho*-Iodobenzoic acid has also been studied under palladium-catalyzed annulation conditions. Under these conditions, *ortho*-iodobenzoic acid was converted to indole derivatives **223** by a one-pot Curtius rearrangement[210]/palladium-catalyzed indolization process (Scheme 180).[211] In this synthetic strategy, the *ortho*-iodoaniline and sodium chloride, which are essential for the cyclization, are produced *in situ* as by-products of the Curtius rearrangement. In addition, when an acylating agent was added under the reaction conditions, indole *N*-carboxamide derivatives **224** were produced (Scheme 180).

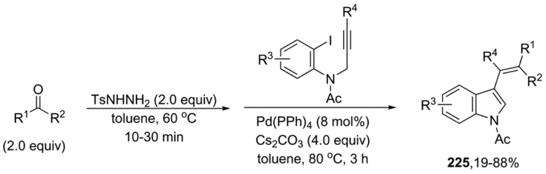
The intramolecular palladium-catalyzed annulation reactions have also been employed in the generation of indole systems. In this case, when *N*-acetyl-*N*-(3-phenylpropynyl)-2-iodoanilines reacted with *N*-tosylhydrazones in the presence of the Pd(PPh$_3$)$_4$ catalyst and Cs$_2$CO$_3$ in toluene at 80 °C, the 3-vinylindoles **225** were obtained in good yields (Scheme 181). These reaction conditions led to the desired 3-vinylindoles **225** *via* carbon–carbon single bond and carbon–carbon double bond formation in a one-step operation. The authors suggested that the migratory insertion of palladium carbene



R$^1$ = R$^2$ = C$_6$H$_5$; R$^1$ = Me, R$^2$ = *t*-C$_4$H$_9$; R$^1$ = C$_6$H$_5$, R$^2$ = TMS

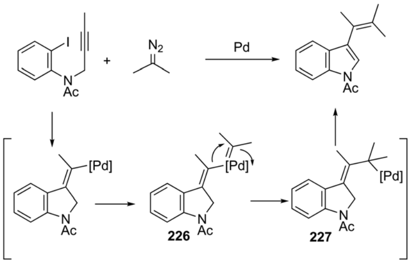
R$^1$ = C$_6$H$_5$, Pr; R$^2$, R$^4$ = morpholine, pyrrolidine

Scheme 180



$R^1 = C_6H_5$, 4-Me-$C_6H_4$, 4-MeO$C_6H_4$, 3-F-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 2,6(Me)$_2$-$C_6H_3$, pyridin-3-yl, 2-naphthyl; $R^2$ = H, Me, $C_6H_5$; $R^3$ = H, 4-Cl, 4-Br, 5-F; $R^4$ = H, $C_6H_5$.

Scheme 181



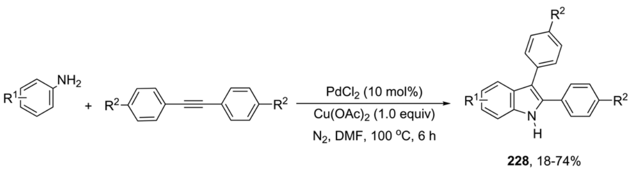
Scheme 182

**226** to form the intermediate **227**, followed by β-hydride elimination, are the principal steps of the cyclization (Scheme 182).

**2.10.4. Indoles *via* palladium-catalyzed carbon–hydrogen activation.** Palladium-catalyzed $Csp^2$–H bond activation has been recognized as an attractive tool in synthetic organic chemistry for carbon–hydrogen functionalization.[131] The use of this concept has been considered by synthetic researchers in the preparation of indoles from alkynes. For example, palladium-catalyzed intermolecular cyclization of anilines and symmetrical diarylalkynes afforded 2,3-diarylindoles **228** or pyrrole derivatives (Scheme 183).[212] Unsymmetrical diarylalkynes gave a mixture of indoles with no regioselectivity. The choice of solvents governed the product distribution, in which the reaction carried out in DMF gave the indoles, whereas the use of 1,4-dioxane as the solvent resulted in pyrrole formation.

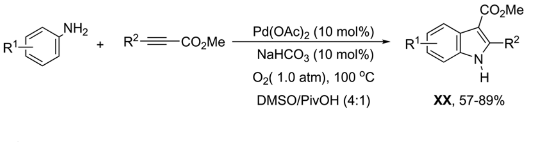
A high regioselectivity was achieved when unsymmetrical electron-deficient alkynes, such as methyl perfluoroalk-2-ynoates, were used in the sequential Michael-type addition and palladium(II)-catalyzed cross-dehydrogenative coupling in the preparation of 2-(perfluoroalkyl)indoles **229** (Scheme 184).[213] After an electrophilic palladation and deprotonation of the nucleophilic enamine, generated by Michael-type addition of aniline and the alkyne, the palladium intermediate **230** is formed. The electrophilic aromatic palladation, followed by reductive elimination from intermediate **231**, gives the desired indole (Scheme 185). The presence of $O_2$ and an acid are crucial to regenerate the active catalyst in the cycle.

A similar strategy based on the direct carbon–hydrogen activation using oxygen as the oxidant was applied to regioselective reactions of anilines and internal alkynes in the preparation of indole derivatives **232** (Scheme 186).[214] Because the oxidant plays an essential role in the catalytic cycle of the carbon–hydrogen activation, the authors performed a complete study to determine the activity of various oxidants, such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, and BQ. The authors indicated dioxygen as an ideal oxidant. Under the optimal reaction conditions, the scope of the reaction was applied to anilines having electron-withdrawing or electron-donating groups and electron-deficient alkynes, and it proceeded efficiently giving



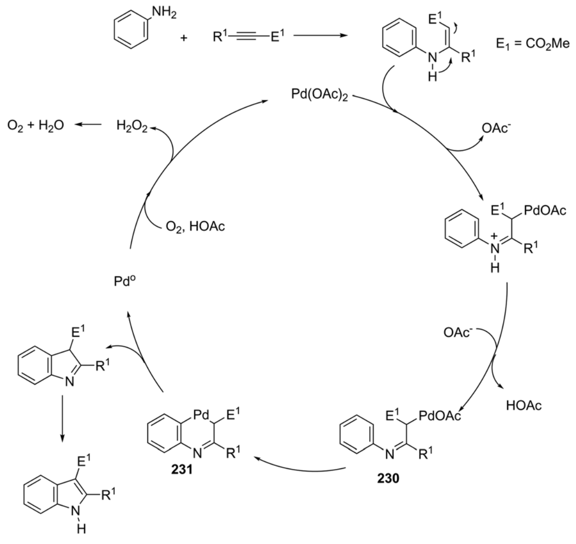
$R^1$ = H, 2-Me, 3-Me, 4-Me, 4-MeO, 2-Cl, 3-Br, 4-Br,4-F; $R^2$ = H, 4-Me, 4-MeO, 4-Br, 4-F, 4-MeOC.

Scheme 183

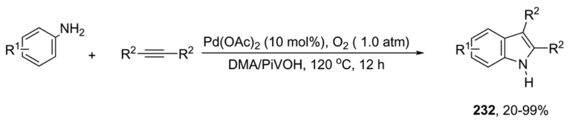


$R^1$ = H, 3-Cl, 4-Cl, 5-Cl, Cl, 6-Cl, 3-Me, 2,6(Me)$_2$, 4-MeO, 4-$F_3$CO, 4-Et$O_2$C, 4-MeOC;
$R^2$ = $F_3C$, $C_2F_5$, n-$C_3F_7$.

Scheme 184



Scheme 185



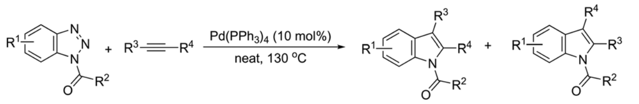
$R^1$ = 4-Cl, 4-F, 4-Me, 6-Me, 5-i-Pr, 4-c-Hex, 4-MeO, 6-MeO, 4,6-(MeO)$_2$, 3,6-(MeO)$_2$, 4,5-(MeO)$_2$, 4-$F_3$CO, 4-Et$O_2$C, 4-HO, indoline, 2-methyl-indoline, tetrahydroquinoline;
$R^2$ = Me$O_2$C, Et$O_2$C, i-Pr$O_2$C.

Scheme 186

the indoles in moderate to excellent yields. Additional reactions demonstrated that the carbon–hydrogen activation is not a reversible reaction and that hydroamination occurs before reductive elimination.

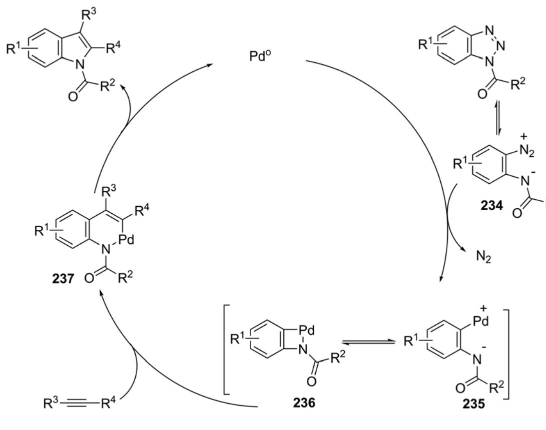
The use of *N*-acylbenzotriazoles to replace *ortho*-haloanilides in the preparation of indoles, *via* palladium-catalyzed annulation reactions, has also been reported. In the palladium-catalyzed dehydrogenative indolization sense, *N*-aroylbenzotriazoles reacted with disubstituted alkynes under $Pd(PPh_3)_4$, in the absence of a solvent at 130 °C to afford the corresponding polysubstituted indoles **233** in good to high yields (Scheme 187).[215] Under these conditions, although asymmetric alkynes gave a mixture of regioisomers, the indoles having a bulkier substituent at the 2-position were obtained as major products. The reaction is believed to occur *via* an initial thermal isomerization of the benzotriazole, giving the corresponding 2-iminobenzenediazonium species **234**. The oxidative addition of the diazonium moiety to palladium(0) leads to intermediate **235** or **236**, which delivers the palladacycle species **236** after insertion of the alkyne. The reductive elimination of palladium(0) from **237** produces the corresponding indoles (Scheme 188).

The use of *N*-acetyl anilines in the palladium carbon–hydrogen activation is an efficient method for the preparation of indoles. In this case, the acetyl group can act as a directing group and the nitrogen atom source for indole cyclization. Thus, the reaction of *N*-aryl amides with internal alkynes catalyzed by $Pd(OAc)_2$ in DMA, using $Cu(OTf)_2$ and $Ag_2O$ as oxidants, gave indoles **238** (Scheme 189).[216] The author also showed that the cyclopalladated complex **239** is the key intermediate of this cyclization and its stoichiometric reaction with internal alkynes in the presence of bipyridine and DMF at 120 °C led also to the formation of indoles in moderate yields.

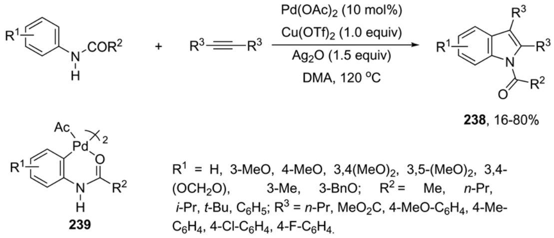


$R^1$ = H, Me, MeO, NC; $R^2$ = Me, EtO, $C_6H_5$, 3,5-$(F_3C)_2$-$C_6H_3$, 4-$F_3C$-$C_6H_4$, 3,5-$F_2$-$C_6H_3$, 4-Ac-$C_6H_4$, 3-F-$C_6H_4$, 4-MeO-$C_6H_4$; $R^3$ = Cy, *t*-Bu, $C_6H_5$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$; $R^4$ =H, Me, *n*-$C_5H_{11}$, *n*-$C_4H_9$.

Scheme 187

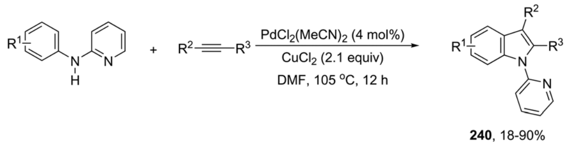


Scheme 188



$R^1$ = H, 3-MeO, 4-MeO, 3,4$(MeO)_2$, 3,5-$(MeO)_2$, 3,4-$(OCH_2O)$, 3-Me, 3-BnO; $R^2$ = Me, *n*-Pr, *i*-Pr, *t*-Bu, $C_6H_5$; $R^3$ = *n*-Pr, $MeO_2C$, 4-MeO-$C_6H_4$, 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$.

Scheme 189

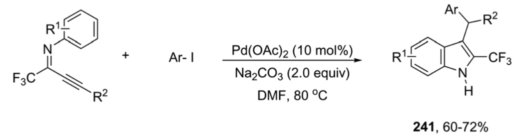


$R^1$ = H, 4-Me, 2-Me, 4-*t*-Bu, 2-MeO, 3-MeO, 4-MeO, 4-Cl, 4-F, 2-Ph, 3,4$(OCH_2O)$; $R^2$ = $R^3$ = *n*-Pr, $C_6H_5$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 2-thiophenyl; $R^2$ = $C_6H_5$ and $R^3$ = Me; $R^2$ = $C_6H_5$ and $R^3$ = *n*-Pr; $R^2$ = 2-thiophenyl and $R^3$ = *n*-Pr.

Scheme 190

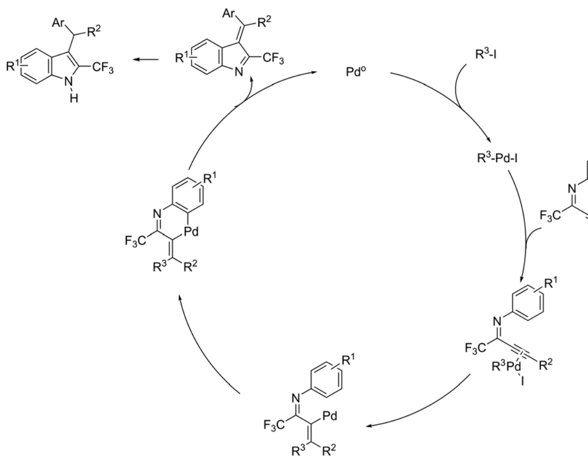
In order to extend the application of different *N*-aryl compounds as substrates for palladium-catalyzed direct functionalization of carbon–hydrogen bonds, *N*-aryl-2-aminopyridines were reacted with internal alkynes under catalysis by $Pd(MeCH_3)_2Cl_2$, using $CuCl_2$ as an oxidant, resulting in the direct formation of *N*-(2-pyridyl)indoles **240** (Scheme 190).[217] When the reaction conditions were applied to internal alkynes, bearing an alkyl chain directly bonded to the carbon–carbon triple bond, a mixture of two regioisomers was obtained. On the other hand, unsymmetrically heteroaryl- and alkyl-substituted alkynes gave the corresponding indoles as a single isomer. The authors attributed the selectivity of the cyclization to the electronic and steric differences between the substituent groups. They also found that the reaction was sensitive to the steric bulk around the pyridine nitrogen and in the *N*-aryl ring and favored by electron-withdrawing groups in the *N*-aryl ring. Wu and co-workers[218] have extended the scope of this reaction using the system palladium/cerium(IV) oxide and $CuCl_2$ in the cyclization of aryl-2-aminopyridines with unsymmetrically aryl- and alkyl-substituted alkynes. *N*-(2-Pyridyl)indoles were obtained in excellent yields and very similar results were obtained for the selectivity, whereas the major product was the indole having the alkyl group at the 3-position.

Alkynylimines have been also employed as substrates in the palladium-catalyzed synthesis of 2-fluoroalkyl-3-methyleneindoles **241** *via* a domino carbopalladation/carbon–hydrogen activation procedure (Scheme 191). In order to find the suitable reaction conditions, the authors studied the influence of palladium salts, bases and solvents in this reaction. After the optimization, the best reaction conditions were established as $Pd(OAc)_2$ and $Na_2CO_3$ in DMF at 80 °C. According to the



$R^1$ = H, MeO; $R^2$ = $C_6H_5$, $n$-$C_4H_9$; $C_6H_5$, 4-Me-$C_6H_4$.

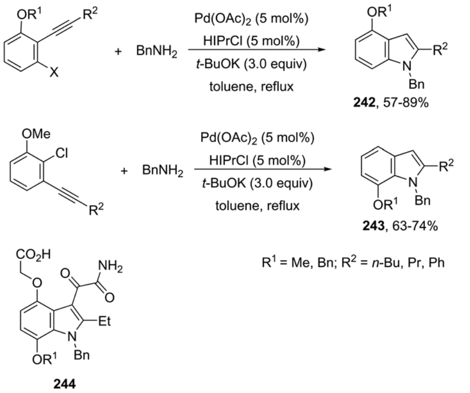
Scheme 191



Scheme 192

authors, the carbon–carbon triple bond of alkynylimines could be activated by the arylpalladium(II) species formed by the oxidative addition of palladium(0) with aryl iodide. The *syn* carbopalladation, followed by carbon–hydrogen activation of alkynylimines, gave a six-membered palladacycle, which after reductive elimination afforded the indoles (Scheme 192).

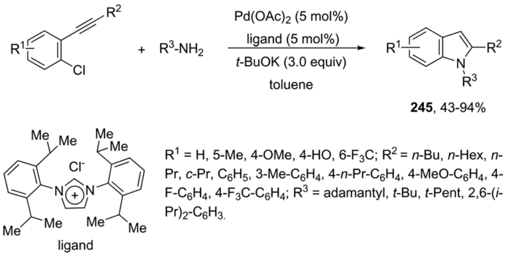
**2.10.5. Indoles *via* a palladium-catalyzed *N*-arylation/hydroamination sequence.** The present section deals with the application of the palladium-catalyzed *N*-arylation hydroamination sequence-type reactions involving aryl halides, alkynes and amines in the preparation of indoles. The reaction pathway for this sequence, in general, involves a consecutive palladium-catalyzed carbon–nitrogen bond formation with a $sp^2$-hybridized carbon, followed by the hydroamination of carbon–carbon triple bonds to promote the cyclization in a 5-*endo-dig* mode. As an example, the reaction of *ortho*-alkynyl-3-halophenyl ethers and *meta*-alkynyl-2-halophenyl ethers with benzylamine under $Pd(OAc)_2$, 1,3-bis-(2,6-diisopropylphenyl) imidazolium chloride (HIPrCl) as the catalyst, in toluene under reflux, and with *t*-BuOK as a base, afforded the alkoxy-*N*-benzyl-2-substituted indoles **242** and **243** *via* a tandem amination/cyclization reaction (Scheme 193).[219] The authors observed a limitation in this protocol when an unprotected hydroxy 2-chloro-3-(phenylethynyl)phenol derivative was used as the substrate. In this case, a 7-hydroxyindole derivative could not be obtained, although, the starting material was completely consumed. This approach has been also utilized for the synthesis of an indole inhibitor of phospholipase A2 **244** that is a secreted phospholipase, found at high levels in patients suffering from inflammatory diseases.



Scheme 193

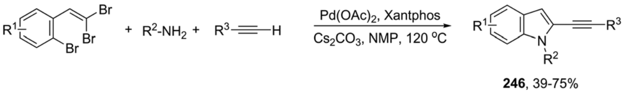
The palladium-catalyzed *N*-arylation/hydroamination sequence can be also performed with bulky alkyl amines. The palladium complex derived from an N-heterocyclic ligand was applied in the reaction of sterically hindered amines with *ortho*-alkynylhaloarenes in the preparation of sterically hindered *N*-substituted indoles **245** (Scheme 194).[220,221] The authors found that the association of $Pd(OAc)_2$ with a sterically hindered unsaturated imidazolium salt gave the best catalytic system, affording the indole derivatives in moderate to high yields. This protocol tolerated *ortho*-alkynylchloroarenes, 1-adamantylamine, and *t*-butylamine, and hindered less nucleophilic anilines.

2-Alkynyl indoles **246** could be synthesized in a one pot procedure from *ortho*-bromo-(2,2-dibromovinyl)benzenes, terminal alkynes, and arylamines *via* a palladium-catalyzed three-component coupling process (Scheme 195).[222] In this reaction, the three reagents were added at the same time in the reaction system, showing a very high chemical selectivity. Important results were obtained in the studies of the reaction mechanism, for example when the reaction was carried out in the



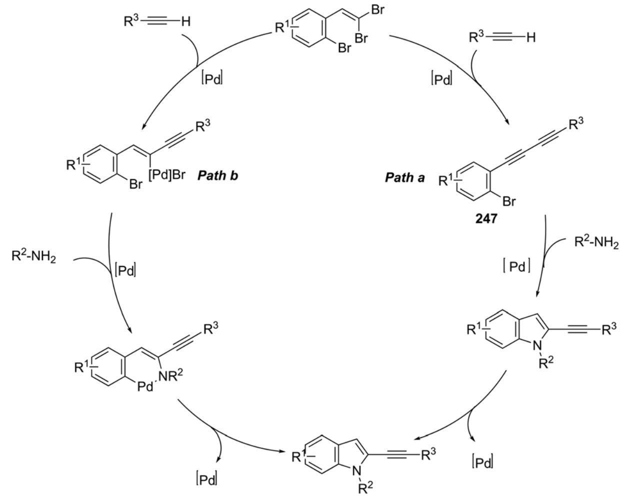
$R^1$ = H, 5-Me, 4-OMe, 4-HO, 6-$F_3C$; $R^2$ = $n$-Bu, $n$-Hex, $n$-Pr, $c$-Pr, $C_6H_5$, 3-Me-$C_6H_4$, 4-$n$-Pr-$C_6H_4$, 4-MeO-$C_6H_4$, 4-F-$C_6H_4$, 4-$F_3C$-$C_6H_4$; $R^3$ = adamantyl, $t$-Bu, $t$-Pent, 2,6-($i$-Pr)$_2$-$C_6H_3$.

Scheme 194



$R^1$ = H, 4-Me, 5-F; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 2-MeO-$C_6H_4$, 4-MeO-$C_6H_4$, 4-F-$C_6H_4$, 4-$O_2N$-$C_6H_4$;
$R^3$ = $C_6H_5$, 4-$F_3C$-$C_6H_4$, 3-MeO-$C_6H_4$, 3-thienyl, 2-pyridyl.

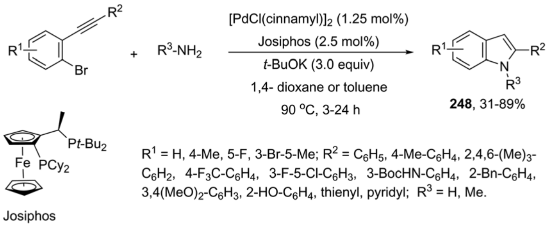
Scheme 195



Scheme 196

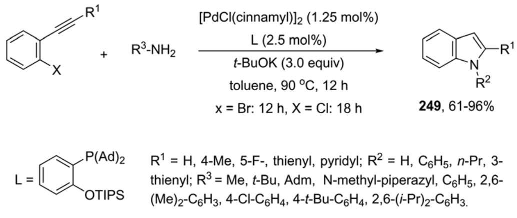
absence of aniline, the 1,3-diyne **247** was obtained (Scheme 196). In addition, when **C** was reacted with aniline, under optimized reaction conditions, the corresponding 2-alkynyl indole was obtained in 65% yield. These last two experiments indicated that the reaction could follow the pathway shown in Scheme 196.

Ammonia has been used as the nitrogen source in the synthesis of 2-arylindoles **248** from *ortho*-alkynylbromoarenes through a tandem cross-coupling/alkyne amination sequence (Scheme 197).[223] The authors carried out a serious study aiming to find a suitable ligand to participate together with the palladium salt as a catalyst of this reaction. They found the best results by using [Pd(cinnamyl)Cl]$_2$ and Josiphos, delivering the indoles in 31–89% yields. They also found that heterocyclic substrates with the heteroatom *ortho* to the bromo or alkyne group and alkynes having silyl, alkyl, or alkenyl groups did not give the products. However, when ammonia was replaced with methylamine, the corresponding *N*-methyl indoles were obtained in good yields. In order to extend the above methodology, the same group found that (silanyloxyphenyl)phosphines were efficient ligands for palladium-catalyzed carbon–nitrogen cross-coupling/cyclization of *ortho*-alkynylhaloarenes with primary amines affording 2-substituted indole derivatives **249** (Scheme 198).[224] Catalytic amounts of [Pd(cinnamyl)Cl]$_2$ and (silanyloxyphenyl)phosphine, in the presence of *t*-BuOK and toluene, were able to promote the cyclization of *ortho*-alkynylhaloarenes bearing alkyl, aryl, and heteroaryl groups with hindered and unhindered aryl amines, including those having electron-donating and electron-withdrawing substituents, to afford indoles containing alkyl, aryl, and heteroaryl substituents at the C2 position.



$R^1$ = H, 4-Me, 5-F, 3-Br-5-Me; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 2,4,6-(Me)$_3$-$C_6H_2$, 4-$F_3C$-$C_6H_4$, 3-F-5-Cl-$C_6H_3$, 3-BocHN-$C_6H_4$, 2-Bn-$C_6H_4$, 3,4(MeO)$_2$-$C_6H_3$, 2-HO-$C_6H_4$, thienyl, pyridyl; $R^3$ = H, Me.

Scheme 197



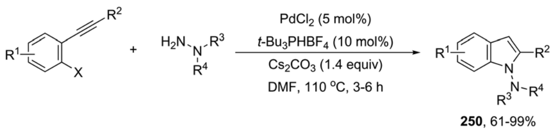
$R^1$ = H, 4-Me, 5-F-, thienyl, pyridyl; $R^2$ = H, $C_6H_5$, *n*-Pr, 3-thienyl; $R^3$ = Me, *t*-Bu, Adm, N-methyl-piperazyl, $C_6H_5$, 2,6-(Me)$_2$-$C_6H_3$, 4-Cl-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 2,6-(*i*-Pr)$_2$-$C_6H_3$.

Scheme 198

*N*,*N*-Disubstituted hydrazines were also used as the nitrogen source in the palladium catalyzed cross-coupling/alkyne amination reaction with *ortho*-alkynylhaloarenes providing a useful method for the synthesis of substituted 1-aminoindoles **250** (Scheme 199).[225] For this cyclization, it was proposed that an initial palladium catalyzed coupling between the *ortho*-alkynylhaloarenes and hydrazines gives *ortho*-alkynylhydrazine, which after an alkyne amination reaction affords the *N*,*N*-disubstituted-1-aminoindole *via* 5-*endo-dig* cyclization (Scheme 200).

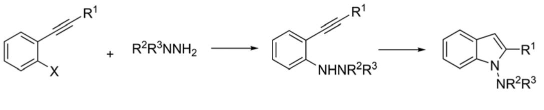
Using *t*-butyl sulfonamide is a useful method for introducing nitrogen-containing moieties in the palladium catalyzed cross-coupling/alkyne amination reaction.[226] In this case, the *t*-butyl sulfonamide, under appropriate conditions, is a suitable ammonia source. Thus, the reaction of *t*-butyl sulfonamides with *ortho*-alkynylbromoarene, in the presence of Pd(OAc)$_2$/Xantphos/$Cs_2CO_3$ as the catalytic system in 1,4-dioxane at 110 °C, gave the 2-aryl-indoles **251** from 71 to 90% yields (Scheme 201).

In the amination reaction of *ortho*-haloaryl alkynyl bromides, amines and amides reacted with high selectivity in Csp instead of Csp$^2$ leading to *o*-haloaryl-substituted ynamides that can be useful in the construction of 2-amido indoles **252**

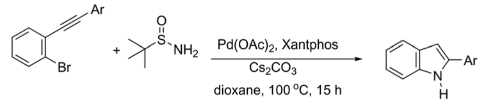


$R^1$ = H, 6-F, 5-$F_3C$, 6-MeO; $R^2$ = *c*-$C_3H_5$, *n*-$C_5H_{11}$, *t*-$C_4H_9$, *t*-$BuOCH_2$, *t*-$BuO_2C$, $C_6H_5$, 4-$F_3F$-$C_6H_4$, pyridyl; $R^3$ = Boc, $EtO_2C$, Me; $R^4$ = Ph; $R^3$ , R4 = pyrrolidine, morpholine, N-methyl-piperazyl, pyrroyl; X = Cl, Br

Scheme 199



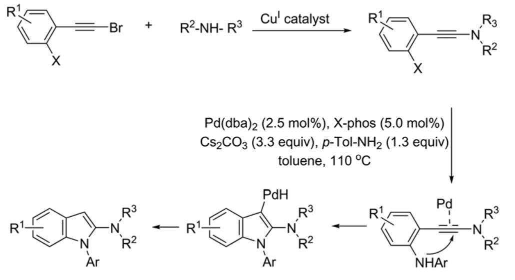
Scheme 200



**251**, 71-90%

Ar = $C_6H_5$, 4-MeO-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 4-F-$C_6H_4$, 4-CN-$C_6H_4$, 4-piperidinyl-$C_6H_4$, 4-$MeO_2C$-$C_6H_4$, 4-$F_3CO$-$C_6H_4$, $EtO_2C$-$C_6H_4$.

Scheme 201



**252**, 60-91%

$R^1$ = 6-Cl-$C_6H_4$, 6-Br-$C_6H_4$, 3-Me-6-Br-$C_6H_3$, 3,4(Me)$_2$-6-Br-$C_6H_2$, 3-$MeO_2C$-6-Cl-$C_6H_3$, 4-$MeO_2C$-6-Br-$C_6H_3$; $R^2$, $R^3$ = oxazolidinone; $R^2$ = Bn and $R^3$ = Me; $R^2$ = Ts and $R^3$ = $TBSOCH_2CH_2$; X = Cl, Br, I

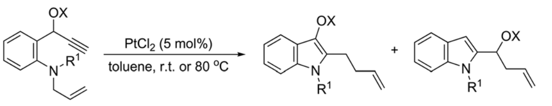
Scheme 202

(Scheme 202).[227] Specifically, *ortho*-haloarylynamides reacted with *p*-Tol-$NH_2$ under catalysis of $Pd_2(dba)_3$, in the presence of X-phos as a ligand, giving 2-amido-indoles in high yields. In these studies, the authors concluded that other phosphine ligands were ineffective and that aryl chlorides and bromides were better suited in this cyclization than aryl iodides.

### 2.11. Platinum-catalyzed synthesis of indoles

Platinum-based catalysts have attracted considerable attention in transition metal catalysis for participating in various transformations in organic chemistry; however, their applications in the preparation of indoles have been limited. Recent reports demonstrated growing interest in this area, and platinum(II) salts have proven to be excellent catalysts for the cyclization of 2-propargyl anilines to give 3-alkoxyindoles **253** (Scheme 203).[228] The reaction conditions and the substituent at the propargyl position and at the nitrogen atom had a dramatic influence on the course of the $PtCl_2$-catalyzed cycloisomerization. For example, when the reaction was carried out at room temperature, the indole **253** was obtained exclusively, whereas on increasing the temperature to 80 °C the reaction gave the indole adduct **254**.

Indole carbamates, indole ureas and indole phosphoranes **255** were prepared by a platinum-catalyzed Hofmann-type rearrangement of *ortho*-alkynylbenzamides and *ortho*-alkynylbenzylamides. The reaction occurred *via* a nucleophilic addition of alcohols and amines to the isocyanate intermediates, followed by an intramolecular aminocyclization (Scheme 204).[229,230]

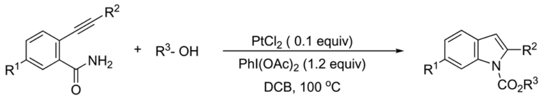


$R^1$ = Me, Allyl, Bn; X = Ac, Me.

**253**, 19-94%

**254**, 13-60%

Scheme 203



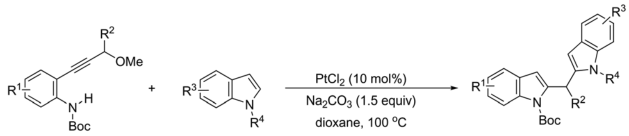
**255**, 33-100%

$R^1$ = H, F, $O_2N$, MeO; $R^2$ = H, *n*-$C_4H_9$, $C_6H_5$, 4-Me-$C_6H_4$, TMS; $R^3$ = Et, Bn, *t*-Bu.

Scheme 204

Another important development in the functionalized indole synthesis is the platinum-catalyzed tandem annulation/arylation reaction. Diindolylmethanes **256** were prepared using propargyl ethers and substituted indoles *via* a platinum-catalyzed tandem indole annulation/arylation cascade (Scheme 205).[231] The electrophilic platinum carbene intermediate was proposed to be the key intermediate in this cascade reaction. This tandem reaction was also attempted using β-dicarbonyl compounds as nucleophiles in the preparation of 2-substituted indoles **257** (Scheme 206).[232] The reaction generated α,β-unsaturated carbene intermediates *via* an intramolecular nucleophilic addition into alkynes bearing propargyl ethers, followed by vinylogous nucleophilic additions using enol as the nucleophile.

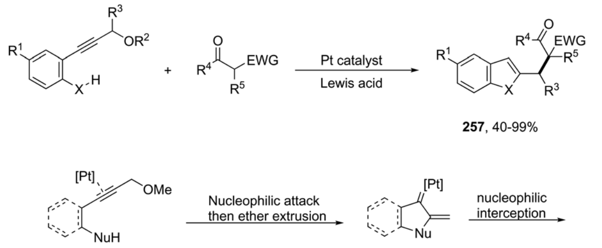
A sequential platinum-catalyzed cyclization/intermolecular addition was performed for the preparation of 2,3-disubstituted indoles **258** (Scheme 207). The reaction involved *ortho*-alkynylanilines with ethyl propiolate, dimethyl acetylene-



**256**, 55-88%

$R^1$ = H, 4-MeO, 4-$EtO_2C$, 4-$HOH_2C$; $R^2$ = H, Me; $R^3$ = H, 3-NC, 4-MeO, 3-Br, 4-Br, 3-Cl, 4-Cl; $R^4$ = H, Me, Boc.

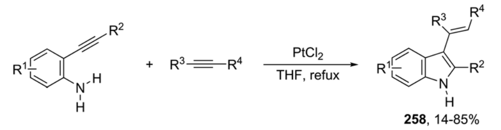
Scheme 205



**257**, 40-99%

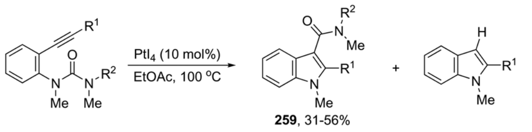
$R^1$ = H, MeO, $O_2N$; $R^2$ = Me, Bn; $R^3$ = H, Me, Et; $R^4$ = Me, Ph, EtO; $R^5$ = H, Me, Et; EWG = MeCO, MeOCO, EtOCO, $Me_2NCO$, $O_2N$, NC; X = NR, O.

Scheme 206



$R^1$ = H, 4-Me, 4-Cl, 4-$O_2N$; $R^2$ = H, Ph, *n*-$C_4H_9$, TMS; $R^3$ = H, $MeO_2C$; $R^4$ = $MeO_2C$, $EtO_2C$.

Scheme 207



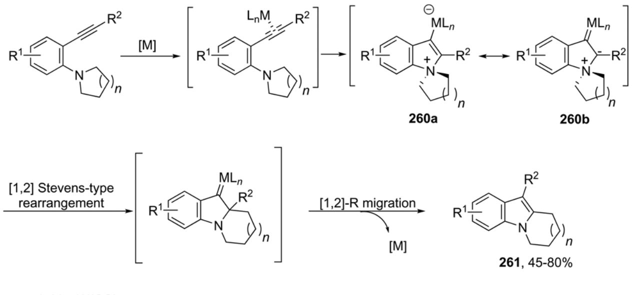
$R^1$ = H, *n*-Pr, $Cl(CH_2)_3$, *c*-$C_3H_5$, $C_6H_5$; $R^2$ = Me, $C_6H_5$, 4-Cl-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-MeO-$C_6H_3$-$CH_2$.

Scheme 208

dicarboxylate and $PtCl_2$ as the catalyst. The platinum catalyst showed a dual action by acting in catalytic π-activation of both *ortho*-alkynylanilines and ethyl propiolate.[233] The platinum-catalyzed cyclization/intramolecular carbon–nitrogen bond formation-[1,3] shift of carbamoyl and ester groups provides another useful route to synthesize indole-3-carbamides and -carboxylates **259** (Scheme 208).[234] The authors concluded, *via* crossover experiments, that the cyclization of *ortho*-alkynylphenyl ureas or *ortho*-alkynylphenyl carbamates, catalyzed by $PtI_4$, occurred in an intramolecular manner instead of an intermolecular manner. In addition, the formation of 3-protonated indole was observed as a by-product in all reactions. It has also been concluded that the proton source was the methyl moiety of the migrating carbamoyl group, which would be eliminated in the [1,3] carbamoyl migration.

### 2.12. Rhenium-catalyzed synthesis of indoles

The cyclization of *ortho*-alkynylaryl piperidines catalyzed by $[ReBr(CO)_5]$ gave *N*-fused tricyclic indole derivatives **261** in moderate to good yields (Scheme 209).[235] The catalytic process assumed by the authors involves the initial formation of metal containing ammonium ylides **260**, which undergo ring expansion through a 1,2-rearrangement, followed by 1,2-alkyl migration to form *N*-fused tricyclic indole derivatives. In addition, the authors found that using *ortho*-alkynylaryl pyrrolidines the best catalytic action was achieved with $[W(CO)_6]$.



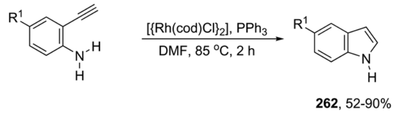
*n* = 1; M = $W(CO)_6$
*n* = 2; M = $ReBr(CO)_5$
$R^1$ = H, 4-$F_3C$, 3-$F_3C$, 4-MeO; $R^2$ = Me, *n*-Pr, $TIPSOCH_2CH_2$.

Scheme 209

### 2.13. Rhodium-catalyzed synthesis of indoles

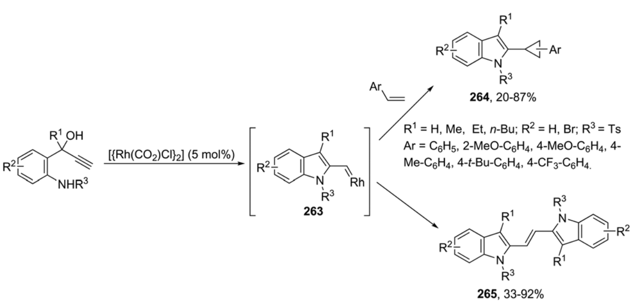
**2.13.1. Rhodium-catalyzed cyclization of *ortho*-alkynylanilines.** For several decades, rhodium-catalyzed transformations have been successfully employed in the development of novel methodologies, which have found widespread use in different areas because of their versatility and diverse applications. In organic synthetic methodologies, rhodium catalysis is broadly applied in olefin functionalization, hydrogenation, carbon–hydrogen functionalization, cycloisomerization, and cycloaddition reactions.[236] In particular, rhodium-catalyzed reactions with alkynes allow the synthesis of diverse carbo- and heterocycles. In this section, we will show the synthetic efforts in developing indoles based on rhodium-catalyzed reactions using alkynes and different nitrogen compounds as substrates. In an early report, rhodium-catalyzed cycloisomerization of unprotected anilines and terminal alkynes proceeded effectively to produce indoles **262** in good yields (Scheme 210).[237] The reaction conditions were carefully optimized indicating that the use of $Rh(cod)Cl_2$ (1 mol%) and $PPh_3$ (4 mol%) in DMF at 85 °C was the optimal conditions to deliver the indoles in best yields.

The intramolecular reaction of propargyl alcohol derivatives with $Rh(CO)_2Cl_2$ generated rhodium(I) carbenes **263**, *via* a dehydrative indole annulation. Depending on the substituent on the aniline nitrogen nucleophile, either a cyclopropanation or dimerization product could be selectively obtained. The results indicated that cyclopropanation products **264** were exclusively formed with *N*-Ts protected aniline, whereas the *N*-Boc-protecting group gave the dimerization products **265** (Scheme 211).[238]



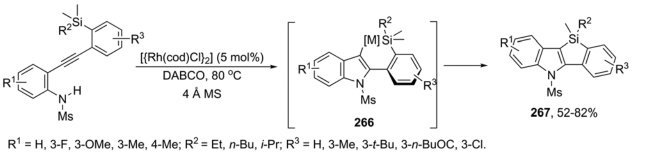
$R^1$ = 4-Me, 4-Cl, 4-$EtO_2C$, 4-NC, 4-MeOC, 4-$O_2N$.

Scheme 210



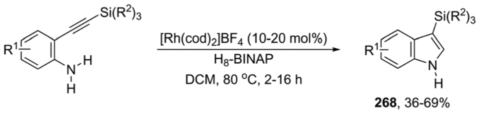
$R^1$ = H, Me, Et, *i*-Pr, *n*-Bu, Ph; $R^2$ = H, Br; $R^3$ = Boc.

Scheme 211



$R^1$ = H, 3-F, 3-OMe, 3-Me, 4-Me; $R^2$ = Et, *n*-Bu, *i*-Pr; $R^3$ = H, 3-Me, 3-*t*-Bu, 3-*n*-BuOC, 3-Cl.

Scheme 212

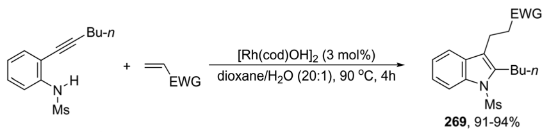


$R^1$ = H, 2-Me, 4-Me, 3-OMe, 4-F; $R^2$ = (Me$_2$, *t*-Bu), (Ph$_2$, *t*-Bu), (Me)$_3$, (Et)$_3$, (*i*-Pr)$_3$.

Scheme 213

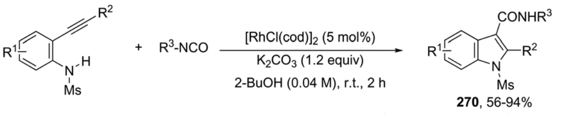
The methylsulfonyl-protected aniline derivatives were successfully utilized for the development of a convenient protocol for the general synthesis of siloles. The intramolecular cyclization of aniline substrates generated an organometallic intermediate **266**, which after the activation of the Csp$^3$–Si bond afforded the desired indole [3,2-*b*] siloles **267** (Scheme 212).[239] Subsequently, 3-silylindole derivatives **268** were formed from the reaction between the 2-silylethynylanilines and cationic rhodium(I)/H8–BINAP complex *via* a 1,2-silicon migration. The authors observed that the use of H8–BINAP in place of BINAP led to obtaining the products in good yields (Scheme 213).[240]

Several 2,3-disubstituted indoles have been obtained through an intramolecular rhodium-catalyzed tandem cyclization–addition sequence using *ortho*-alkynylanilines as substrates and an electrophile source. For example, the cyclization of *ortho*-alkynylanilines catalyzed by Rh(I)/BINAP with a subsequent reaction with electrophilic alkenes gave the indole derivatives **269** having an alkyl chain at the C3-position (Scheme 214).[241] When isocyanates were used as an electrophile source in the cyclization of *ortho*-alkynylanilines catalyzed by [RhCl(COD)]$_2$ (5 mmol%), K$_2$CO$_3$ and 2-BuOH, the indole-3-carboxamides **270** were formed in excellent yields (Scheme 215).[242] The authors confirmed, *via* a control experiment, that the formation of a 3-rhodium indolyl intermediate occurred during the cyclization process rather than after indole formation. In the same way, the rhodium(III)-catalyzed cascade cyclization/electrophilic amidation of *ortho*-alkynylanilines, using *N*-pivaloyloxylamides as the electrophilic nitrogen source, gave 3-amidoindoles **271** (Scheme 216).[243]



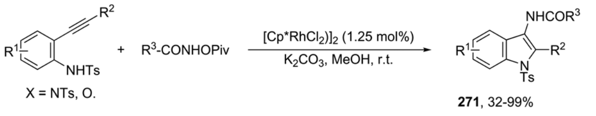
EWG = CN, EtOC, EtO$_2$C.

Scheme 214



$R^1$ = H, 4-Br, 3-Cl, 4-Cl, 4-F, 3-MeO, 4-Meo, 4-MeO$_2$C, 4-NC; $R^2$ = Ph, *n*-Bu, *t*-Bu; $R^3$ = *n*-Pr, *i*-Pr, Bn, Cy, C$_6$H$_5$, 4-MeO-C$_6$H$_4$.

Scheme 215

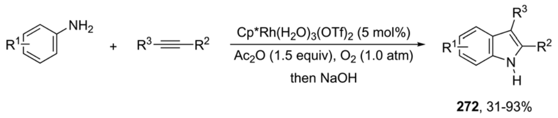


$R^1$ = H, 4-Cl, 4-F, 4-O$_2$N, 4-CF$_3$, 4-EtO$_2$C, 4-Me; $R^2$ = H, *n*-Bu, C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-F-C$_6$H$_4$; $R^3$ = Bn, CH$_2$Cl, CH$_2$(4-MeC$_6$H$_4$), CH$_2$(3-Cl-C$_6$H$_4$), CH$_2$(4-Br-C$_6$H$_4$), CH$_2$(2-I-C$_6$H$_4$), CH=CH$_2$, MeC=CHMe, PhC=CH$_2$.

Scheme 216

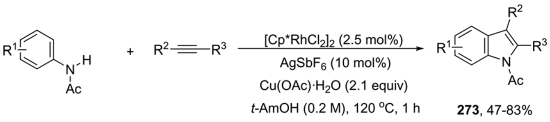
**2.13.2. Indoles *via* rhodium-catalyzed carbon–hydrogen activation.** The rhodium-catalyzed annulation reaction of alkynes *via* carbon–hydrogen activation is a valuable method for the synthesis of heterocycles.[244] The cyclization basically involves the reaction of an aromatic system with a highly electrophilic rhodium species to give a rhodacycle intermediate. Subsequently, the insertion of the rhodacycle into the carbon–carbon bond of the unsaturated substrate, followed by reductive elimination, releases the product and rhodium catalyst. In an attempt to prepare 1,2-disubstituted indoles **272**, *via* rhodium-catalyzed annulation, simple anilines were reacted with symmetrical and unsymmetrical internal alkynes in the presence of the rhodium(III) catalyst under aerobic conditions (Scheme 217).[245] The advance of this methodology is the evidence that the rhodium(I) species is oxidized to rhodium(III) species *via* molecular oxygen in the presence of an appropriate acid.

The acetanilide derivatives were successfully utilized for the development of a convenient protocol for the general synthesis of 1,2-disubstituted indoles **273** (Scheme 218).[246–248] In the



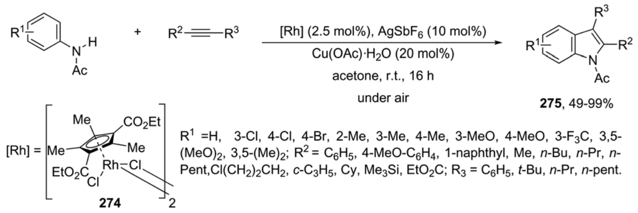
$R^1$ = H, 3-Me, 4-Me, 3-*t*-Bu, 4-*t*-Bu, 4-MeO, 3,4-(MeO)$_2$, 3,5-(MeO)$_2$, 4-CF$_3$O, 4F, 3-Cl, 4-Cl, 4-Br, 4-NC, 4-CH$_3$O$_2$C, 1-naphthyl; $R^2$ = C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-CH$_3$O-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, 3,5-(CF$_3$)$_2$-C$_6$H$_3$; $R^3$ = C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-CH$_3$O-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Br-C$_6$H$_4$, CH$_3$, Bn.

Scheme 217



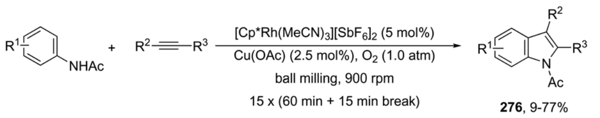
$R^1$ = 3-OMe, 4-MeO, 4-F, 4-Cl, 4-MeO$_2$C, 2-Me, 4-Me, 3,5-(Me)$_2$, 3,5-(F$_2$); $R^2$ = C$_6$H$_5$, *n*-Pr, (CH$_3$)$_2$CHCH$_2$CH$_2$, Me, *n*-Bu, *n*-Hex, *c*-C$_3$H$_5$, EtO$_2$CH$_2$, (EtO$_2$)$_2$CHCH$_2$, TBSOCH$_2$CH$_2$; $R^3$ = C$_6$H$_5$, *p*-MeO-C$_6$H$_4$, *o*-Cl-C$_6$H$_4$, 2-thienyl, Me, *n*-Pr, TMS.

Scheme 218



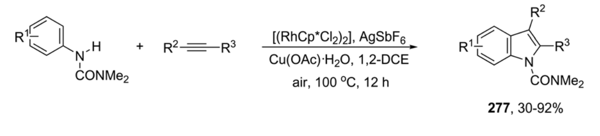
$R^1$ =H, 3-Cl, 4-Cl, 4-Br, 2-Me, 3-Me, 4-Me, 3-MeO, 4-MeO, 3-$F_3C$, 3,5-$(MeO)_2$, 3,5-$(Me)_2$; $R^2$ = $C_6H_5$, 4-MeO-$C_6H_4$, 1-naphthyl, Me, *n*-Bu, *n*-Pr, *n*-Pent,$Cl(CH_2)_2CH_2$, *c*-$C_3H_5$, Cy, $Me_3Si$, $EtO_2C$; $R_3$ = $C_6H_5$, *t*-Bu, *n*-Pr, *n*-pent.

Scheme 219



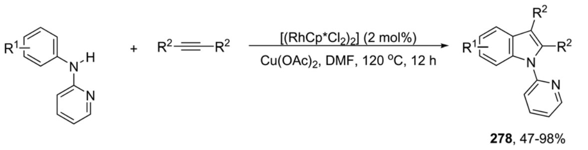
$R^1$ = H, 4-F, 4-MeO, 2-Me, 3-Me, 2-MeO; $R^2$ = Me, Et, *n*-Pr; $R^3$ = Ph, *n*-Pr.

Scheme 220



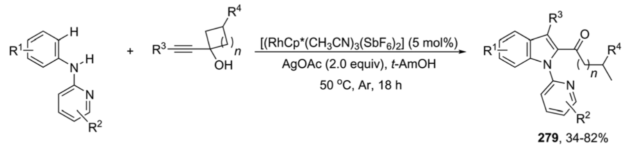
$R^1$ = H, 2-MeO, 4-MeO, 3,4-$(MeO)_2$, 2-Me, 3-Me, 4-Me, 3,4-$(Me)_2$, 4-Et 4-F, 4-Cl, 4-Br; $R_2$ = Et, *n*-Pr, *n*-Bu, $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 2-thienyl, 1-naphthyl, 2-naphthyl; $R^3$ = Et, *n*-Pr, $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 2-thienyl, 1-naphthyl, 2-naphthyl.

Scheme 221



$R^1$ = 2-Me, 4-Me, 2, Me, 3-MeO, 4-MeO, 4-F, 2-Ph, 2-Cl; $R^2$ = *n*-Pr, $C_6H_5$, 4-MeO-$C_6H_4$.

Scheme 222



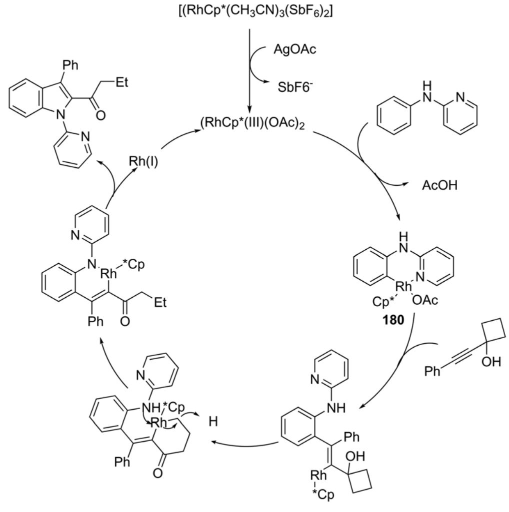
$R^1$ = H, 4-Br, 4-Cl, 4-F, 4-$EtO_2C$, 3-Me, 4-Me, 4-MeO, 4-Ph; $R^2$ = H, 4-Me, 5-Me, 5-MeO, 5-Br, 5-Cl, 5-F, 5-$EtO_2C$, 5-$NO_2$, 5-$CF_3$; $R^3$ = 4-Me-$C_6H_4$, 4-Et-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 3-F-$C_6H_4$, 4-F-$C_6H_4$, 4-$CF_3$-$C_6H_4$, $R^4$ = H, $C_6H_4$, 4-Me-$C_6H_4$; *n* = 1, 2.

Scheme 223

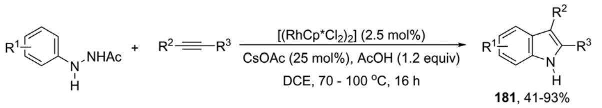
preliminary study, the reaction was carried out at high temperature (120 °C) using $[Cp^*RhCl_2]_2$ as a precatalyst and a stoichiometric amount of $Cu(OAc)_2$ as an oxidant. A broad study to improve these reaction conditions showed that the combination of $[Cp^*RhCl_2]_2$, $AgSbF_6$, and $Cu(OAc)_2$ $H_2O$ was the best catalytic system to form the indoles in higher yields. It was also observed that molecular oxygen worked as the internal oxidant, reactivating the reduced rhodium(I), which allowed the reaction to be carried out at mild temperatures (60 °C). This permitted the expansion of the compatibility of the reaction to include a range of internal alkynes bearing useful functional groups. As an alternative to improve the yields of the less reactive alkynes, the dicationic analogue $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was efficiently employed as a catalyst. The rhodium-catalyzed oxidative annulation of acetanilides with internal alkynes, under ambient conditions, was also carried out using an *in situ* generated electron-deficient dicationic rhodium(III) complex **274**, derived from $\eta^5$-cyclopentadienyl rhodium(III). The authors reported a high catalytic activity under ambient conditions, at room temperature, and under air, giving the desired indoles **275** in 49–99% yields (Scheme 219).[249] Very recently, in an alternative strategy for the generation of indoles **276**, Bolm and co-workers reported a mechanochemical rhodium(III)-catalyzed carbon–hydrogen bond functionalization, involving oxidative coupling of acetanilides and alkynes, in a planetary mill and in the absence of any solvent and heating (Scheme 220).[250] The reaction conditions required $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%) as a catalyst, and a catalytic amount of $Cu(OAc)_2$ in association with dioxygen as a terminal oxidant.

Substituted indole derivatives **277** were synthesized from *N*-arylureas and internal alkynes *via* a rhodium-catalyzed carbon–hydrogen activation strategy, in which *N*-arylurea assisted the activation of the carbon–hydrogen bond and a copper salt acted as an oxidant, closing the catalytic cycle under aerobic conditions (Scheme 221).[251] The optimized reaction conditions were compatible with electron-donating and electron-withdrawing functional groups in the substituted *N*-arylurea; however, strongly electron-withdrawing groups, such as nitro and cyano groups, did not give the corresponding indoles. The sterically hindered *ortho*-F and *ortho*-Br substituted arylureas were other limitations observed, which yielded the indoles in a trace amount. *N*-(2-Pyridyl)anilines were also suitable substrates for the directing group in the rhodium-catalyzed oxidative coupling with alkynes to give *N*-(2-pyridyl) indoles **278** (Scheme 222).[252] The results indicated that groups containing the oxygen atom and the electronic effects of the aryl ring directly bonded to the nitrogen atom governed the high selectivity achieved in the cyclization. *N*-(2-Pyridyl)anilines can also be efficiently used in rhodium-catalyzed carboamination of unsymmetric alkynyl cycloalkanols leading to 1,2,3-trisubstituted indoles **279** (Scheme 223).[253] The authors carried out a number of control experiments to elucidate the reaction mechanism, which confirmed that the formation of indoles **279** proceeds through a sequential aryl carbon–hydrogen/$Csp^3$–$Csp^3$ activation process, whereas the pyridyl nitrogen intermediate **280** plays an important role in chelation assistance (Scheme 224).

A regioselective synthesis of indoles **181** from primary 2-acetyl-1-arylhydrazines and internal alkynes was described to occur *via* a rhodium(III)-catalyzed hydrazine-directed carbon–hydrogen activation (Scheme 225).[254] The advance of this methodology was the application of 2-acetyl-1-arylhydrazines



Scheme 224

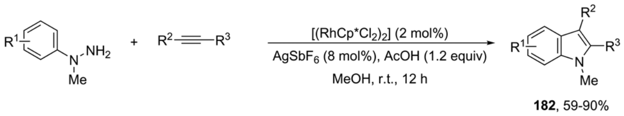


**181**, 41-93%

$R^1$ = H, 3-Me, 4-Me, 3,4-(Me)$_2$, 4-MeO, 4-Br, 4-Cl, 2-F, 4-F, 3,4-(Cl)$_2$, (3-I, 4-Me), 4-$F_3CO$, 4-$MeO_2C$, 4-NC, 4-Ph; $R^2$ = $C_6H_5$, 4-Me-$C_6H_4$, 3-MeO-$C_6H_4$, 4-OMe-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, Me, Et, *n*-Pr, *n*-Bu; $R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 3-MeO-$C_6H_4$, 4-OMe-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, Et, *n*-Pr, *n*-Bu.

Scheme 225

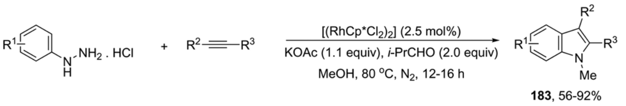
as directing groups and the use of mild conditions for the nitrogen–nitrogen bond cleavage that typically requires harsh reaction conditions when it is used in redox-neutral reactions. The arylhydrazine derivatives were excellent precursors for the regioselective synthesis of indoles **182** (Scheme 226).[255] The products were obtained in high yields when the reaction of arylhydrazines with internal alkynes was carried out using $[RhCp^*Cl_2]_2$ (2 mol%) and $AgSbF_6$ (8 mol%), in the presence of HOAc and MeOH as the solvent. In this reaction, the oxidant required for rhodium-catalyzed carbon–hydrogen bond activation was produced in an internal oxidation mechanism through the cleavage of the nitrogen–nitrogen bond with the formation of $NH_3$, which was captured by AcOH. Another external-oxidant-free rhodium(III)-catalyzed carbon–hydrogen activation of aryl hydrazines with alkynes used hydrazone as a directing group to prepare indoles **183** (Scheme 227).[256] The hydrazone group was formed *in situ via* condensation of hydrazines with isobutyraldehyde. In this methodology, the nitrogen–nitrogen bond worked as an internal oxidant without the necessity of the pre-installation and post-cleavage of the directing group. Similarly, the regioselective synthesis of indoles **184**, using the hydrazone group, prepared *in situ* by condensation of arylhydrazine hydrochloride with diethyl ketones as a directing group and an internal oxidant, was also described (Scheme 228).[257] 1,3-Dinitrobenzene was also used as an external oxidant in rhodium-catalyzed oxidative annulation of hydrazines with alkynes in the preparation of 1-aminoindoles **185** (Scheme 229).[258] Mechanistic studies demonstrated that 1,3-dinitrobenzene served as an oxidant during the reaction, consuming the leaving hydrogen atoms and regenerating the active rhodium catalyst.



**182**, 59-90%

$R^1$ = H, 2-Me, 4-Me, 5-Me, 4-Br, 4-Cl, 2-F, 4-F, 5-F, 4-MeO, 4-MeOSC, 4-NC; $R^2$ = Me, Et, *n*-Bu, *n*-Pr, allyl, $C_6H_5$, $R^3$ = $C_6H_5$, Et, *n*-Bu.

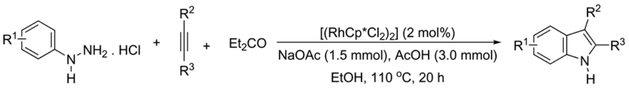
Scheme 226



**183**, 56-92%

$R^1$ = H, 2-Me, 3-Me, 4-Me, 4-MeO, (2-Me, 4-MeO), 4-Br, 4-Cl, 4-F, (2-Me, 5-F), (2-Me, 4-Cl), (3-Cl, 4-Me); $R^2$ = $R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$; $R^2$ = $HOCH_2CH_2$ and $R_3$ = $C_6H_5$; $R^2$ = $HOCH_2CH_2$ and $R^3$ = thienyl; $R^2$ = Me and $R^3$ = $C_6H_5$; $R^2$ = H and $R^3$ = *t*-Bu.

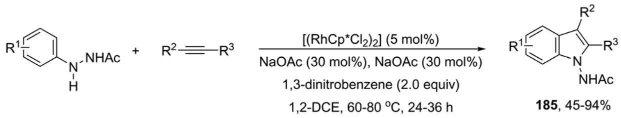
Scheme 227



**184**, 71-90%

$R^1$ = H, 4-Me, 2-Me, 4-*t*-Bu, 4-MeO, 4-Br, 2-Br, 4-Cl, 4-F, 4-I, 4-$F_3C$, 4-$HO_2C$, 4-HO; $R^2$ = $R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 4-F-$C_6H_4$; $R^2$ = $C_6H_5$ and $R^3$ = Me, Et, $EtO_2C$, $MeO_2C$, MeO, Br, Cl.

Scheme 228

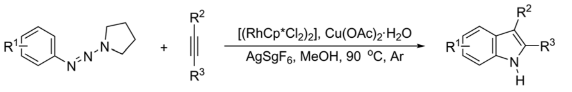


**185**, 45-94%

$R^1$ = H, 4-Me, 4-MeO, 4-Cl, 4-F, 4-$CF_3O$, 4-NC; $R^2$ = $R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 2-thienyl; $R^2$ = $C_6H_5$ and $R^3$ = *n*-$C_6H_{13}$, $Ph(CH_2)_3$, $HOCH_2$, $HOCH_2CH_2$, $HO(CH_2)_3$.

Scheme 229

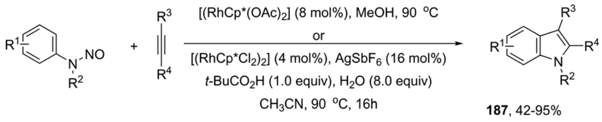
In another variation of the rhodium-catalyzed carbon–hydrogen bond activation, triazenes have successfully transformed in unprotected indoles **186** *via* reaction with internal alkynes (Scheme 230).[259,260] This reaction is proposed to undergo a 1,2-rhodium shift ring contraction, in which tria-



**186**, 42-95%

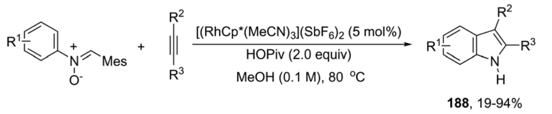
$R^1$ = H, NC, $MeO_2C$, Ac, (3-Me, 4-Br), (2-F, 4-$O_2N$), (2-MeO, 4-$O_2N$), (3-Cl, 4-F), (2-Cl, 4-Me), 3-Cl, 4-Cl, 3-Br, 4-Br, 4-F, 2-I, 4-$O_2N$, 2-$HOCH_2$, 4-Me; $R^2$=$R^3$ = $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, *n*-Pr; $R^2$ = Me and $R^3$ = $C_6H_5$, *c*-$C_6H_{11}$.

Scheme 230



R$^1$ = H, 4-Me, 4-MeO, 4-Br, 4-F, 4-MeO$_2$C, 4-Ac, 3,4-(MeO$_2$); R$^2$ = Me, Et, $i$-Pr, Ph, Bn; R$^3$=R$^4$ = C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-$t$-Bu-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-MeS-C$_6$H$_4$; R$^3$ = Me, R$^4$ = 4-BnO-C$_6$H$_4$; R$^3$ = $n$-Bu, R$^4$ = C$_6$H$_5$.

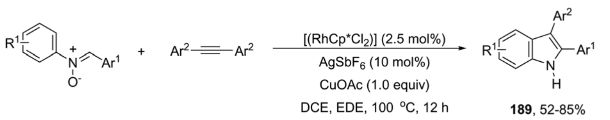
Scheme 231



R$^1$ = H, 3-Me, 4-Me, 5-Me, 3-MeO, 3-Br, 3-Cl, 3-F, 3-NC, 3,4-(Me)$_2$, 3,4 (F)$_2$; R$^2$ = R$^3$ = 2-Me-C$_6$H$_4$, 3-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-F-C$_6$H$_4$, naphthyl; R$^2$ = C$_6$H$_5$, R$^3$ = 4-O$_2$N-C$_6$H$_4$, Me, $n$-C$_4$H$_9$, $t$-Bu; R$^2$ = 4-O$_2$N-C$_6$H$_4$; R$^3$ = $n$-Bu; R$^2$ = 4-EtO$_2$C-C$_6$H$_4$; R$^3$ = $n$-Bu; R$^2$ = 4-MeOC-C$_6$H$_4$; R$^3$ = $n$-Bu.

Scheme 232

zene behaved as an internal cleavable directing group. The studies using HRMS and theoretical calculations suggested that a 1,2-alkyl migration might be responsible for the *in situ* cleavage of the directing group. *N*-Nitrosoanilines and alkynes, in the presence of the rhodium catalyst, were employed in the synthesis of *N*-alkyl indoles **187**, *via* redox-neutral carbon–hydrogen activation and annulation, using a traceless nitroso directing group (Scheme 231).[261,262] The *N*-nitroso group serves as both a directing group for carbon–hydrogen activation and an internal oxidant for catalyst turnover. The construction of indole derivatives **188** was also successfully described using a nitrone as the oxidizing directing group (Scheme 232).[263] The presence of a sterically hindered Mes group on the carbon center of the nitrones was decisive in forming indoles in high yields. In a similar reaction, nitrones were used to selectively prepare unsymmetrical 2,3-diaryl substituted indoles **189** (Scheme 233).[264] The rhodium(III)-catalyzed carbon–hydrogen annulation of anilines with internal alkynes afforded the unsymmetrical 2,3-diaryl substituted indoles with poor regioselectivity. The authors used an excellent alternative to control this selectivity, in which they carried out the rhodium(III)-catalyzed annulation of nitrones with symmetrical diaryl alkynes, giving 2,3-diaryl-substituted *N*-unprotected indoles having two different aryl groups. Because one of the aryl substituents came from the N═C-aryl group present in the nitrone and the other came from the alkyne, the methodology delivered the corresponding indoles with an exclusive regioselectivity.

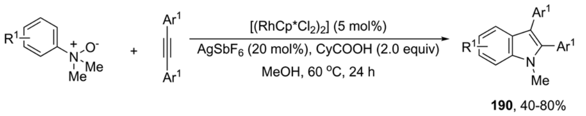


R$^1$ = H, 4-Me, 4-Br, 4-Cl, 5-MeO, 4-EtO$_2$C; Ar$^1$ = C$_6$H$_5$, 4-MeO-C$_6$H$_4$, 4-F$_3$C-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 2-Me-C$_6$H$_4$, 1-naphthyl, $n$-Pr; Ar$^2$ = C$_6$H$_5$, 4-MeO-C$_6$H$_4$, 4-F$_3$C-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-O$_2$N-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 2-thienyl, 2-furyl.

Scheme 233

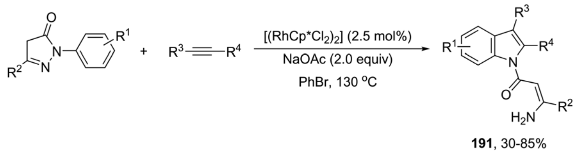
Another example of a rhodium-catalyzed carbon–hydrogen bond activation was the regioselective annulation of tertiary aniline *N*-oxides with alkynes, giving *N*-alkylindoles **190** (Scheme 234).[265] The reaction proceeds *via* a sequential Csp$^2$–H and Csp$^3$–*N* activation, in which the *N*-oxide acts as a traceless directing group, avoiding the use of metal oxidants. A related process was employed in an approach to the synthesis of indoles bearing an *N*-(3-aminobutenoyl) substituent **191** through rhodium(III)-catalyzed redox-neutral carbon–hydrogen bond activation of pyrazolones and alkynes (Scheme 235).[266] The key step was the formation of a bicyclic metallacycle rhodium(V) intermediate *via* a 1,2-rhodium migration, accompanied by the nitrogen–nitrogen bond cleavage of the pyrazolone ring, without loss of the N-terminus.

A concise route to substituted indoles **192** was based on a rhodium-catalyzed denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazoles and 1-ethynylcyclohexenes (Scheme 236).[267] In this reaction, the key rhodium-stabilized iminocarbene intermediate **193** was generated *via* ring-chain isomerization and nitrogen extrusion. The methodology based on rhodium(II)-catalyzed denitrogenative annulation of *N*-sulfonyl-1,2,3-triazoles was also applied to the construction



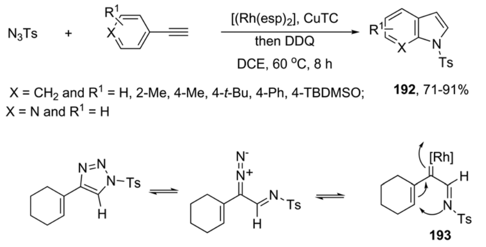
R$^1$ = H, 3-Me, 4-Me, 4-$t$-Bu, 4-MeO, 4-Br, 3-Br, 3-Cl, 3-F, 3-EtO$_2$C; Ar$^1$ = C$_6$H$_5$, 3-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-$t$-Bu-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-F$_3$C-C$_6$H$_4$.

Scheme 234



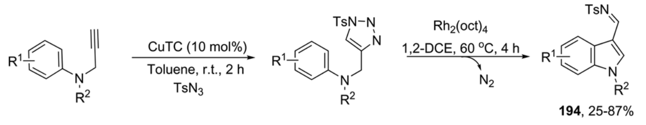
R$^1$ = H, 4-Me, 4-MeO, 4-Cl, 4-Br, 3-F, 5-F, 3,4(Me)$_2$, (3-Cl, 4-Me); R$^2$ = Me, Et, $i$-Pr; R$^3$ = R$^4$ = C$_6$H$_5$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 3-Cl-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 3-F-C$_6$H$_4$, 3-F$_3$C-C$_6$H$_4$, 4-$t$-Bu-C$_6$H$_4$.

Scheme 235



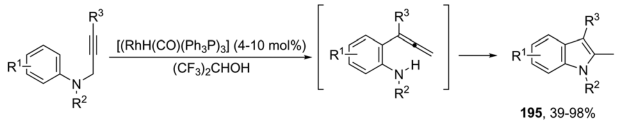
X = CH$_2$ and R$^1$ = H, 2-Me, 4-Me, 4-$t$-Bu, 4-Ph, 4-TBDMSO;
X = N and R$^1$ = H

Scheme 236



$R^1$ = H, 4-Br, 3-Cl, 4-Cl, 4-F, 4-I, 4-*n*-Bu, 3-$O_2N$, 4-$O_2N$, 2,3-naphthyl; $R^2$ = H, Me, Et, *n*-Pr, *n*-$C_4H_9$, *n*-$C_6H_{13}$, Bn, Boc, Bz, $CH_2$=$CH_2CH_2$.

Scheme 237



$R^1$ = H, 2-MeO, 3-MeO, 4-MeO, 4-Br, 4-F, 4-$F_3C$, 3,5$(F)_2$; $R^2$ = H, Bn, Et; $R^3$ = H, Me, *n*-$C_5H_{11}$, Ph.

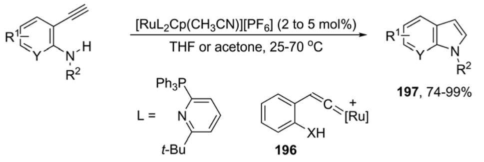
Scheme 238

of 3-indolylimines **194** using *N*-propargylanilines as the starting material (Scheme 237).[268]

The amino-Claisen rearrangement of *N*-propargylaniline derivatives involves the [3,3]-sigmatropic shift of *N*-alkenyl-*N*-arylamine to furnish *ortho*-allenylanilines. An alternative version of this rearrangement has been reported in the synthesis of 2,3-substituted indole derivatives **195** using the $[Rh(cod)_2]OTf$ catalyst in hexafluoroisopropyl alcohol (HFIP) (Scheme 238).[269,270] The authors confirmed by single-crystal X-ray crystallographic analysis that $[Rh(CO)(Ph_3P)_2]OCH(CF_3)_2$ is the active catalyst, which was generated *in situ* from $RhH(CO)(Ph_3P)_3$ and HFIP. In addition, they also confirmed that *ortho*-allenylaniline is the intermediate of the cyclization. The catalytic system was also active for the one-pot synthesis of indoles by reacting *N*-alkylanilines with propargyl bromide in the presence of $K_2CO_3$ in HFIP.

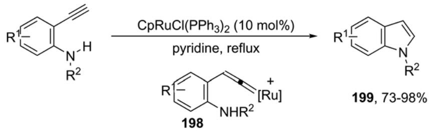
## 2.14. Ruthenium-catalyzed synthesis of indoles

Ruthenium can form a large number of different complexes with oxidation states ranging from divalent negative to octavalent positive, although the complexes with oxidation states 0, II and III are most common. This characteristic makes the salts of ruthenium versatile catalysts with extensive applications. Among them, the intramolecular carbon–hydrogen activation, hydrogenation reactions, reduction, oxidation, isomerization, carbon–carbon bond formation, and hydrogen transfer reactions have been commonly applied.[271] Ruthenium complexes have been proven to be highly efficient at converting acyclic substrates in carbon- and heterocycles *via* metathesis and nonmetathesis reactions.[272] In this section, we will cover the main methods described for the preparation of indoles using alkynes in ruthenium-catalyzed cyclization. Among them, *ortho*-ethynylanilines were used as substrates, in an alkyne hydration reaction catalyzed by $[RuL_2Cp(CH_3CN)][PF_6]$, to form indoles **197** (Scheme 239).[273] The experimental evidence indicated that the ruthenium vinylidene **196** is the key intermediate for this intramolecular cyclization.



$R^1$ = H, 3-$O_2N$, (2-ethynyl, 4-Me); $R^2$ = H, Ts, allyl, 4-Me-$C_6H_4CH_2$; Y = CH, N.

Scheme 239



$R^1$ = H, 4-$O_2N$, 4- NC, 4-$MeO_2C$, 3- $MeO_2C$; $R^2$ = H, Ms, Ts.

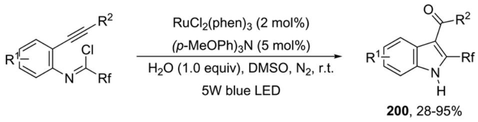
Scheme 240

The ruthenium catalyst, with triphenylphosphine instead of bifunctional pyridine–phosphine as the ligand, was employed in the catalytic cyclization of *ortho*-alkynylanilines for the preparation of indoles **199** (Scheme 240).[274] This cycloisomerization process occurred regioselectively *via* a 5-*endo* cyclization mode, where the ruthenium vinylidene **198** is the key intermediate. The catalytic activity of $CpRuCl(PPh_3)_2$ was supported by the presence of an amine/ammonium base–acid pair which can also offer higher conversions of *ortho*-alkynylanilines.

A very efficient method to form 2-trifluoromethyl indoles **200** involved the ruthenium-catalyzed intramolecular radical cyclization of trifluoroacetimidoyl chlorides (Scheme 241).[275] This photoreaction was carried out *via* a reductive cleavage of the carbon($sp^2$)–chlorine bond of trifluoroacetimidoyl chloride by $Ru(phen)^{3+}$, prepared *in situ* by photoexcitation and single-electron transfer of $Ru(phen)_3{}^{2+}$.

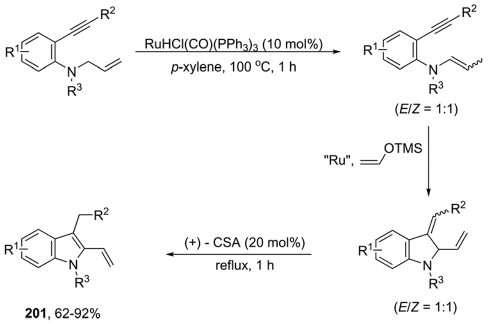
Recently, another example of a nonmetathesis reaction with the use of a ruthenium carbene catalyst has been described for the preparation of 2,3-disubstitued indoles **201** *via* a cycloisomerization of *N*-acyl-*N*-vinyl-2-silylalkynylaniline derivatives (Scheme 242).[276] The results obtained from the control experiments suggest that the cycloisomerization proceeds *via* ruthenium hydride **202**, generated *in situ* from the Grubbs II catalyst, which activates the alkyne to give the corresponding indole (Scheme 243).

Intramolecular ruthenium-catalyzed annulation of nitrogen-functionalized alkynes, followed by carbon-migration has been the key to synthesize 3-substituted indoles. In one



$R^1$ = H, 3-Me, 4-Me, 2,4-$(Cl)_2$; $R^2$ = H, *n*-$C_4H_9$, *c*-$C_3H_5$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-NC-$C_6H_4$, naphthyl, 3-thienyl, TMS.

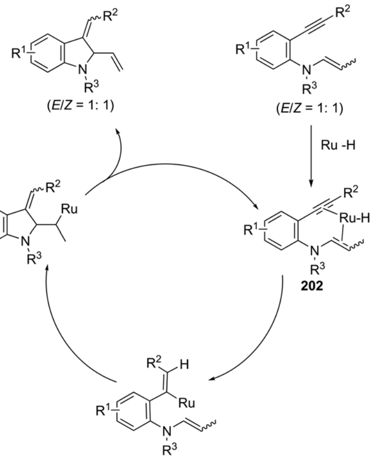
Scheme 241



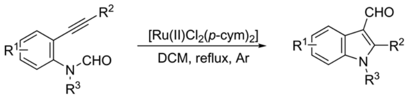
**201**, 62-92%

$R^1$ = H, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 4-Me, 5-Me, 4-MeO, 4-$MeO_2C$; $R^2$ = $Me_3Si$, $PhMe_2Si$, $BnM_2Si$, *t*-Bu, *i*-PrMeOSi, H; $R^3$ = CHO, Ts.

Scheme 242



Scheme 243

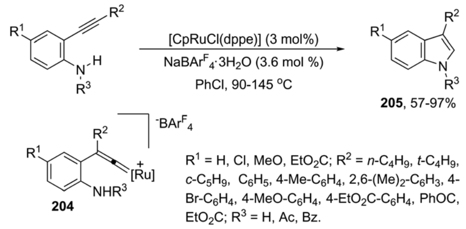


**203**, 30-99%

$R^1$ = H, 4-Me, 4-Cl, 4-Br, 4-F, 4-$F_3C$; $R^2$ = *n*-$C_6H_{13}$, *c*-$C_3H_5$, *c*-$C_6H_9$, $HOCO(CH_2)_3$, $C_6H_5$, 4-Me $C_6H_4$, 2-Br-$C_6H_4$, 4- MeOC, 1-naphthyl, 2-thienyl; $R^3$ = H, Bn, Me.

Scheme 244

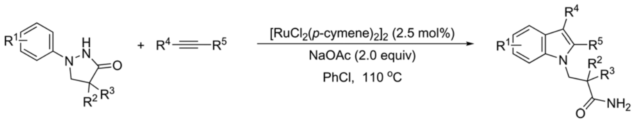
example, 1*H*-indole-3-carbaldehydes **203** were prepared by ruthenium-catalyzed intramolecular annulation of *ortho*-alkynylamides (Scheme 244).[277] The reaction involved formyl translocation, which occurred *via* cleavage of the N–CHO bond alone, instead of a cleavage of the aldehyde C–H bond. In another example, the ruthenium-catalyzed cycloisomerization of *ortho*-alkynylanilides afforded 3-substituted indoles **205** (Scheme 245).[278] Experimental evidence related to the reaction mechanism was addressed in detail indicating that the catalytic process proceeds *via* a ruthenium vinylidene intermediate **204**, which is formed by 1,2-carbon migration.



**205**, 57-97%

$R^1$ = H, Cl, MeO, $EtO_2C$; $R^2$ = *n*-$C_4H_9$, *t*-$C_4H_9$, *c*-$C_5H_9$, $C_6H_5$, 4-Me-$C_6H_4$, 2,6-$(Me)_2$-$C_6H_3$, 4-Br-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$EtO_2C$-$C_6H_4$, PhOC, $EtO_2C$; $R^3$ = H, Ac, Bz.

Scheme 245



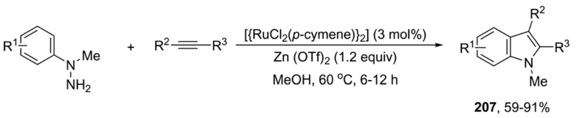
**206**, 53-92%

$R^1$ = H, 2-Me, 3-Me, 4-Me, 4-MeO, 4-Br, 4-Cl, 4-F, 4-NC, 4-$F_3CO$, 4-$F_3C$, 4-$O_2N$; $R^2$ = H and $R^3$ = Me; $R^2$ = $R^3$ = H, Me; $R^4$ = H, Me, $Me(CH_2)_3$, $Me(CH_2)_5$; $R^5$ = $C_6H_5$, 4-Ph-$C_6H_4$, 2-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-*t*-Bu-$C_6H_4$, 2-Cl-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 4-CN-$C_6H_4$, 3-$MeO_2C$-$C_6H_4$, *n*-$C_5H_{11}$, $BnOCH_2$.

Scheme 246

Ruthenium-catalyzed carbon–hydrogen activation and annulation of alkynes is an attractive method for the synthesis of indoles with concomitant introduction of two substituents at 2- and 3-positions. It has been employed in the conversion of pyrazolidinones into 2,3-substituted indoles **206** (Scheme 246).[279] In this reaction, carbon–hydrogen was activated for expending a nitrogen–nitrogen bond cleavage of the pyrazolidinones, which work as both a directing group and an internal oxidant. The hydrazine group was also applied for the directed carbon–hydrogen functionalization of alkynes affording the indole derivatives. Thus, the reaction of aryl hydrazines with internal alkynes under catalysis of ruthenium (II) and $Zn(OTf)_2$ allowed the formation of 2,3-substituted indoles **207** (Scheme 247).[280] The authors determined that the best catalytic action was achieved by using Ru(*p*-cymene)$(OTf)_2$ as the catalyst, which was prepared *in situ* by reacting $RuCl_2$(*p*-cymene)$_2$ and $Zn(OTf)_2$ in an anion exchange reaction.

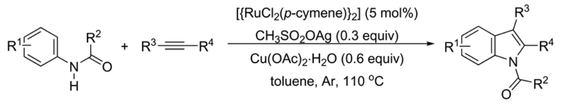
The use of an external oxidant in the ruthenium(II)-catalyzed carbon–hydrogen activation process has also been reported. The reaction between *N*-phenylacetamides and internal alkynes, under the catalysis of $RuCl_2$(*p*-cymene)$_2$, gave the best yields of the *N*-acyl indole derivatives **208** when $Cu(OAc)_2·H_2O$ was used as an external oxidant (Scheme 248).[281] Besides copper salt, the presence of the oxygen atom from the amide, to direct the cyclometalation at the *ortho* carbon–hydro-



**207**, 59-91%

$R^1$ = H, 4-Me, 4-MeO, 4-Br, 4-Cl, 4-F, 4-$MeO_2C$, 4-NC; $R^2$ = Me and $R^3$ = Ph; $R^2$ = Ph and $R^3$ = H; $R^2$ = Ph and $R^3$ = Et, *n*-Pr, allyl, Ph; $R^2$ = $R^3$ = Et, *n*-Pr, *n*-Bu,

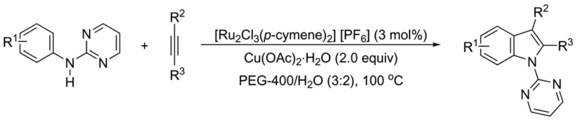
Scheme 247



**208**, 34-83%

$R^1$ = H, 2-Me, 3-Me, 4-Me, 4-MeO, 4-$O_2N$, 4-Cl, 4-I; $R^2$ = Me, Et, *i*-Pr, cyclohexyl; $R^3$ = $R^4$ = 2-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, *n*-$C_4H_9$; $R^3$ = $C_6H_5$ and $R^4$ = $EtO_2C$, *t*-$C_4H_9$; $R^3$ = *t*-$C_4H_9$ and $R^4$ = $C_6H_5$.

Scheme 248



**209**, 61-96%

$R^1$ = H, 2-Me, 3-Me, 2-MeO, 2-$F_3C$, naphthyl; $R^2$ = $R^3$ = Ph, Et; $R^2$ = Me, Et, *n*-Bu; $R^3$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-HO-$C_6H_4$, 4-MeOC-$C_6H_4$, 4-OHC-$C_6H_4$.

Scheme 249

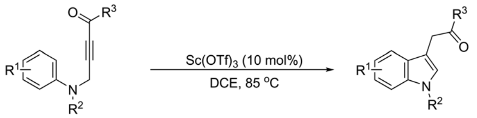
gen activation, and the temperature were essential in the catalytic system. The 2-pyrimidyl-substituent in the anilines was also used as a directing group in oxidative annulation of alkynes. For example, the reaction of *N*-2-pyrimidyl-substituted anilines with alkynes, in the presence of $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ as the catalyst, $Cu(OAc)_2 \cdot H_2O$ as the oxidant and PEG-400/$H_2O$ as the solvent, resulted in the formation of 1-(pyrimidinyl)-1*H*-indole **209** (Scheme 249).[282] The PEG-400/$H_2O$ catalytic system was recycled and reused six times without any loss of catalytic activity.

### 2.15. Scandium-catalyzed synthesis of indoles

Scandium salts have also been used as catalysts in the cyclization reaction of alkynes and nitrogen source to prepare indoles. The Friedel–Crafts reaction of 5-(arylamino)pentynones using $Sc(OTf)_3$ as a catalyst has been described for the synthesis of 3-substituted indoles **210** (Scheme 250).[283] The mechanism proposed by the authors most likely involves the coordination of the carbonyl moiety to the $Sc(OTf)_3$ catalyst, followed by the nucleophilic attack of the aromatic ring on the carbon–carbon triple bond giving the allene intermediate, which after an isomerization, followed by a 1,3-H shift, delivers the indole derivatives (Scheme 251).

### 2.16. Silver-catalyzed synthesis of indoles

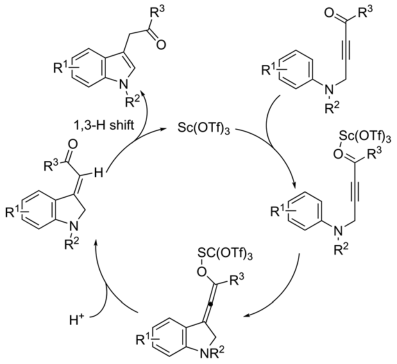
Because of their electronic configuration and mild π-acidity, silver salts are very efficient at alkyne activation.[284] These special properties make silver salts highly effective at promoting cyclization reactions providing a facile access to heterocycles. An interesting application of the properties of silver was in the synthesis of indole *N*-carboximidamides or *N*-carboximidoates **211** using silver(I)-catalyzed regioselective cyclization of iminophosphoranes (Scheme 252).[285] The reaction of iminophosphoranes with isocyanates gave the carbodiimides, which after reaction with secondary amines afforded the (2-alkynylphenyl)guanidine (or isourea) intermediates. The *in situ* addition of a catalytic amount of $AgNO_3$, at room temperature, promoted the cyclization affording the indole *N*-carboximidamides or *N*-carboximidoates in good yields (Scheme 252). A variation of this silver-catalyzed cyclization involved the cycloisomerization of *N*-imidoyl-2-alkynylanilines to form indole derivatives **212** (Scheme 253).[286] The authors suggested that the structure of the silver–alkyne complex **213** would be beneficial for the 5-*endo-dig* *N*-nucleophilic attack (pathway a, complex **213**). In a similar way, the reaction of *ortho*-alkynyl isothiocyanates with secondary amines, catalyzed by silver triflate, led to the formation of *N*-thiourea indoles **214** *via* a 5-*endo-dig* mode (Scheme 254).[287]



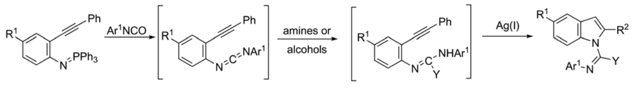
**210**, 30-81%

$R^1$ = H, 2-Me, 4-Me, 4-MeO, 3-Cl, 4-Cl; $R^2$ = Me, Bn, Ph, propargyl, allyl; $R^3$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$.

Scheme 250



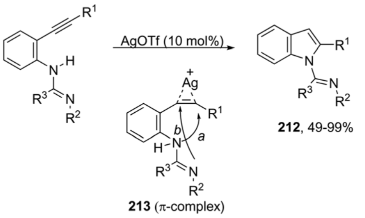
Scheme 251



**211**, 68-93%

$R^1$ = H, Me; $Ar^1$ = $C_6H_5$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 3-Me-$C_6H_4$; amines = $Et_2NH$, *n*-$Pr_2NH$, morpholine, pyrrolidine, piperidine; alcohols = MeOH, EtOH.

Scheme 252

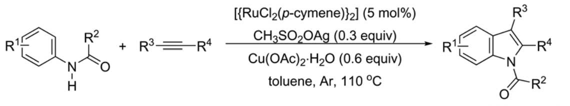


**212**, 49-99%

**213** (π-complex)

$R^1$ = *n*-Pr, *i*-Pr, *t*-Bu, $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$F_3C$-$C_6H_4$; $R^2$ = *n*-Pr, $C_6H_5$; $R^3$ = Et, $C_6H_5$.

Scheme 253



**208**, 34-83%

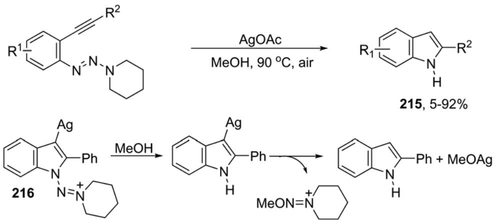
$R^1$ = H, 2-Me, 3-Me, 4-Me, 4-MeO, 4-$O_2N$, 4-Cl, 4-I; $R^2$ = Me, Et, *i*-Pr, cyclohexyl; $R^3$ = $R^4$ = 2-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, *n*-$C_4H_9$; $R^3$ = $C_6H_5$ and $R^4$ = $EtO_2C$, *t*-$C_4H_9$; $R^3$ = *t*-$C_4H_9$ and $R^4$ = $C_6H_5$.

Scheme 254

The 2-substituted *NH*-indoles **215** were synthesized by a regioselective cyclization reaction from 2-aryltriazene alkynes *via* a silver(I) salt mediated nitrogen–nitrogen bond cleavage (Scheme 255).[288] The authors postulated that the solvolysis of the intermediate **216** by MeOH led to the corresponding indoles and AgOMe. The absence of catalytic activity of the silver salt can be attributed to the decomposition of MeOAg. A similar route was also used to describe the preparation of *N*-cyano-2-substituted indoles **218** using 2-aryltetrazole alkynes as the starting material in a silver(I) catalyzed intramolecular cyclization (Scheme 256).[289] The advance of the methodology is the identification of a cyclopropyl argentium cationic intermediate **217**, which could be responsible for the use of a catalytic amount of the silver salt.

Silver-catalyzed cascade cyclization/3-carbon functionalization represents a versatile strategy for construction of 3-functionalized indoles because of its efficiency, atom economy and ability to deliver the product in a single reaction step. Listed below are a number of silver-catalyzed cascade cyclization examples that led to the formation of 3-substituted indoles. A silver(I)-catalyzed activation of *ortho*-alkynylanilines and aldehydes gave 2,2′-disubstituted bisindolylarylmethanes **219**, *via* a domino 5-*endo-dig* indole annulation, addition to the carbonyl group, second indole annulation, and dehydroxylative sequence (Scheme 257). Another example applying silver-catalyzed cascade cyclization has been used in the preparation of 3-fluoroindoles **220** (Scheme 258).[290] In this reaction, *ortho*-alkynylanilines, having an electron-withdrawing group directly bonded to the alkyne, in the presence of catalytic amounts of $AgNO_3$ and Selectfluor, gave the corresponding 3-fluoroindoles in moderate yields, even by adding a base in the medium to prevent the formation of the 3-unsubstituted indoles.

A recent study described the preparation of 3-phosphinoylindoles **221** through silver-mediated cycloaddition between *N*-Ts-*ortho*-alkynylanilines and *H*-phosphine oxides (Scheme 259).[291] On the basis of experimental evidence, the authors proposed that a radical pathway is involved in this phosphinoylation–cyclization–desulfonylation sequence. Also in this topic, 2-tributylstannylfuran was used in the silver-catalyzed cascade cyclization–stannylation of *ortho*-alkynylanilines to introduce a stannyl substituent at the 3-carbon of the indole ring giving (3-indolyl)stannanes **222** (Scheme 260).[292] The reaction mechanism studies indicated that the stannylation did not occur by the carbon–hydrogen functionalization of indole.

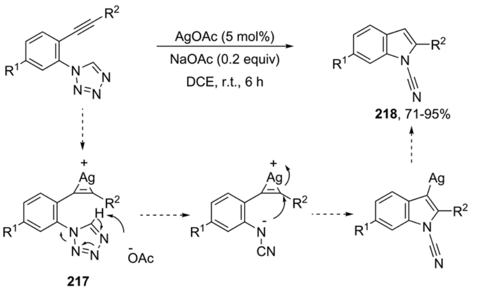


**215**, 5-92%

**216**

$R^1$ = H, 4-Cl, 2,4-$(Cl)_2$, 4-F, (2-$MeO_2C$, 4-Cl); $R^2$ = *n*-$C_6H_{13}$, c-$C_3H_5$, *c*-$C_6H_{11}$, $C_6H_5$, 4-F-$C_6H_4$, 3-$NH_2$-$C_6H_4$, 3-Me-$C_6H_4$, 3-pyridyl,

Scheme 255

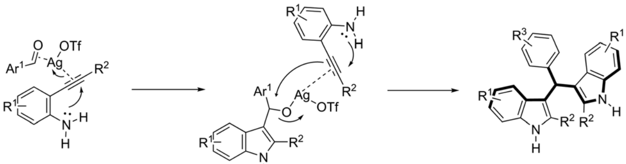


**218**, 71-95%

**217**

$R^1$ = H, 4-Cl, 3-Cl, 4-F, 4-Me; $R^2$ = *n*-$C_4H_9$, *n*-$C_6H_{13}$, *t*-Pr, *t*-Bu, *c*-$C_3H_5$, *c*-$C_5H_9$, *c*-$C_6H_{11}$, $C_6H_5$, 4-Cl-$C_6H_4$, 4-$F_3C$-$C_6H_4$, 4-HO-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$MeO_2CCH_2$, $PhCH_2CH_2$, $HOCH_2$.

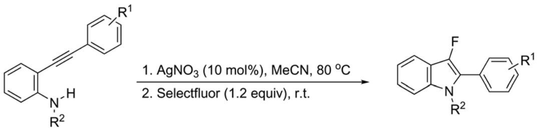
Scheme 256



**219**, 69-95%

$R^1$ = H, 3-Cl, 4-Cl, $R^2$ = *n*-$C_4H_9$, $HOCH_2CH_2$, $PhCO_2CCH_2CH_2$, $C_6H_5$; $R^3$ = 4-Me, 2-Cl, 4-Cl, 4-$O_2N$, (3-MeO, 4-HO), 2-thienyl, 2-furyl.

Scheme 257



**220**, 30-58%

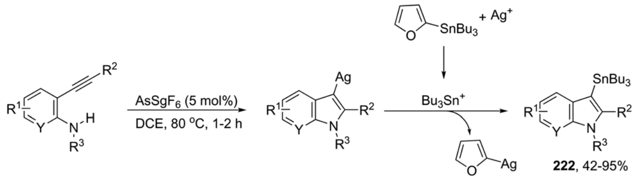
$R^1$ = 4-Cl, 2-F, 3,5-$(F_3C)_2$, Ac; $R^2$ = H, Me, Bn.

Scheme 258

**221**, 28-74%

$R^1$ = H, 4-Me, 4-Cl, 4-F, 4-NC; $R^2$ = H, 3-Me, 4-Me, 4-Et, 4-Ph, 4-MeO, 4-Br, 4-Cl, 3-F, 4-F, 4-$MeO_2C$, 4-CHO, 4-NC, 4-MeOC, *c*-$C_3H_5$, *n*-$C_4H_9$, 2-thienyl; $R^3$ = $R^4$ = 3-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-MeO-$C_6H_4$; $R^3$ = *n*-$C_4H_9$ and $R^4$ = $C_6H_5$; $R^3$ = EtO and $R^4$ = $C_6H_5$.

Scheme 259



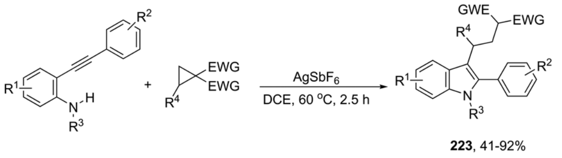
$R^1$ = H, Cl; $R^2$ = $C_6H_5$, 4-MeO-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-$EtO_2C$-$C_6H_4$, 2-thienyl, 2-pyridyl, *n*-$C_4H_9$, *c*-$C_3H_5$, *c*-$C_6H_{11}$; $R^3$ = Ts, Ms, PhOC, MeOC, Me; Y = CH, N.

Scheme 260

The authors proposed that the reaction of electrophilic $Bu_3Sn^+$ with a 3-indolyl silver(I) intermediate could lead to product formation. The stannyl electrophilic species is produced *via* a silver-catalyzed destannylation of 2-tributylstannylfuran through transmetalation and protodemetalation.

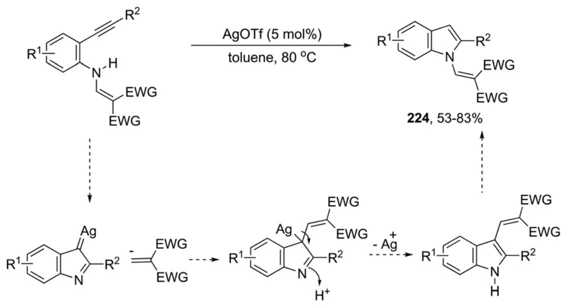
*N*-Protected *ortho*-alkynylanilines underwent a $AgSbF_6$-catalyzed cascade involving the ring opening of donor–acceptor cyclopropanes to produce 2,3-disubstituted indoles **223** (Scheme 261).[293] The silver catalyst presented dual action by activating the carbon–carbon bond, promoting the cyclization of the aniline and activating the cyclopropanes toward the nucleophilic attack of the 3-indolyl silver intermediate.

When iminoethers are incorporated into nitrogen of the anilines, a silver-catalyzed two-component condensation, followed by a tandem silver-induced cycloisomerization and 1,3-alkenyl shift to the silver-activated carbon, formed 2,3-disubstituted indoles **224** (Scheme 262).[294] Not only can silver(I) catalyze the 5-*endo-dig* cyclization but also the silver carbene may be formed, which increases the electron density on the nitrogen atom driving the 1,3-alkenyl migration.



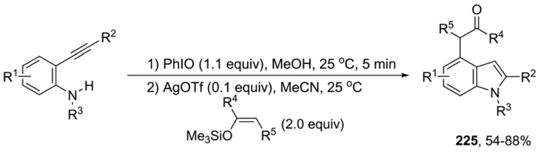
$R^1$ = H, 4-Me, 3-$F_3C$, 4-Cl; $R^2$ = H, *n*-$C_4H_9$, 4-MeO, 4-Me, 3-F, 4-F, 2-$EtO_2C$, TMS, phenylacetyle; $R^3$ = 4-Me-$C_6H_4$, 4-Ph-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, (4-F, 3-Cl)-$C_6H_3$, 4-MeO-$C_6H_4$, 3,4-$(MeO)_2$-$C_6H_3$, 4-$MeO_2C$-$C_6H_4$, 2-furyl; EWG = NC, $MeO_2C$, H.

Scheme 261



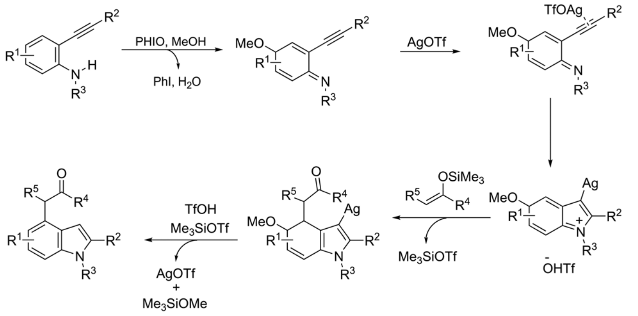
$R^1$ = H, 4-MeO, 4-$O_2N$; $R^2$ = *n*-$C_4H_9$, *t*-Bu, *c*-$C_6H_{11}$, $C_6H_5$, 4-MeO-$C_6H_4$, 1-naphthyl, $PhOCO(CH_2)_4$, $TBSOCH_2CH_2$; EWG = NC, $MeO_2C$.

Scheme 262



$R^1$ = 4-Me, *n*-$C_4H_9$, $C_6H_5$; $R^2$ = H, $C_6H_5$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, TMS; $R^3$ = Ts, Bz; $R^4$ = 4-MeO-$C_6H_4$, 3-Br-$C_6H_4$, 4-Br-$C_6H_4$, 2-Me-$C_6H_4$, 3-Me-$C_6H_4$; $R^5$ = H, Me.

Scheme 263

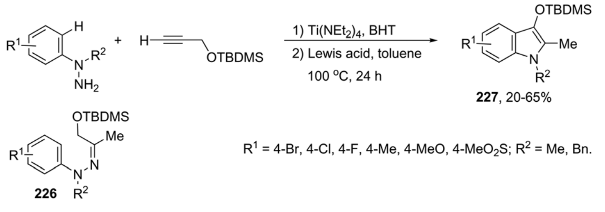


Scheme 264

An oxidative dearomatization of *ortho*-alkynylanilines, followed by a silver(I)-catalyzed domino reaction with silyl enol ethers, provided an expedient approach to synthesize 4-acetonylindoles **225** (Scheme 263).[295] In this sequence, the PhIO mediated oxidative dearomatization of *ortho*-alkynylanilines gave *ortho*-alkynylcyclohexadienimines, whereas AgOTf promoted the heterocyclization of *ortho*-alkynylcyclohexadienimines, which led to 4-acetonylindoles after a Mukaiyama-Michael addition with silyl enol ethers (Scheme 264).

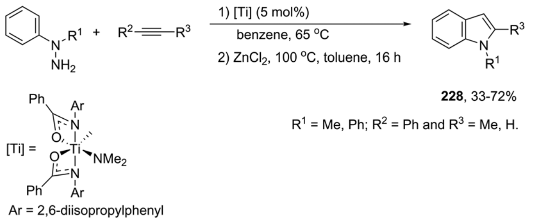
## 2.17. Titanium-catalyzed synthesis of indoles

Indoles can be directly obtained from alkynes and a nitrogen substrate in an intra- or intermolecular reaction of titanium-catalyzed cyclization. Although, titanium-catalyzed cyclization is less commonly used, the reactions show impressive reactivity and good control in the regioselectivity. A very efficient method for the synthesis of substituted 3-(*tert*-butyldimethylsilyloxy)indoles **227** *via* titanium-catalyzed hydrohydrazination of a protected propargyl alcohol derivative has been developed (Scheme 265).[296] The reaction gave regioselectively the key intermediate **226**, *via* a Markovnikov addition, which afforded exclusively the 2,3-disubstituted indoles. The anti-Markovnikov



$R^1$ = 4-Br, 4-Cl, 4-F, 4-Me, 4-MeO, 4-$MeO_2S$; $R^2$ = Me, Bn.

Scheme 265



**228**, 33-72%

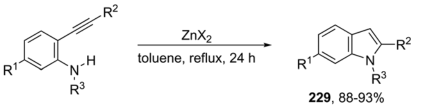
$R^1$ = Me, Ph; $R^2$ = Ph and $R^3$ = Me, H.

Scheme 266

hydroamination of alkynes was achieved in the reaction of a hydrazine-catalyzed bis-(amidate)-bis-(amido)titanium complex, which gave indoles **228** as products (Scheme 266).[297]

### 2.18. Zinc-catalyzed synthesis of indoles

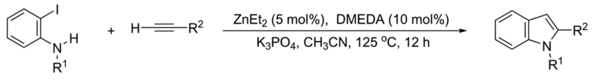
For improving the efficiency of the transition metal-catalyzed reactions in terms of price, toxicity, availability, and production of waste, zinc chemistry is a very attractive option. Many different examples of classical processes that employ zinc have been well established, including the Reformatsky reaction, Fukuyama coupling, and Negishi coupling. In these reactions, because of the filled d-orbitals, zinc acts as a promoter rather than a catalyst. However, in the last few years many efforts have focused on increasing the effectiveness of zinc as a catalyst. As an example, the zinc-catalyzed intramolecular or intermolecular cyclization reaction between alkynes and a nitrogen moiety is efficiently used for the preparation of indoles. An interesting method using a catalytic amount of $ZnBr_2$ as a Lewis acid to promote the cyclization of *ortho*-2-alkynylanilines was described for the synthesis of 2-substituted indoles **229** (Scheme 267).[298] In a related study, the tandem zinc-based Sonogashira cross-coupling, followed by a 5-*endo-dig* cyclization of *ortho*-anilines with terminal alkynes, led to the formation of 1,2-disubstituted indoles **230** (Scheme 268).[299] The reaction required the presence of *N*,*N*′-dimethylethylenediamine in a 1 : 2 ratio of zinc to form a Zn–DMEDA complex, which catalyzed the tandem process. The cascade sequence was also used to synthesize indolo[1,2-*c*]quinazolines. Thus, the reaction of *N*-2-[(2-aminophenyl)ethynyl] phenylamides with $ZnBr_2$ gave indolo[1,2-*c*]quinazolines **231** *via* a zinc bromide-promoted domino sequence involving a 5-*endo-dig* hydroamination and the intramolecular cyclization sequence (Scheme 269).[300]



**229**, 88-93%

$R^1$ = H, MeO, Br, Cl; $R^2$ = $C_6H_5$, *n*-Pr, *n*-Pent; $R^3$ = H, Ts; X = Br, Cl, I.

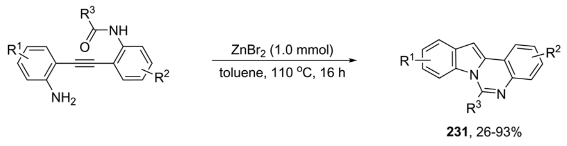
Scheme 267



$R^1$ = H, MeOC; $R^2$ = $C_6H_5$, 4-Me-$C_6H_5$.

**230**, 54-89%

Scheme 268

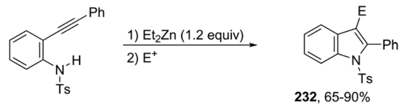


**231**, 26-93%

$R^1$ =H, 4-Cl, 4-Me, 3,4-$OCH_2O$; $R^2$ = H, 4-Cl, 4-Me, 3,4-$OCH_2O$; $R^3$ = H, Me, Et, *i*-Pr, $F_3C$, $C_6H_5$, 4-$O_2N$-$C_6H_4$, 4-MeO-$C_6H_4$, PhCH=CH.

Scheme 269

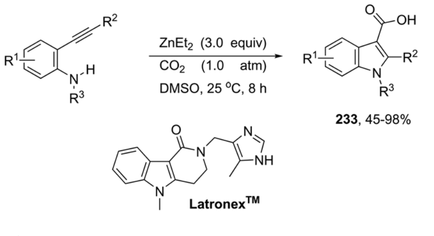
Another interesting cascade reaction is the zinc-catalyzed intramolecular hydroamination and cyclization-nucleophilic addition of *ortho*-alkynylanilines to form 2,3-disubstituted indoles. Thus, *N*-tosyl-protected aliphatic *ortho*-aminoalkynes reacted with diethylzinc in toluene, followed by the electrophile addition to give the corresponding 2,3-disubstituted indoles **232** (Scheme 270).[301] When carbon dioxide was used as the electrophile, the reaction produced indole-3-carboxylic acids **233** (Scheme 271). The methodology was applied to the synthesis of Lotronex, a drug molecule used for the treatment of irritable bowel syndrome.[302] More recently, in a tandem cyclization, dizinc *ortho*-ethynylaniline was found to act as a nucleophile in the formation of 2,3-dimetalloindole, which was functionalized with one or two electrophiles to give 2,3-disusbtituted indoles **234** (Scheme 272).[303] The authors discussed the structures of zinc intermediates and concluded that the key intermediate could be a dimeric structure, where the $ZnCl_2$ group is coordinated to the indole π-system to form a zwitterion, with the C3-carbon being tetrahedral and the C2-carbon being trigonal. The domino alkyne-amination–Fischer-indole sequence was described for the preparation of indole-



**232**, 65-90%

$E^+$ = PhCOCl, EtCOCl, acryloyl chloride, 2-furyl chloride, cyclopropanecarboxylic acid chloride, pivaloyl chloride, NBS.

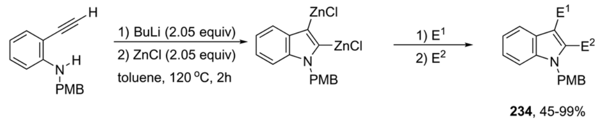
Scheme 270



**233**, 45-98%

$R^1$ = H, 2-Cl, 3-Cl, 4-Cl, 4-Br, 2-F, 4-F, 4-$F_3C$, 4-$MeO_2C$, 4-NC, 4-$O_2N$, 4-MeO, 2-Me, 3-Me, 4-Me; $R^2$ = H, *c*-$C_3H_5$, *n*-$C_4H_9$, *n*-$C_6H_{13}$, *c*-$C_6H_{11}$, *n*-$C_8H_{17}$, $PhCH_2CH_2$, $Cl(CH_2)_3$, $NC(CH_2)_3$, $AcCH_2CH_2$, $HOCH_2CH_2$, $BnOCH_2$, $C_6H_5$, 4-MeO-$C_6H_4$,

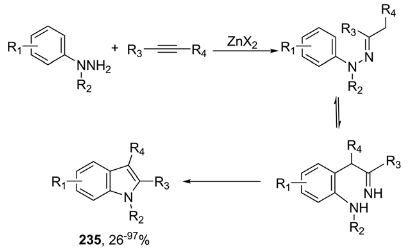
Scheme 271



**234**, 45-99%

$E^1 = D_2O$, $I_2$, MeI, 4-MeO-$C_6H_4OCCl$, PhI, CyI, $BrCH_2CH{=}CH_2$, $Ph_2OC$, $Me_3SnCl$; $E^2 = NH_4Cl$, $D_2O$, PhI, $BrCH_2CH{=}CH_2$.

Scheme 272



**235**, 26-97%

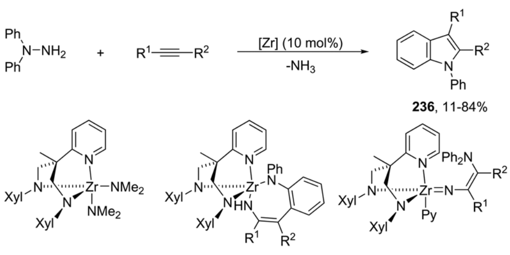
$R_1$ = H, 2-Me, 4-Me, 4-*i*-Pr, 4-*t*-Bu, 4-MeO, 4-Br, 4-Cl, 4-F, 4-$F_3C$, 4-$MeO_2S$; $R_2$ = H, Me, Bn; $R_3$ = H and $R_4$ = $C_5H_{11}CH_2$, *n*-$C_6H_{13}$, Bn, *c*-$C_5H_9CH_2$, $TBDMSOCH_2CH_2$, $HO(CH_2)_3$, $MeO_2CCH_2CH_2$, $TBDMSOCH_2$, $MeOCH_2$, $R_2NHCH_2$; $R_3 = R_4 = EtO_2C$; $R_3$ = $EtO_2C$ and $R_4$ = Ph.

Scheme 273

2,3-dicarboxylates,[304] 2-methyl-3-substituted-indoles[305] and 2-methyl-3-amino-indoles.[306] The method was based on the reaction of phenylhydrazines with terminal or internal alkynes promoted by $ZnCl_2$, $ZnBr_2$, or $Zn(OTf)_2$ affording the indole derivatives **235** (Scheme 273). In these reactions, the zinc salts participate in the intramolecular hydroamination of the arylhydrazine with terminal alkynes forming the arylhydrazone intermediate to promote the [3,3]-sigmatropic cyclization to the corresponding indoles (Scheme 273).

### 2.19. Zirconium-catalyzed synthesis of indoles

Reports on zirconium-catalyzed cyclization of alkynes to prepare indoles are not extensive in organic chemistry in the last ten years. A detailed study regarding the influence of the reaction mechanism on the selectivity in domino reactions of hydrazine zirconium complexes with alkynes was described in the preparation of indoles **236** (Scheme 274).[307,308] The authors showed that the reaction of diarylhydrazines with terminal and internal alkynes using zirconium complex **237** at room temperature gave the corresponding indole derivatives. Although the reaction mechanism is relatively complex, the structures **238** and **239** represent the key reaction intermediates.



**236**, 11-84%

**237** **238** **239**

$R^1$ = Me, Et, $C_6H_5$, 4-$F_3C$-$C_6H$, 6-MeO-naphthyl; $R^2$ = H, Me, Et, 4-$F_3C$-$C_6H$.

Scheme 274

## 3. Conclusion

Transition metal-catalyzed activation of alkynes, followed by an intramolecular or intermolecular nucleophile addition, has become a powerful tool for the construction of the indole ring. Transition metal complexes containing bismuth, cobalt, copper, gold, indium, iridium, iron, manganese, mercury, nickel, palladium, platinum, rhenium, ruthenium, scandium, silver, titanium, tungsten, zinc, and zirconium have been employed as active catalysts for the activation of alkynes. The synthetic approaches to form indole derivatives developed in the last ten years using transition metal-catalyzed cyclization of alkynes with nitrogen compounds were summarized in this review. Further studies related to indole synthesis will undoubtedly lead to the discovery of new structures with biological activity and consequently the development of new medical and pharmacological applications. This will guide the new studies to overcome the challenges and keep this important class of N-heterocycles active for many years. It is our hope that this review article will assist the chemists in choosing the suitable methodology for indole preparation and stimulate the development of new synthetic methods for their synthesis.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The authors are grateful for financial support from the CNPq, CAPES and FAPERGS. We also want to thank the students from our research group who helped to draw the chemical structures.

## References

1 T. P. Singh and O. M. Singh, *Mini-Rev. Med. Chem.*, 2018, **18**, 9–25.
2 S. Suzen, *Curr. Org. Chem.*, 2017, **21**, 2068–2076.
3 K. Walton and J. P. Berry, *Mar. Drugs*, 2016, **14**, 28.
4 Y. M. Ma, X. A. Liang, Y. Kong and B. Jia, *J. Agric. Food Chem.*, 2016, **64**, 6659–6671.
5 S. M. Li, *Nat. Prod. Rep.*, 2010, **27**, 57–78.
6 Z. R. Owczarczyk, W. A. Braunecker, A. Garcia, R. Larsen, A. M. Nardes, N. Kopidakis, D. S. Ginley and D. C. Olson, *Macromolecules*, 2013, **46**, 1350–1360.

7 G. M. Nie, Z. M. Bai, W. Y. Yu and L. Zhang, *J. Polym. Sci., Part A: Polym. Chem.*, 2013, **51**, 2385–2392.

8 M. Manickam, P. Iqbal, M. Belloni, S. Kumar and J. A. Preece, *Isr. J. Chem.*, 2012, **52**, 917–934.

9 D. V. Vorobyeva and S. N. Osipov, *Synthesis*, 2018, **50**, 227–240.

10 M. Petrini, *Chem. – Eur. J.*, 2017, **23**, 16115–16151.

11 I. Szatmari, J. Sas and F. Fulop, *Curr. Org. Chem.*, 2016, **20**, 2038–2054.

12 E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390–2402.

13 W. W. Zi, Z. W. Zuo and D. W. Ma, *Acc. Chem. Res.*, 2015, **48**, 702–711.

14 A. H. Sandtorv, *Adv. Synth. Catal.*, 2015, **357**, 2403–2435.

15 R. Dalpozzo, *Chem. Soc. Rev.*, 2015, **44**, 742–778.

16 H. Wu, Y. P. He and F. Shi, *Synthesis*, 2015, **47**, 1990–2016.

17 N. Thirupathi, Y. K. Kumar, R. Kant and M. S. Reddy, *Adv. Synth. Catal.*, 2014, **356**, 1823–1834.

18 S. Lancianesi, A. Palmieri and M. Petrini, *Chem. Rev.*, 2014, **114**, 7108–7149.

19 G. Bartoli, R. Dalpozzo and M. Nardi, *Chem. Soc. Rev.*, 2014, **43**, 4728–4750.

20 E. Fischer and F. Jourdan, *Eur. J. Inorg. Chem.*, 1883, **16**, 2241–2245.

21 A. Bischler, *Eur. J. Inorg. Chem.*, 1892, **25**, 2860–2879.

22 A. Reissert, *Eur. J. Inorg. Chem.*, 1897, **30**, 1030–1053.

23 W. Madelung, *Eur. J. Inorg. Chem.*, 1912, **45**, 1128–1134.

24 C. Nenitzescu, *Bull. Soc. Chim. Romania*, 1929, **11**, 37–43.

25 R. J. Sundberg and T. Yamazaki, *J. Org. Chem.*, 1967, **32**, 290–294.

26 H. Hemetsberger and D. Knittel, *Monath. Chem.*, 1972, **103**, 194–204.

27 P. G. Gassman, T. Van Bergen and G. Gruetzmacher, *J. Am. Chem. Soc.*, 1973, **95**, 6508–6509.

28 A. D. Batcho and W. Leimgruber, *Org. Synth.*, 1985, **63**, 214–220.

29 J.-B. Baudin and S. A. Julia, *Tetrahedron Lett.*, 1986, **27**, 837–840.

30 G. Bartoli, G. Palmieri, M. Bosco and R. Dalpozzo, *Tetrahedron Lett.*, 1989, **30**, 2129–2132.

31 R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689–6690.

32 T. Fukuyama, X. Chen and G. Peng, *J. Am. Chem. Soc.*, 1994, **116**, 3127–3128.

33 D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195.

34 L. Zhang, Z. Li and R. Fan, *Org. Lett.*, 2012, **14**, 6076–6079.

35 A. Lerchen, S. Vásquez-Céspedes and F. Glorius, *Angew. Chem., Int. Ed.*, 2016, **55**, 3208–3211.

36 S. Zhou, J. Wang, L. Wang, K. Chen, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 3806–3809.

37 Y. Liang and N. Jiao, *Angew. Chem.*, 2016, **128**, 4103–4107.

38 H. Wang, M. Moselage, M. A. J. González and L. Ackermann, *ACS Catal.*, 2016, **6**, 2705–2709.

39 Z.-Z. Zhang, B. Liu, J.-W. Xu, S.-Y. Yan and B.-F. Shi, *Org. Lett.*, 2016, **18**, 1776–1779.

40 S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang and D. Ma, *Angew. Chem., Int. Ed.*, 2017, **56**, 16136–16179.

41 A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727–7729.

42 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13–31.

43 N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442.

44 S. Song, M. Huang, W. Li, X. Zhu and Y. Wan, *Tetrahedron*, 2015, **71**, 451–456.

45 M. J. García-Muñoz, F. Foubelo and M. Yus, *J. Org. Chem.*, 2016, **81**, 10214–10226.

46 Z.-Q. Wang, X. Zhang, L.-T. Yu, W.-T. Mao, C.-Z. Chen and K. Xu, *Org. Biomol. Chem.*, 2015, **13**, 6931–6934.

47 F. Liu and D. Ma, *J. Org. Chem.*, 2007, **72**, 4844–4850.

48 T. Ponpandian and S. Muthusubramanian, *Tetrahedron Lett.*, 2012, **53**, 4248–4252.

49 R. Wang, S. Mo, Y. Lu and Z. Shen, *Adv. Synth. Catal.*, 2011, **353**, 713–718.

50 H. Li, X. Li, H.-Y. Wang, G. N. Winston-McPherson, H.-M. J. Geng, I. A. Guzei and W. Tang, *Chem. Commun.*, 2014, **50**, 12293–12296.

51 L. Ackermann, S. Barfuesser and H. K. Potukuchi, *Adv. Synth. Catal.*, 2009, **351**, 1064–1072.

52 J. Gao, Y. Shao, J. Zhu, J. Zhu, H. Mao, X. Wang and X. Lv, *J. Org. Chem.*, 2014, **79**, 9000–9008.

53 H. Wang, Y. Li, L. Jiang, R. Zhang, K. Jin, D. Zhao and C. Duan, *Org. Biomol. Chem.*, 2011, **9**, 4983–4986.

54 M. Yang, J. Tang and R. Fan, *Chem. Commun.*, 2012, **48**, 11775–11777.

55 H. Ohno, Y. Ohta, S. Oishi and N. Fujii, *Angew. Chem., Int. Ed.*, 2007, **46**, 2295–2298.

56 Y. Ohta, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2009, **74**, 7052–7058.

57 S. Cacchi, G. Fabrizi, A. Iazzetti, C. Molinaro, R. Verdiglione and A. Goggiamani, *Adv. Synth. Catal.*, 2015, **357**, 1053–1059.

58 L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 968–971.

59 T. Xiao, X. Dong and L. Zhou, *Org. Biomol. Chem.*, 2013, **11**, 1490–1497.

60 Z. Shen and X. Lu, *Adv. Synth. Catal.*, 2009, **351**, 3107–3112.

61 N. K. Swamy, A. Yazici and S. G. Pyne, *J. Org. Chem.*, 2010, **75**, 3412–3419.

62 M. Yamashita, T. Noro and A. Iida, *Tetrahedron Lett.*, 2013, **54**, 6848–6851.

63 Z. Li, L. Hong, R. Liu, J. Shen and X. Zhou, *Tetrahedron Lett.*, 2011, **52**, 1343–1347.

64 N. Matsuda, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **77**, 617–625.

65 Y. Oda, N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *Synthesis*, 2012, 1515–1520.

66 A. Sagadevan, A. Ragupathi and K. C. Hwang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13896–13901.

67 H. E. Ho, K. Oniwa, Y. Yamamoto and T. Jin, *Org. Lett.*, 2016, **18**, 2487–2490.

68 J. Yu, D. Zhang-Negrerie and Y. Du, *Org. Lett.*, 2016, **18**, 3322–3325.

69 A. Gogoi, S. Guin, S. K. Rout and B. K. Patel, *Org. Lett.*, 2013, **15**, 1802–1805.

70 S. Murru, A. A. Gallo and R. S. Srivastava, *Eur. J. Org. Chem.*, 2011, 2035–2038.

71 D. Gao and T. G. Back, *Chem. – Eur. J.*, 2012, **18**, 14828–14840.

72 L. Cao, D. Shen, J. Wei, J. Chen, H. Deng, M. Shao, J. Shi, H. Zhang and W. Cao, *Eur. J. Org. Chem.*, 2014, **2014**, 2460–2467.

73 B. Alcaide and P. Almendros, *Acc. Chem. Res.*, 2014, **47**, 939–952.

74 I. Ambrogio, A. Arcadi, S. Cacchi, G. Fabrizi and F. Marinelli, *Synlett*, 2007, 1775–1779.

75 K. Majumdar, S. Samanta and B. Chattopadhyay, *Tetrahedron Lett.*, 2008, **49**, 7213–7216.

76 S. Liang, L. Hammond, B. Xu and G. B. Hammond, *Adv. Synth. Catal.*, 2016, **358**, 3313–3318.

77 P. Li, L. Wang, M. Wang and F. You, *Eur. J. Org. Chem.*, 2008, 5946–5951.

78 M. Xu, Q. Hou, S. Wang, H. Wang and Z.-J. Yao, *Synthesis*, 2011, 626–634.

79 P. Kothandaraman, S. R. Mothe, S. S. M. Toh and P. W. H. Chan, *J. Org. Chem.*, 2011, **76**, 7633–7640.

80 H. Peng, N. G. Akhmedov, Y.-F. Liang, N. Jiao and X. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 8912–8915.

81 M. Michalska and K. Grela, *Synlett*, 2016, 599–603.

82 D. Ye, J. Wang, X. Zhang, Y. Zhou, X. Ding, E. Feng, H. Sun, G. Liu, H. Jiang and H. Liu, *Green Chem.*, 2009, **11**, 1201–1208.

83 J. Zhu, H. Xie, Z. Chen, S. Li and Y. Wu, *Org. Biomol. Chem.*, 2012, **10**, 516–523.

84 X. Zhang and A. Corma, *Angew. Chem.*, 2008, **120**, 4430–4433.

85 Y. Yamane, X. Liu, A. Hamasaki, T. Ishida, M. Haruta, T. Yokoyama and M. Tokunaga, *Org. Lett.*, 2009, **11**, 5162–5165.

86 A. La-Venia, S. A. Testero, M. P. Mischne and E. G. Mata, *Org. Biomol. Chem.*, 2012, **10**, 2514–2517.

87 I. Nakamura, U. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Angew. Chem.*, 2007, **119**, 2334–2337.

88 X. Zeng, R. Kinjo, B. Donnadieu and G. Bertrand, *Angew. Chem.*, 2010, **122**, 954–957.

89 K. Majumdar, S. Hazra and B. Roy, *Tetrahedron Lett.*, 2011, **52**, 6697–6701.

90 A. Gimeno, A. Rodríguez-Gimeno, A. B. Cuenca, C. R. de Arellano, M. Medio-Simón and G. Asensio, *Chem. Commun.*, 2015, **51**, 12384–12387.

91 B. Subba Reddy, M. Swain, S. M. Reddy, J. Yadav and B. Sridhar, *J. Org. Chem.*, 2012, **77**, 11355–11361.

92 G. Abbiati, A. Arcadi, M. Chiarini, F. Marinelli, E. Pietropaolo and E. Rossi, *Org. Biomol. Chem.*, 2012, **10**, 7801–7808.

93 C. Praveen, K. Karthikeyan and P. Perumal, *Tetrahedron*, 2009, **65**, 9244–9255.

94 N. T. Patil, V. Singh, A. Konala and A. K. Mutyala, *Tetrahedron Lett.*, 2010, **51**, 1493–1496.

95 B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem.*, 2011, **123**, 8508–8512.

96 C. Qu, S. Zhang, H. Du and C. Zhu, *Chem. Commun.*, 2016, **52**, 14400–14403.

97 J. E. Perea-Buceta, T. Wirtanen, O. V. Laukkanen, M. K. Mäkelä, M. Nieger, M. Melchionna, N. Huittinen, J. A. Lopez-Sanchez and J. Helaja, *Angew. Chem., Int. Ed.*, 2013, **52**, 11835–11839.

98 C.-H. Shen, L. Li, W. Zhang, S. Liu, C. Shu, Y.-E. Xie, Y.-F. Yu and L.-W. Ye, *J. Org. Chem.*, 2014, **79**, 9313–9318.

99 E. Chong and S. A. Blum, *J. Am. Chem. Soc.*, 2015, **137**, 10144–10147.

100 G. Cera, S. Piscitelli, M. Chiarucci, G. Fabrizi, A. Goggiamani, R. S. Ramón, S. P. Nolan and M. Bandini, *Angew. Chem., Int. Ed.*, 2012, **51**, 9891–9895.

101 Y. Zhang, J. P. Donahue and C.-J. Li, *Org. Lett.*, 2007, **9**, 627–630.

102 S. Cai, K. Yang and D. Z. Wang, *Org. Lett.*, 2014, **16**, 2606–2609.

103 N. T. Patil and A. Konala, *Eur. J. Org. Chem.*, 2010, 6831–6839.

104 H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 794–797.

105 Y. Wang, L. Ye and L. Zhang, *Chem. Commun.*, 2011, **47**, 7815–7817.

106 D. B. Huple, B. D. Mokar and R. S. Liu, *Angew. Chem., Int. Ed.*, 2015, **54**, 14924–14928.

107 Y. Matsuda, S. Naoe, S. Oishi, N. Fujii and H. Ohno, *Chem. – Eur. J.*, 2015, **21**, 1463–1467.

108 J. Liu, M. Chen, L. Zhang and Y. Liu, *Chem. – Eur. J.*, 2015, **21**, 1009–1013.

109 J. S. Kim, J. H. Han, J. J. Lee, Y. M. Jun, B. M. Lee and B. H. Kim, *Tetrahedron Lett.*, 2008, **49**, 3733–3738.

110 N. Sakai, K. Annaka, A. Fujita, A. Sato and T. Konakahara, *J. Org. Chem.*, 2008, **73**, 4160–4165.

111 K. Murai, S. Hayashi, N. Takaichi, Y. Kita and H. Fujioka, *J. Org. Chem.*, 2008, **74**, 1418–1421.

112 E. Kumaran and W. K. Leong, *Tetrahedron Lett.*, 2014, **55**, 5495–5498.

113 E. Kumaran, W. Y. Fan and W. K. Leong, *Org. Lett.*, 2014, **16**, 1342–1345.

114 K. Y. Ye, L. X. Dai and S. L. You, *Chem. – Eur. J.*, 2014, **20**, 3040–3044.

115 T. Shibata, H. Hirashima, M. Kasagawa, K. Tsuchikama and K. Endo, *Synlett*, 2011, 2171–2176.

116 P. Zhang, T. Xiao, S. Xiong, X. Dong and L. Zhou, *Org. Lett.*, 2014, **16**, 3264–3267.

117 F. Gao, J.-T. Wang, L.-L. Liu, N. Ma, C. Yang, Y. Gao and W. Xia, *Chem. Commun.*, 2017, **53**, 8533–8536.

118 C. Bolm, J. Legros, J. Le Paih and L. Zani, *Chem. Rev.*, 2004, **104**, 6217–6254.

119 I. Bauer and H.-J. Knölker, *Chem. Rev.*, 2015, **115**, 3170–3387.

120 S. L. Buchwald and C. Bolm, *Angew. Chem.*, 2009, **121**, 5694–5695.

121 K. C. Majumdar, N. De, T. Ghosh and B. Roy, *Tetrahedron*, 2014, **33**, 4827–4868.

122 V. Terrasson, J. Michaux, A. Gaucher, J. Wehbe, S. Marque, D. Prim and J. M. Campagne, *Eur. J. Org. Chem.*, 2007, 5332–5335.

123 H. A. Du, R. Y. Tang, C. L. Deng, Y. Liu, J. H. Li and X. G. Zhang, *Adv. Synth. Catal.*, 2011, **353**, 2739–2748.

124 A. Speranca, B. Godoi, P. H. Menezes and G. Zeni, *Synlett*, 2013, 1125–1132.

125 A. A. Lamar and K. M. Nicholas, *Tetrahedron*, 2009, **65**, 3829–3833.

126 T. Kurisaki, T. Naniwa, H. Yamamoto, H. Imagawa and M. Nishizawa, *Tetrahedron Lett.*, 2007, **48**, 1871–1874.

127 M. Zheng, K. Chen and S. Zhu, *Synthesis*, 2017, 4173–4182.

128 N. Maizuru, T. Inami, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2011, **13**, 1206–1209.

129 S. A. Patil, R. Patil and D. D. Miller, *Curr. Med. Chem.*, 2009, **16**, 2531–2565.

130 K. Krüger, A. Tillack, M. Beller, M. Zeng, Q. Kang, Q.-L. He and S.-L. You, *Adv. Synth. Catal.*, 2008, **350**, 2153–2167.

131 D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238.

132 J. J. Li and G. W. Gribble, *Palladium in heterocyclic chemistry: a guide for the synthetic chemist*, Elsevier, 2006.

133 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911.

134 S. Patil and J. K. Buolamwini, *Curr. Org. Synth.*, 2006, **3**, 477–498.

135 S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.

136 R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922.

137 D. Wang and S. Gao, *Org. Chem. Front.*, 2014, **1**, 556–566.

138 R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084–5121.

139 I. Ambrogio, S. Cacchi and G. Fabrizi, *Tetrahedron Lett.*, 2007, **48**, 7721–7725.

140 S. Ye, Q. Ding, Z. Wang, H. Zhou and J. Wu, *Org. Biomol. Chem.*, 2008, **6**, 4406–4412.

141 G. Qiu, Q. Ding, H. Ren, Y. Peng and J. Wu, *Org. Lett.*, 2010, **12**, 3975–3977.

142 Y. Morimoto, S. Shimizu, A. Mokuya, N. Ototake, A. Saito and O. Kitagawa, *Tetrahedron*, 2016, **72**, 5221–5229.

143 N. Ototake, Y. Morimoto, A. Mokuya, H. Fukaya, Y. Shida and O. Kitagawa, *Chem. – Eur. J.*, 2010, **16**, 6752–6755.

144 H. Sakai, K. Tsutsumi, T. Morimoto and K. Kakiuchi, *Adv. Synth. Catal.*, 2008, **350**, 2498–2502.

145 R. Sanz, V. Guilarte and A. Pérez, *Tetrahedron Lett.*, 2009, **50**, 4423–4426.

146 K. Dooleweerdt, T. Ruhland and T. Skrydstrup, *Org. Lett.*, 2008, **11**, 221–224.

147 R. M. Rao, U. R. CH, N. Mulakayala, M. Alvala, M. Arunasree, R. R. Poondra, J. Iqbal and M. Pal, *Org. Biomol. Chem.*, 2011, **9**, 3808–3816.

148 A. Ahmed, M. Ghosh, P. Sarkar and J. K. Ray, *Tetrahedron Lett.*, 2013, **54**, 6691–6694.

149 A. Ahmed, M. Ghosh, S. Dhara and J. K. Ray, *Synlett*, 2014, 2455–2458.

150 M. Yamaguchi and K. Manabe, *Org. Lett.*, 2014, **16**, 2386–2389.

151 A. Bruneau, K. Gustafson, N. Yuan, C.-W. Tai, I. Persson, X. Zou and J.-E. Bäckvall, *Chem. – Eur. J.*, 2017, **23**, 12886–12891.

152 Y. Chen, N. A. Markina and R. C. Larock, *Tetrahedron*, 2009, **65**, 8908–8915.

153 S. Cacchi, G. Fabrizi, A. Goggiamani, A. Perboni, A. Sferrazza and P. Stabile, *Org. Lett.*, 2010, **12**, 3279–3281.

154 V. Guilarte, M. P. Castroviejo, P. García-García, M. A. Fernández-Rodríguez and R. Sanz, *J. Org. Chem.*, 2011, **76**, 3416–3437.

155 B. Z. Lu, H.-X. Wei, Y. Zhang, W. Zhao, M. Dufour, G. Li, V. Farina and C. H. Senanayake, *J. Org. Chem.*, 2013, **78**, 4558–4562.

156 Q. Zhou, Z. Zhang, Y. Zhou, S. Li, Y. Zhang and J. Wang, *J. Org. Chem.*, 2016, **82**, 48–56.

157 H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635–646.

158 H. Minami, T. Kanayama, R. Tanaka, N. Okamoto, T. Sueda and R. Yanada, *Eur. J. Org. Chem.*, 2016, 5990–6000.

159 S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti and R. Verdiglione, *Synthesis*, 2017, 4163–4172.

160 A. Arcadi, R. Cianci, G. Ferrara and F. Marinelli, *Tetrahedron*, 2010, **66**, 2378–2383.

161 B. Tréguier, E. Rasolofonjatovo, A. Hamze, O. Provot, J. Wdzieczak-Bakala, J. Dubois, J. D. Brion and M. Alami, *Eur. J. Org. Chem.*, 2011, 4868–4876.

162 R. Álvarez, C. Martinez, Y. Madich, J. G. Denis, J. M. Aurrecoechea and A. R. de Lera, *Chem. – Eur. J.*, 2010, **16**, 12746–12753.

163 S. Cacchi, G. Fabrizi, A. Goggiamani and A. Sferrazza, *Org. Biomol. Chem.*, 2011, **9**, 1727–1730.

164 Q. Wang, L. Huang, X. Wu and H. Jiang, *Org. Lett.*, 2013, **15**, 5940–5943.

165 D. Janreddy, V. Kavala, C.-W. Kuo, T.-S. Kuo, C.-H. He and C.-F. Yao, *Tetrahedron*, 2013, **69**, 3323–3330.

166 V. Reddy and R. Vijaya Anand, *Org. Lett.*, 2015, **17**, 3390–3393.

167 J. Chen, X. Han and X. Lu, *Angew. Chem., Int. Ed.*, 2017, **56**, 14698–14701.

168 S. Tang, Y.-X. Xie, J.-H. Li and N.-X. Wang, *Synthesis*, 2007, 1841–1847.

169 H.-P. Zhang, S.-C. Yu, Y. Liang, P. Peng, B.-X. Tang and J.-H. Li, *Synlett*, 2011, 982–988.

170 X. Han and X. Lu, *Org. Lett.*, 2010, **12**, 3336–3339.

171 F. Zhao, D. Zhang, Y. Nian, L. Zhang, W. Yang and H. Liu, *Org. Lett.*, 2014, **16**, 5124–5127.

172 B. Gabriele, L. Veltri, G. Salerno, R. Mancuso and M. Costa, *Adv. Synth. Catal.*, 2010, **352**, 3355–3363.

173 B. Gabriele, L. Veltri, R. Mancuso, G. Salerno and M. Costa, *Eur. J. Org. Chem.*, 2012, 2549–2559.

174 J. Chen, X. Han and X. Lu, *J. Org. Chem.*, 2017, **82**, 1977–1985.

175 X.-F. Xia, L.-L. Zhang, X.-R. Song, Y.-N. Niu, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 1410–1412.

176 X. Zhang, P. Li, C. Lyu, W. Yong, J. Li, X. Zhu and W. Rao, *Org. Biomol. Chem.*, 2017, **15**, 6080–6083.

177 G. Qiu, C. Chen, L. Yao and J. Wu, *Adv. Synth. Catal.*, 2013, **355**, 1579–1584.

178 Z. Hu, J. Wang, D. Liang and Q. Zhu, *Adv. Synth. Catal.*, 2013, **355**, 3290–3294.

179 G. Qiu, X. Qiu, J. Liu and J. Wu, *Adv. Synth. Catal.*, 2013, **355**, 2441–2446.

180 Z. Hu, S. Luo and Q. Zhu, *Adv. Synth. Catal.*, 2015, **357**, 1060–1064.

181 B. Yao, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2012, **51**, 12311–12315.

182 B. Yao, Q. Wang and J. Zhu, *Chem. – Eur. J.*, 2015, **21**, 7413–7416.

183 J. Huang, S. J. Macdonald and J. P. Harrity, *Chem. Commun.*, 2010, **46**, 8770–8772.

184 Y. J. Guo, R. Y. Tang, J. H. Li, P. Zhong and X. G. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2615–2618.

185 J. Li, C. Li, S. Yang, Y. An, W. Wu and H. Jiang, *J. Org. Chem.*, 2016, **81**, 2875–2887.

186 J. Sheng, S. Li and J. Wu, *Chem. Commun.*, 2014, **50**, 578–580.

187 C. Wu, F. Zhao, Y. Du, L. Zhao, L. Chen, J. Wang and H. Liu, *RSC Adv.*, 2016, **6**, 70682–70690.

188 B. Gabriele, R. Mancuso, G. Salerno, E. Lupinacci, G. Ruffolo and M. Costa, *J. Org. Chem.*, 2008, **73**, 4971–4977.

189 S. Cacchi, G. Fabrizi and E. Filisti, *Synlett*, 2009, 1817–1821.

190 S. Cacchi, G. Fabrizi, A. Goggiamani, C. Molinaro and R. Verdiglione, *J. Org. Chem.*, 2013, **79**, 401–407.

191 I. Ambrogio, S. Cacchi, G. Fabrizi and A. Prastaro, *Tetrahedron*, 2009, **65**, 8916–8929.

192 N. Thirupathi, M. Hari Babu, V. Dwivedi, R. Kant and M. Sridhar Reddy, *Org. Lett.*, 2014, **16**, 2908–2911.

193 Y. Liu, Y. Huang, H. Song, Y. Liu and Q. Wang, *Chem. – Eur. J.*, 2015, **21**, 5337–5340.

194 B. Das, P. Kundu and C. Chowdhury, *Org. Biomol. Chem.*, 2014, **12**, 741–748.

195 C. Chowdhury, B. Das, S. Mukherjee and B. Achari, *J. Org. Chem.*, 2012, **77**, 5108–5119.

196 X. Cui, J. Li, Y. Fu, L. Liu and Q.-X. Guo, *Tetrahedron Lett.*, 2008, **49**, 3458–3462.

197 N. Batail, A. Bendjeriou, T. Lomberget, R. Barret, V. Dufaud and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 2055–2062.

198 N. Batail, V. Dufaud and L. Djakovitch, *Tetrahedron Lett.*, 2011, **52**, 1916–1918.

199 Y. Monguchi, S. Mori, S. Aoyagi, A. Tsutsui, T. Maegawa and H. Sajiki, *Org. Biomol. Chem.*, 2010, **8**, 3338–3342.

200 W. J. Ang, C.-H. Tai, L.-C. Lo and Y. Lam, *RSC Adv.*, 2014, **4**, 4921–4929.

201 S. E. Denmark and J. D. Baird, *Tetrahedron*, 2009, **65**, 3120–3129.

202 P. Danner, M. Morkunas and M. E. Maier, *Org. Lett.*, 2013, **15**, 2474–2477.

203 A. Kondoh, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2010, **12**, 1476–1479.

204 K. Goswami, I. Duttagupta and S. Sinha, *J. Org. Chem.*, 2012, **77**, 7081–7085.

205 W. Hao, W. Geng, W. X. Zhang and Z. Xi, *Chem. – Eur. J.*, 2014, **20**, 2605–2612.

206 W. Hao, J. Wei, W. Geng, W. X. Zhang and Z. Xi, *Angew. Chem., Int. Ed.*, 2014, **53**, 14533–14537.

207 W. Hao, H. Wang, P. J. Walsh and Z. Xi, *Org. Chem. Front.*, 2015, **2**, 1080–1084.

208 C. Zhu and S. Ma, *Org. Lett.*, 2013, **15**, 2782–2785.

209 P. K. R. Panyam and T. Gandhi, *Adv. Synth. Catal.*, 2017, **359**, 1144–1151.

210 T. Curtius, *Eur. J. Inorg. Chem.*, 1890, **23**, 3023–3033.

211 O. Leogane and H. Lebel, *Angew. Chem., Int. Ed.*, 2008, **47**, 350–352.

212 X. Chen, X. Li, N. Wang, J. Jin, P. Lu and Y. Wang, *Eur. J. Org. Chem.*, 2012, 4380–4386.

213 D. Shen, J. Han, J. Chen, H. Deng, M. Shao, H. Zhang and W. Cao, *Org. Lett.*, 2015, **17**, 3283–3285.

214 Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572–4576.

215 I. Nakamura, T. Nemoto, N. Shiraiwa and M. Terada, *Org. Lett.*, 2009, **11**, 1055–1058.

216 F. Zhou, X. Han and X. Lu, *Tetrahedron Lett.*, 2011, **52**, 4681–4685.

217 J. Chen, Q. Pang, Y. Sun and X. Li, *J. Org. Chem.*, 2011, **76**, 3523–3526.

218 J. Chen, L. He, K. Natte, H. Neumann, M. Beller and X. F. Wu, *Adv. Synth. Catal.*, 2014, **356**, 2955–2959.

219 R. Sanz, M. P. Castroviejo, V. Guilarte, A. Pérez and F. J. Fañanás, *J. Org. Chem.*, 2007, **72**, 5113–5118.

220 L. Ackermann, R. Sandmann, M. Schinkel and M. V. Kondrashov, *Tetrahedron*, 2009, **65**, 8930–8939.

221 L. Ackermann, R. Sandmann and M. V. Kondrashov, *Synlett*, 2009, 1219–1222.

222 Y. Liang, T. Meng, H.-J. Zhang and Z. Xi, *Synlett*, 2011, 911–914.

223 P. G. Alsabeh, R. J. Lundgren, L. E. Longobardi and M. Stradiotto, *Chem. Commun.*, 2011, **47**, 6936–6938.

224 C. B. Lavery, R. McDonald and M. Stradiotto, *Chem. Commun.*, 2012, **48**, 7277–7279.

225 N. Halland, M. Nazare, J. Alonso, O. R'kyek and A. Lindenschmidt, *Chem. Commun.*, 2011, **47**, 1042–1044.

226 A. Prakash, M. Dibakar, K. Selvakumar, K. Ruckmani and M. Sivakumar, *Tetrahedron Lett.*, 2011, **52**, 5625–5628.

227 P.-Y. Yao, Y. Zhang, R. P. Hsung and K. Zhao, *Org. Lett.*, 2008, **10**, 4275–4278.

228 K. Cariou, B. Ronan, S. Mignani, L. Fensterbank and M. Malacria, *Angew. Chem., Int. Ed.*, 2007, **46**, 1881–1884.

229 N. Okamoto, Y. Miwa, H. Minami, K. Takeda and R. Yanada, *Angew. Chem.*, 2009, **121**, 9873–9876.

230 N. Okamoto, K. Takeda and R. Yanada, *J. Org. Chem.*, 2010, **75**, 7615–7625.

231 D. Shu, G. N. Winston-McPherson, W. Song and W. Tang, *Org. Lett.*, 2013, **15**, 4162–4165.

232 P. A. Allegretti, K. Huynh, T. J. Ozumerzifon and E. M. Ferreira, *Org. Lett.*, 2015, **18**, 64–67.

233 X. Li, J.-Y. Wang, W. Yu and L.-M. Wu, *Tetrahedron*, 2009, **65**, 1140–1146.

234 I. Nakamura, Y. Sato, S. Konta and M. Terada, *Tetrahedron Lett.*, 2009, **50**, 2075–2077.

235 J. Takaya, S. Udagawa, H. Kusama and N. Iwasawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 4906.

236 D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2009, **110**, 624–655.

237 B. Trost and A. McClory, *Angew. Chem., Int. Ed.*, 2007, **46**, 2074.

238 X. Li, H. Li, W. Song, P. S. Tseng, L. Liu, I. A. Guzei and W. Tang, *Angew. Chem., Int. Ed.*, 2015, **54**, 12905–12908.

239 Q. W. Zhang, K. An and W. He, *Angew. Chem., Int. Ed.*, 2014, **53**, 5667–5671.

240 H. Kanno, K. Nakamura, K. Noguchi, Y. Shibata and K. Tanaka, *Org. Lett.*, 2016, **18**, 1654–1657.

241 N. Isono and M. Lautens, *Org. Lett.*, 2009, **11**, 1329–1331.

242 A. Mizukami, Y. Ise, T. Kimachi and K. Inamoto, *Org. Lett.*, 2016, **18**, 748–751.

243 Z. Hu, X. Tong and G. Liu, *Org. Lett.*, 2016, **18**, 2058–2061.

244 G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651–3678.

245 G. Zhang, H. Yu, G. Qin and H. Huang, *Chem. Commun.*, 2014, **50**, 4331–4334.

246 D. R. Stuart, M. Bertrand-Laperle, K. M. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474–16475.

247 D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 18326–18339.

248 M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, *Angew. Chem.*, 2011, **123**, 1374–1377.

249 Y. Hoshino, Y. Shibata and K. Tanaka, *Adv. Synth. Catal.*, 2014, **356**, 1577–1585.

250 G. N. Hermann, C. L. Jung and C. Bolm, *Green Chem.*, 2017, **19**, 2520–2523.

251 S. Kathiravan and I. A. Nicholls, *Chem. Commun.*, 2014, **50**, 14964–14967.

252 J. Chen, G. Song, C.-L. Pan and X. Li, *Org. Lett.*, 2010, **12**, 5426–5429.

253 X. Hu, X. Chen, Y. Zhu, Y. Deng, H. Zeng, H. Jiang and W. Zeng, *Org. Lett.*, 2017, **19**, 3474–3477.

254 D. Zhao, Z. Shi and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12426–12429.

255 S. Zhou, J. Wang, F. Zhang, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 2427–2430.

256 L. Zheng and R. Hua, *Chem. – Eur. J.*, 2014, **20**, 2352–2356.

257 K. Muralirajan and C. H. Cheng, *Adv. Synth. Catal.*, 2014, **356**, 1571–1576.

258 D. Y. Li, H. J. Chen and P. N. Liu, *Org. Lett.*, 2014, **16**, 6176–6179.

259 C. Wang, H. Sun, Y. Fang and Y. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 5795.

260 H. Sun, C. Wang, Y.-F. Yang, P. Chen, Y.-D. Wu, X. Zhang and Y. Huang, *J. Org. Chem.*, 2014, **79**, 11863–11872.

261 C. Wang and Y. Huang, *Org. Lett.*, 2013, **15**, 5294–5297.

262 B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 16625–16631.

263 Z. Zhou, G. Liu, Y. Chen and X. Lu, *Adv. Synth. Catal.*, 2015, **357**, 2944–2950.

264 H. Yan, H. Wang, X. Li, X. Xin, C. Wang and B. Wan, *Angew. Chem., Int. Ed.*, 2015, **54**, 10613–10617.

265 X. Huang, W. Liang, Y. Shi and J. You, *Chem. Commun.*, 2016, **52**, 6253–6256.

266 Z. Fan, S. Song, W. Li, K. Geng, Y. Xu, Z.-H. Miao and A. Zhang, *Org. Lett.*, 2014, **17**, 310–313.

267 J. S. Alford, J. E. Spangler and H. M. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 11712–11715.

268 B. Rajagopal, C.-H. Chou, C.-C. Chung and P.-C. Lin, *Org. Lett.*, 2014, **16**, 3752–3755.

269 A. Saito, A. Kanno and Y. Hanzawa, *Angew. Chem.*, 2007, **119**, 4005–4007.

270 A. Saito, S. Oda, H. Fukaya and Y. Hanzawa, *J. Org. Chem.*, 2009, **74**, 1517–1524.

271 B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705.

272 B. Schmidt, *Angew. Chem., Int. Ed.*, 2003, **42**, 4996–4999.

273 R. N. Nair, P. J. Lee, A. L. Rheingold and D. B. Grotjahn, *Chem. – Eur. J.*, 2010, **16**, 7992–7995.

274 A. Varela-Fernández, J. A. Varela and C. Saa, *Adv. Synth. Catal.*, 2011, **353**, 1933–1937.

275 X. Dong, Y. Hu, T. Xiao and L. Zhou, *RSC Adv.*, 2015, **5**, 39625–39629.

276 K. Takamoto, S. Ohno, N. Hyogo, H. Fujioka and M. Arisawa, *J. Org. Chem.*, 2017, **82**, 8733–8742.

277 C.-Y. Wu, M. Hu, Y. Liu, R.-J. Song, Y. Lei, B.-X. Tang, R.-J. Li and J.-H. Li, *Chem. Commun.*, 2012, **48**, 3197–3199.

278 T. Watanabe, Y. Mutoh and S. Saito, *J. Am. Chem. Soc.*, 2017, **139**, 7749–7752.

279 Z. Zhang, H. Jiang and Y. Huang, *Org. Lett.*, 2014, **16**, 5976–5979.

280 S. Zhou, J. Wang, P. Chen, K. Chen and J. Zhu, *Chem. – Eur. J.*, 2016, **22**, 14508–14512.

281 H. Lin, S.-S. Li and L. Dong, *Org. Biomol. Chem.*, 2015, **13**, 11228–11234.

282 Y. Liao, T. Wei, T. Yan and M. Cai, *Tetrahedron*, 2017, **73**, 1238–1246.

283 F. Yang, K.-G. Ji, S. Ali and Y.-M. Liang, *J. Org. Chem.*, 2011, **76**, 8329–8335.

284 G. Fang and X. Bi, *Chem. Soc. Rev.*, 2015, **44**, 8124–8173.

285 N.-Y. Huang, M.-G. Liu and M.-W. Ding, *J. Org. Chem.*, 2009, **74**, 6874–6877.

286 T. Otani, X. Jiang, K. Cho, R. Araki, N. Kutsumura and T. Saito, *Adv. Synth. Catal.*, 2015, **357**, 1483–1492.

287 M. Kaname and H. Sashida, *Tetrahedron Lett.*, 2012, **53**, 748–751.

288 Y. Fang, C. Wang, S. Su, H. Yu and Y. Huang, *Org. Biomol. Chem.*, 2014, **12**, 1061–1071.

289 S. Panaka, R. Trivedi, T. Sony, S. Prabhakar and L. R. Chowhan, *Org. Chem. Front.*, 2017, **4**, 1574–1579.

290 L. Yang, Y. Ma, F. Song and J. You, *Chem. Commun.*, 2014, **50**, 3024–3026.

291 Y. Gao, G. Lu, P. Zhang, L. Zhang, G. Tang and Y. Zhao, *Org. Lett.*, 2016, **18**, 1242–1245.

292 J. Liu, X. Xie and Y. Liu, *Chem. Commun.*, 2013, **49**, 11794–11796.

293 R. Karmakar, A. Suneja and V. K. Singh, *Org. Lett.*, 2016, **18**, 2636–2639.

294 C. H. Oh, S. Karmakar, H. Park, Y. Ahn and J. W. Kim, *J. Am. Chem. Soc.*, 2010, **132**, 1792–1793.

295 X. Feng, H. Wang, B. Yang and R. Fan, *Org. Lett.*, 2014, **16**, 3600–3603.

296 N. Schwarz, K. Alex, I. A. Sayyed, V. Khedkar, A. Tillack and M. Beller, *Synlett*, 2007, 1091–1095.

297 J. C.-H. Yim, J. A. Bexrud, R. O. Ayinla, D. C. Leitch and L. L. Schafer, *J. Org. Chem.*, 2014, **79**, 2015–2028.

298 K. Okuma, J.-I. Seto, K.-I. Sakaguchi, S. Ozaki, N. Nagahora and K. Shioji, *Tetrahedron Lett.*, 2009, **50**, 2943–2945.

299 A. P. Thankachan, K. S. Sindhu, S. M. Ujwaldev and G. Anilkumar, *Tetrahedron Lett.*, 2017, **58**, 536–540.

300 M. Xu, K. Xu, S. Wang and Z.-J. Yao, *Tetrahedron Lett.*, 2013, **54**, 4675–4678.

301 Z. Chai, W.-Y. Ma and G. Zhao, *Synthesis*, 2008, 4036–4040.

302 B. Miao, S. Li, G. Li and S. Ma, *Org. Lett.*, 2016, **18**, 2556–2559.

303 L. Ilies, M. Isomura, S.-I. Yamauchi, T. Nakamura and E. Nakamura, *J. Am. Chem. Soc.*, 2016, **139**, 23–26.

304 I. A. Sayyed, K. Alex, A. Tillack, N. Schwarz, D. Michalik and M. Beller, *Eur. J. Org. Chem.*, 2007, 4525–4528.

305 K. Alex, A. Tillack, N. Schwarz and M. Beller, *Angew. Chem., Int. Ed.*, 2008, **47**, 2304–2307.

306 A. Pews-Davtyan and M. Beller, *Org. Biomol. Chem.*, 2011, **9**, 6331–6334.

307 T. Gehrmann, J. Lloret Fillol, S. A. Scholl, H. Wadepohl and L. H. Gade, *Angew. Chem., Int. Ed.*, 2011, **50**, 5757–5761.

308 T. Gehrmann, S. A. Scholl, J. L. Fillol, H. Wadepohl and L. H. Gade, *Chem. – Eur. J.*, 2012, **18**, 3925–3941.