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Catalytic Synthesis of Indoles from Alkynes

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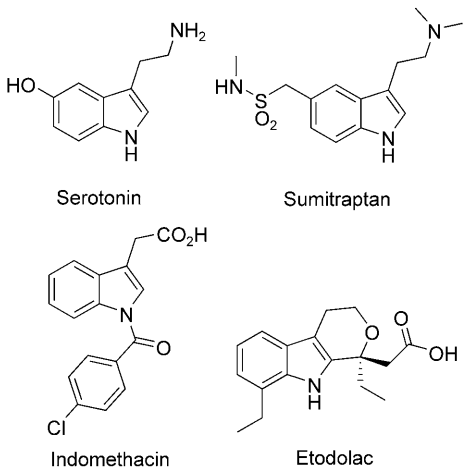
Abstract: In the past decade alkynes have become attractive starting materials for the synthesis of a variety of indole derivatives. This review summarizes the development of diverse homogeneous catalytic methods for the synthesis of indoles from alkynes and different N nucleophiles such as arylhydrazines, aniline derivatives, aryl isonitriles and nitroarenes.

Keywords: alkynes; anilines; hydrazines; indoles; isonitriles; nitroarenes

1 Introduction

The indole ring system is the most widely distributed heterocycle found in nature. Since indole was first isolated by treatment of indigo dye with oleum, the name indole is a combination of the words *indigo* and *oleum*. Among the numerous structurally diverse derivatives many indoles show significant biological activity such as tryptamine, tryptophan, and serotonin. Hence, it is not surprising that this structural motif is also an important component in many of today's pharmaceuticals (Scheme 1).



Scheme 1. Selected examples of biologically active indoles.

Clearly, a number of practical methods have been developed for the synthesis of indoles in the past century. Besides the well-established Fischer indole synthesis, other classical procedures include the Bischler–Möhlau synthesis from α-bromoacetophenones and an excess of aniline, the Batcho–Leimgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, the Gassmann synthesis from *N*-haloanilines, the Madelung–Houlihan cyclization, and the reductive cyclization of *o*-nitrobenzyl carbonyl compounds.[1] Nevertheless, the diversity of indoles as well as their biological and pharmaceutical relevance, is still motivating academic and industrial researchers to look for new and improved syntheses for indole derivatives.[2]

More recently, especially transition metal catalysis has become a powerful tool for synthetic methodology. For example, with the aid of catalysis the formation of C–N bonds *via* addition of nitrogen-containing nucleophiles across C–C unsaturated bonds can be easily realized. This general principle of activation has been used for the preparation of indoles, too. More specifically, the electrophilic activation of alkynes in the presence of late transition metal complexes and subsequent intramolecular as well as intermolecular addition reactions has become a popular strategy to prepare functionalized indoles. Here, we summarize the latest achievements in this area. In particular, known methods for the synthesis of functionalized indoles from alkynes and different N nucleophiles such as arylhydrazines, anilines, aryl isonitriles

Karolin Krüger (née Alex) was born in Rostock, Germany. She studied at the University of Rostock and received her Diploma degree in chemistry in 2005. Working in the group of Professor Matthias Beller she has nearly completed her Ph.D. studies in which she researched the zinc-catalyzed and -mediated synthesis of N-heterocycles and amines.

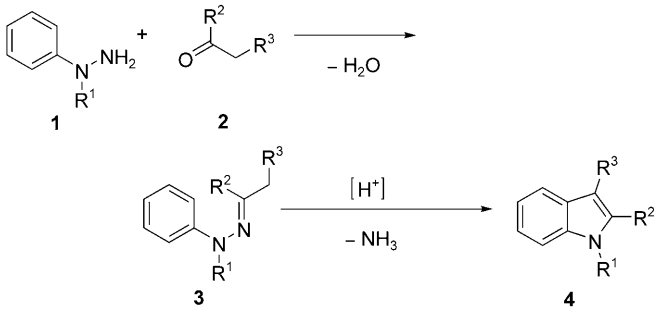
Annegret Tillack (née Kinting), born 1949 in Bad Wilsnack (Germany), studied chemistry at the University of Rostock and obtained her Ph.D. degree in 1977 working in the field of organosilicon chemistry. She then moved to LIKAT. Since 1998 she is a project leader in the group of Prof. Beller. Her research interests include catalytic hydroamination of olefins and alkynes, amination of alcohols and synthesis of indoles *via* hydrohydrazination of alkynes.

Matthias Beller, born 1962 in Gudensberg, studied chemistry at the University of Göttingen, Germany, where he completed his Ph.D. thesis in 1989 in the group of Prof. Tietze. As recipient of a Liebig scholarship, he then spent a one-year in the group of Prof. Sharpless at the MIT. From 1991 to 1995, Beller was an employee of Hoechst AG, where he most recently directed the "Homogeneous Catalysis" project in the company's central research unit. In 1996 he moved to the TU München as C3 Professor. In 1998 he relocated to the University of Rostock to head the Institute for Organic Catalysis (IfOK). Since 2006 Matthias Beller is director of the newly formed Leibniz-Institute for Catalysis. His scientific work has been published in more than 340 original publications and review articles. In addition, >80 patent applications have been filed in the last decade. Matthias Beller has received several awards such as the Otto-Roelen Medal (1997), the Merck-Frost-Lectureship (2002), the Novartis-Chemistry-Lectureship (2002), the Degussa-Lecturer (2003), the Novo Nordisk-Lecturer (2005), and in 2006 the Leibniz-Price of the Deutsche Forschungsgemeinschaft. In 2006 he was also awarded "Entrepreneur of the Year" of the city of Rostock and he received the German Federal Cross of Merit. Matthias Beller is head of the GDCH working group "Sustainable Chemistry" and a member of the Association for Technical Sciences of the Union of German Academies of Sciences and Humanities as well as the Academy of Science of Hamburg.

and nitroarenes will be described and recent improvements will be presented in detail.

2 Metal-Catalyzed Hydroamination of Alkynes with Arylhydrazines

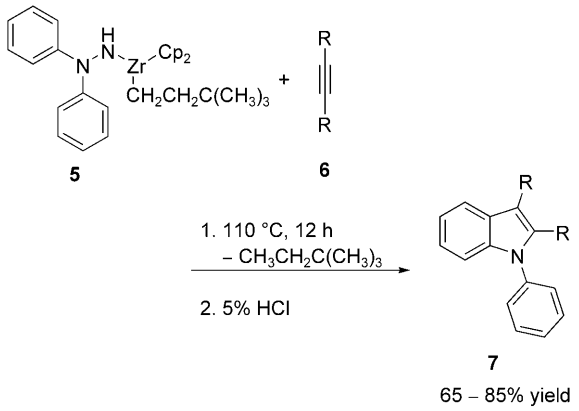
Since its discovery in 1883, the Fischer indole reaction has remained an essential method for the synthesis of a variety of indoles **4** *via* cyclization of *N*-arylhydrazones **3** (Scheme 2).[1] These *N*-arylhydrazones **3** are typically obtained by reacting arylhydrazines **1** with



Scheme 2. Fischer indole cyclization.

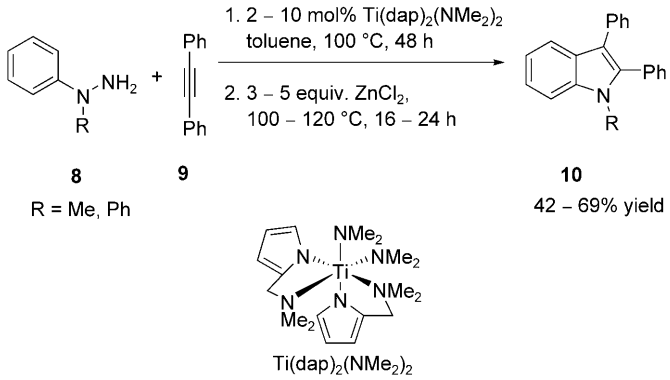
ketones or aldehydes **2**. More recently, the catalytic hydrohydrazination of alkynes has become a feasible method for their synthesis.

In 1991, Bergman and co-workers reported the first zirconium-mediated domino hydroamination-Fischer indole cyclization by trapping a hydrazidozirconocene complex **5** with alkynes **6** and subsequent addition of hydrochloric acid (Scheme 3).[3]



Scheme 3. Zirconium-mediated indole synthesis.

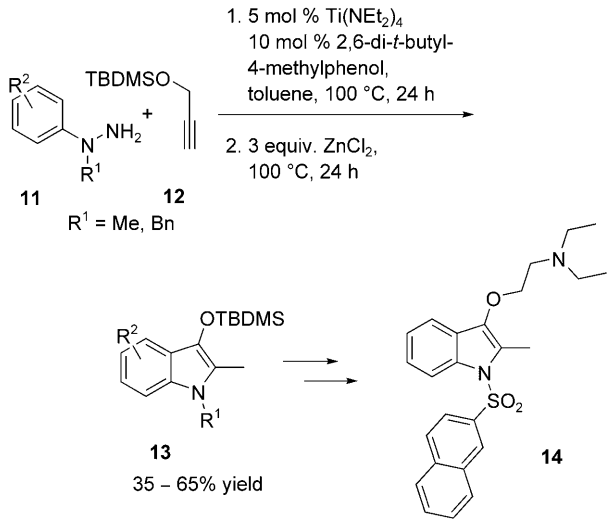
Later on, Odom and co-workers described the first catalytic procedure. In the presence of titanium catalysts intermolecular hydroamination of arylhydrazines **8** with alkynes **9** smoothly takes place (Scheme 4).[4]



Scheme 4. Titanium-catalyzed synthesis of indoles.

Notably, the arylhydrazones obtained underwent further Fischer indole reaction by *in situ* addition of $ZnCl_2$ to provide *N*-alkyl- and *N*-arylindoles **10** in high yields.

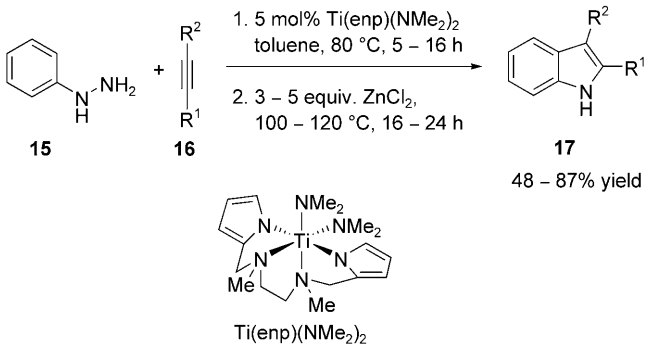
Based on this elegant approach the titanium-catalyzed synthesis of tryptamines and tryptamine homologues, and trypthophols and tryptophol derivatives, starting from commercially available arylhydrazines and alkynes was developed in our group.[5] In addition, Ackermann and Born reported the use of a combination of $TiCl_4$ and *t*-$BuNH_2$ as catalyst for domino hydroamination-Fischer indole cyclizations.[6] A problem which prevents widespread use of this methodology is the sensitivity of the titanium complexes towards functional groups, and the necessity for hydrazine protection and indole deprotection steps. Based on our work in the tryptophol synthesis starting from 3- and 4-silyloxyalkynes,[5a] we studied the reaction of arylhydrazines **11** with silyl-protected propargyl alcohol **12** in the presence of $Ti(NEt_2)_4$ and 2,6-di-*tert*-butyl-4-methylphenol (Scheme 5).[7] After the addition of



Scheme 5. Synthesis of 3-silyloxy-2-methylindoles.

$ZnCl_2$ a variety of new electron-rich functionalized 3-silyloxy-2-methylindoles **13** are accessible with high regioselectivity.[8] These 3-silyloxyindoles were further used as intermediates for the synthesis of potential 5-HT_6 receptor ligands **14**.[9]

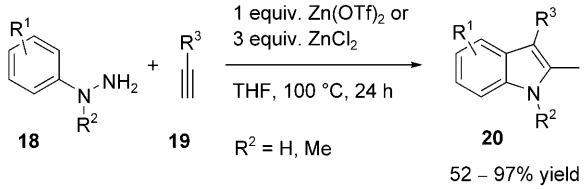
More recently, Odom and co-workers reported an improved titanium-catalyzed hydrohydrazination of unprotected arylhydrazines **15** with terminal and internal alkynes **16** for the synthesis of the free indole **17** (Scheme 6).[10] However, for unsymmetrical alkynes often a mixture of indole products is observed.



Scheme 6. Titanium-catalyzed synthesis of free indoles.

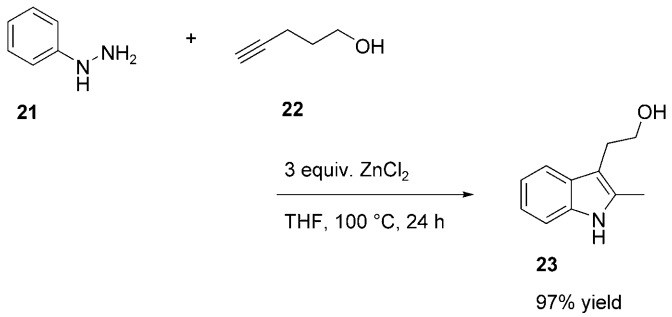
Noteworthy, this novel reaction was facilitated by changing the ancillary ligand from two bidentate $[Ti(dap)_2(NMe_2)_2]$ to a tetradentate ligand $[Ti(enp)(NMe_2)_2]$, which led to a higher protolytic stability of the ligand.

Surprisingly, new investigations by us showed no necessity of a titanium catalyst for the one-pot synthesis of substituted indoles **20**. Hence, starting from commercially available arylhydrazines **18** and terminal alkynes **19**, a range of pharmaceutically relevant indole building blocks are obtained in excellent Markovnikov regioselectivity in the presence of either $Zn(OTf)_2$ or $ZnCl_2$ (Scheme 7).[11] Apparently, the Zn-based Lewis acid catalyzed both the hydrohydrazination of the alkyne as well as the Fischer indole cyclization.



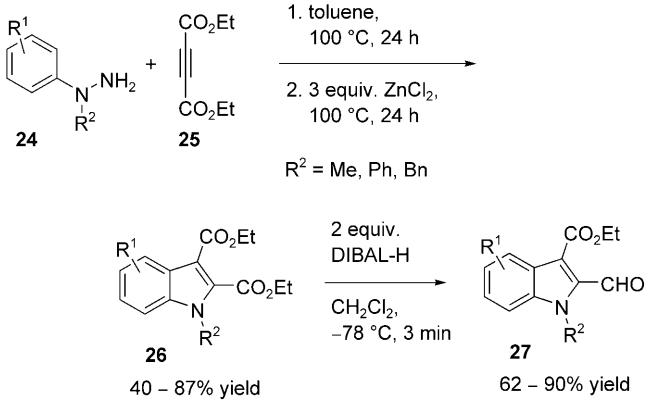
Scheme 7. Zinc-mediated indole synthesis.

The particular advantage of this reaction is that by using Zn salts, there is no need for protecting groups at the alkyne and the arylhydrazine units. For example, the free tryptophol derivative **23** is directly available from the unprotected pentyn-1-ol **22** and *N*-phenylhydrazine **21** in excellent yield in the presence of $ZnCl_2$ (Scheme 8).



Scheme 8. Synthesis of a free tryptophol derivative.

In addition, a transition metal-free one-pot synthesis of indole-2,3-dicarboxylates **26** from arylhydrazines **24** and acetylenedicarboxylates **25** was reported (Scheme 9).[12] Here, a domino amination-Fischer indole cyclization sequence gave the corresponding products from commercially available substrates in good yields. In a first step the arylhydrazine and acetylenedicarboxylate reacted to the corresponding arylhydrazone. Due to the high reactivity of the acetylenedicarboxylate no catalyst for activation is necessary. Subsequent treatment of the reaction mixture with 3 equivalents of $ZnCl_2$ allowed the cyclization of this *in situ* generated arylhydrazone to yield the corresponding diethyl indole-2,3-dicarboxylate **26**. Noteworthy, when $ZnCl_2$ is added in the beginning of reaction, the desired products are also obtained, albeit in lower yield. Based on this work a selective reduction of **26** to 2-formyl-1-alkylindole-3-carboxylates **27** was also developed.[13]



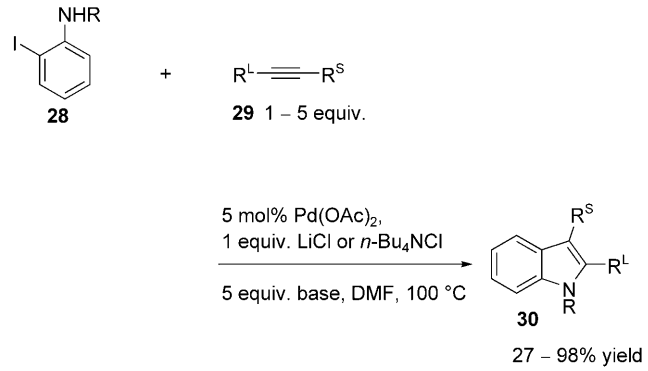
Scheme 9. One-pot method for the synthesis of indole-2,3-dicarboxylates.

3 Indoles from Aniline Derivatives

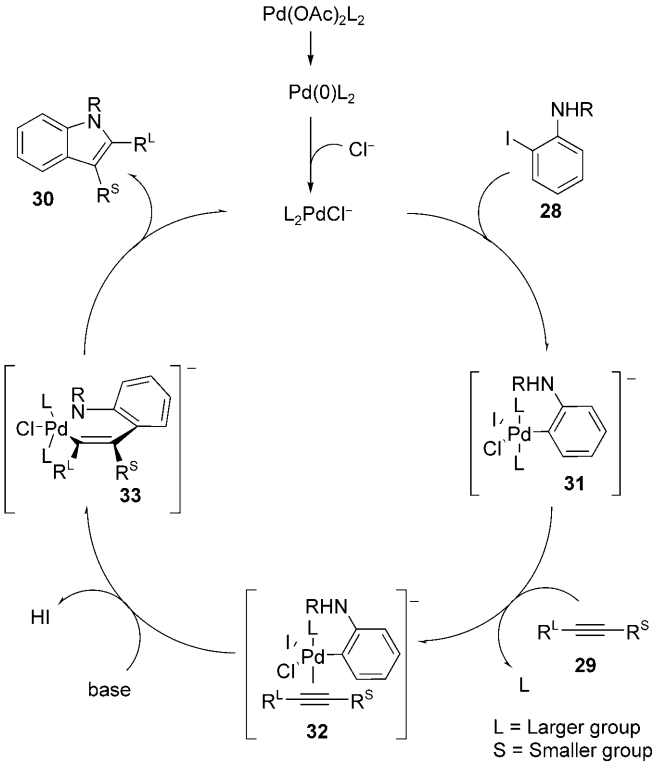
3.1 Annulation of *o*-Haloanilines with Alkynes

An attractive method for the synthesis of 2,3-disubstituted indoles **30** in a single operation is the so-called Larock heteroannulation process. In 1991, Larock and co-workers reported this useful method for the preparation of indoles for the first time. Here, palladium-catalyzed heteroannulation of internal alkynes **29** with *N*-protected *o*-iodoanilines gave the corresponding derivatives **30** (Scheme 10).[14] The cyclization is regioselective with unsymmetrical alkynes, wherein the more sterically hindered group (R^L) of the alkyne is recovered in the 2-position of the indole. For example, trimethylsilyl-substituted alkynes always afford a single indole product in which the silyl group is found in the 2-position.

As shown in Scheme 11 the reaction involves the reduction of $Pd(OAc)_2$ to an active Pd(0) species. Oxidative addition of Pd(0) to the aryl iodide and coordination of the alkyne to the palladium centre gave the aryl-Pd intermediate **32**. Then, the more sterically demanding group (R^L) is inserted away from the sterically encumbered aryl group. Subsequent regioselective *syn*-insertion into the aryl-Pd bond, nitrogen displacement of the halide in the resulting vinylic Pd in-



Scheme 10. The Larock heteroannulation for the synthesis of 2,3-disubstituted indoles.



Scheme 11. Mechanism for the Larock heteroannulation.

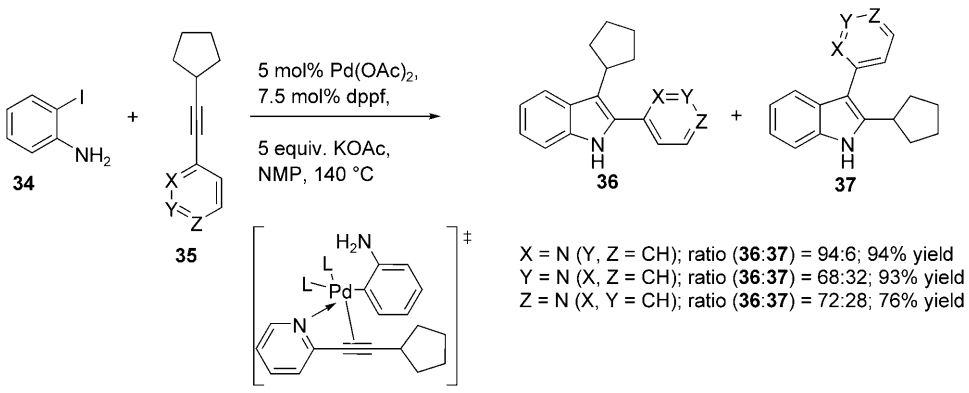
termediate to form a six-membered palladacycle **33**, and reductive elimination forms the indole with regeneration of the active catalyst.[15]

A special example of the regioselective Larock heteroannulations was published by Roschangar and coworkers.[16] In the presence of $Pd(OAc)_2$ and dppf 2-alkynylpyridines **35** and 2-iodoaniline **34** were reacted to 3-substituted 2-pyridinylindoles **36** (Scheme 12). Different regioselectivities are observed depending on the heterocyclic moiety. For example, alkynes with a pyridin-2-yl substituent provided a significantly higher ratio of regioisomeric indoles **36** and **37** (94:6) compared to alkynes with pyridin-3-yl or pyridin-4-yl substituents (68:32 or 72:28).

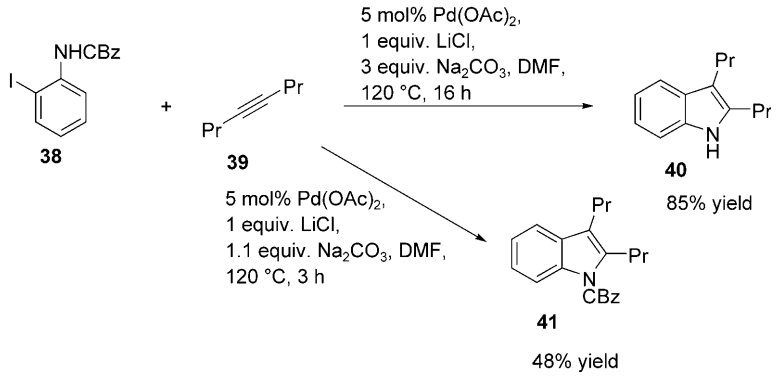
This observation is explained by the special coordination of the pyridin-2-yl moiety, which is known to act as a ligand for palladium complexes. It favours *syn*-insertion of the aryl-palladium complex in such a way to maintain coordination of palladium to the pyridyl nitrogen *via* a four-membered ring. Such a coordination effect is not possible for pyridin-3-yl and pyridin-4-yl substituents.

Based on Larock's procedure carbamate substrates were used for the palladium-catalyzed indolization with alkynes.[17] In the presence of 1.1 equivalents of Na_2CO_3 the annulation reaction of benzyl 2-iodophenylcarbamate (**38**) and 4-octyne (**39**) yielded the carbobenzoxy (CBz) protected indole **41** in 48% after three hours (Scheme 13).[18] Using an excess of base and longer reaction time the unprotected indole **40** was isolated in high yield (85%). Moreover, Lebel and co-worker described a multicomponent process for the synthesis of indole derivatives by a one-pot Curtius rearrangement/palladium-catalyzed indolization process, in which the 2-iodophenylcarbamate substrate is formed *in situ* from the corresponding 2-iodobenzoic acid.

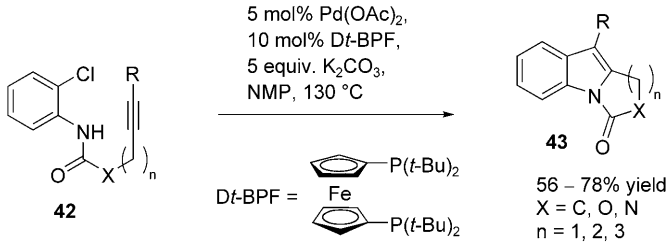
An intramolecular heteroannulation of **42** for the synthesis of a polycyclic indole skeleton **43** was reported by Lu and Senanayake (Scheme 14).[19] Based on their work on the regioselective palladium-cata-



Scheme 12. Regioselective synthesis of 3-substituted-2-pyridinylindoles.



Scheme 13. Application of carbamates for the synthesis of indoles.



Scheme 14. Intramolecular heteroannulation of carbamate and urea derivatives.

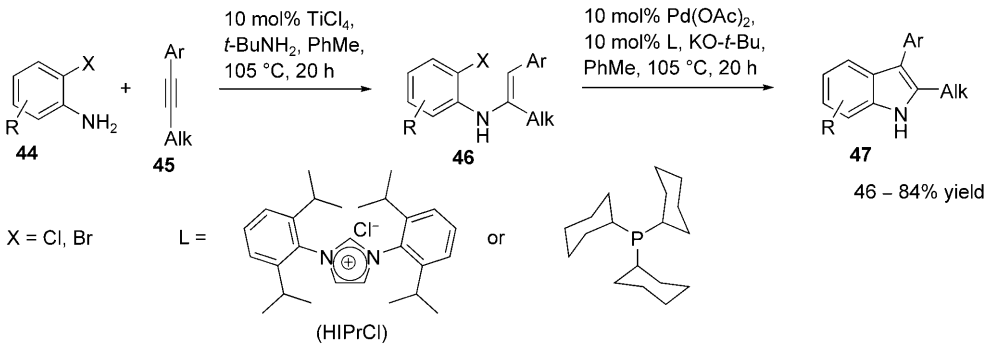
lyzed indolization of 2-bromo- and 2-chloroanilines with internal alkynes,[20] the authors applied $Pd(OAc)_2$ and 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D*t*-BPF) as ligand. More specifically, five-, six- and seven-membered annulated indole derivatives are formed in good yield.

Another elegant concept of reacting 2-haloanilines with internal alkynes was reported by Ackermann and co-workers, who developed a highly regioselective annulation reaction of unsymmetrically substituted alkynes **45** by 2-bromo- or 2-chloroanilines **44** to 3-aryl-2-alkylindoles **47** (Scheme 15).[21] Their one-pot synthesis started with a regioselective $TiCl_4$-catalyzed intermolecular hydroamination followed by a subsequent palladium-catalyzed intramolecular aza-Heck reaction. The best results for the Heck reaction are obtained by applying palladium complexes with either PCy_3 or the sterically hindered imidazolium salt HIPrCl as precursor. In addition, Ackermann and co-worker reported a ruthenium-catalyzed hydroamination as the first step of this one-pot procedure followed by the Heck reaction.[22]

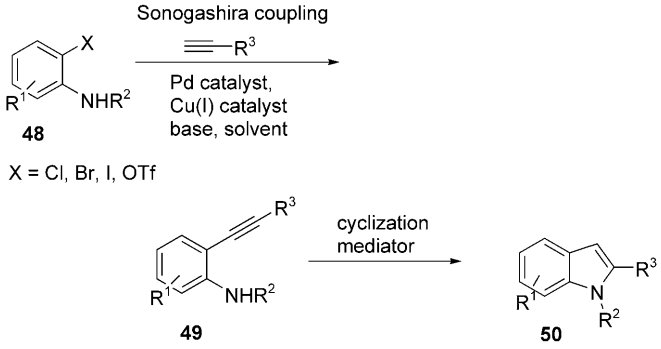
3.2 Cyclization of *o*-Alkynylaniline Derivatives

The transition metal-catalyzed hydroamination of *o*-alkynylaniline derivatives **49** has become an established approach for the preparation of 2-substituted indoles **50**. This method usually requires two steps: 1) introduction of the alkynyl moiety to give arene **49** through Sonogashira reactions[23] and 2) a subsequent cyclization reaction (Scheme 16).

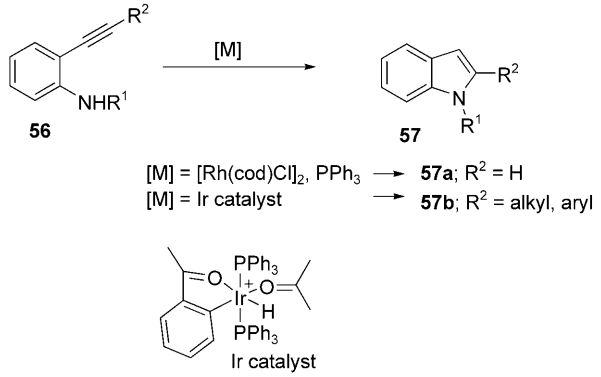
Throughout the last decade numerous examples have been reported for indole syntheses from *o*-alkynylaniline derivatives, including basic conditions,[24] ammonium fluoride-mediated reactions,[25] and transition metal-catalyzed reactions. In the following paragraphs different transition metals for the cyclization reaction are mentioned and the most recent examples will be presented. In the past years molybdenum[26] and indium complexes[27] were reported to be active



Scheme 15. $TiCl_4$-catalyzed intermolecular hydroamination followed by a subsequent palladium-catalyzed intramolecular aza-Heck reaction.



Scheme 16. Sonogashira reaction and cyclization approach to indoles.



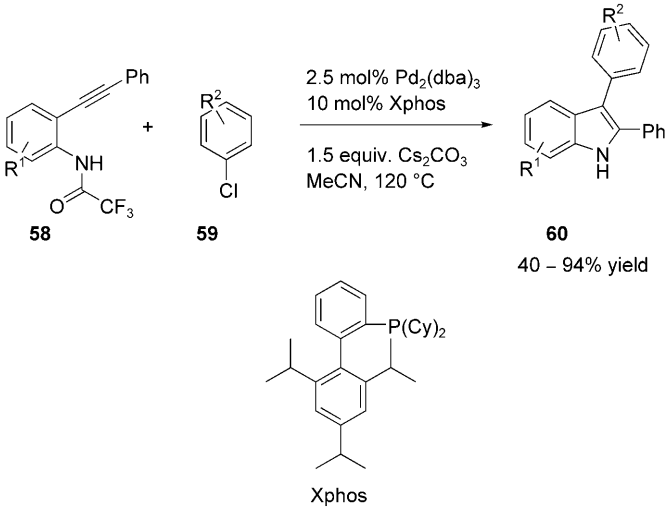
Scheme 18. Rhodium- and iridium-catalyzed indole synthesis.

for the indole cyclization reaction of *o*-alkynylaniline derivatives. Recently, another unusual method was presented by Nishizawa and co-workers.[28] Using $Hg(OTf)_2$ in catalytic amounts *N*-tosyl-*o*-alkynylaniline derivatives **51** afforded 2-substituted *N*-tosylindole derivatives **55** in excellent yield under mild reaction conditions (Scheme 17).

In agreement with traditional work on alkyne activation, the reaction is initiated by π-complexation of the alkyne with $Hg(OTf)_2$ (**52**). Nucleophilic attack of the amide generates TfOH to form intermediate **53**. Protonation of **53** gave the nitronium ion **54**, which undergoes demercuration to produce indole **55** under regeneration of the catalyst. In spite of using $Hg(OTf)_2$ in catalytic amounts, the use of such toxic metals should be avoided in state-of-the-art organic synthesis.

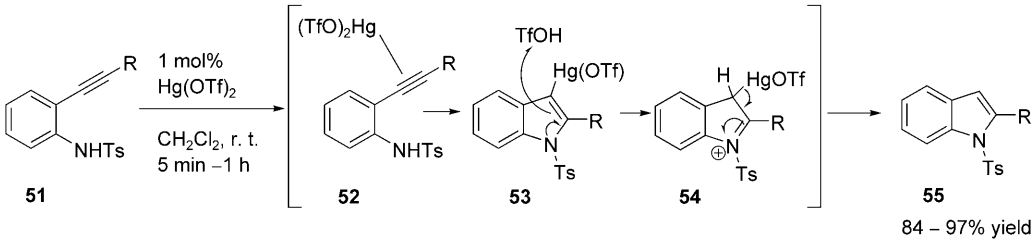
Trost and co-workers discovered a rhodium-catalyzed cycloisomerization reaction to give indole **57a** ($R^2 = H$) (Scheme 18).[29] Herein, only terminal alkynes reacted successfully to yield 2,3-unsubstituted indoles. Interestingly, Crabtree and co-workers reported a different reactivity when using an iridium catalyst.[30] The latter catalytic process is limited to internal alkynes. Thus, 2-substituted indole derivatives **57b** resulted as products (R^2 = alkyl, aryl) (Scheme 18).

Clearly, the most frequently used transition metal reagents or catalysts for the ring-closing reactions of *o*-alkynylaniline derivatives are palladium complexes. In the past years the work concentrated on the synthesis of 2,3-disubstituted indoles **60** *via* palladium-catalyzed reactions of aryl iodides, bromides, and triflates with *o*-alkynyltrifluoroacetanilides **58**. For example, Cacchi and co-workers published an extension of this procedure to aryl chlorides **59** (Scheme 19).[31]



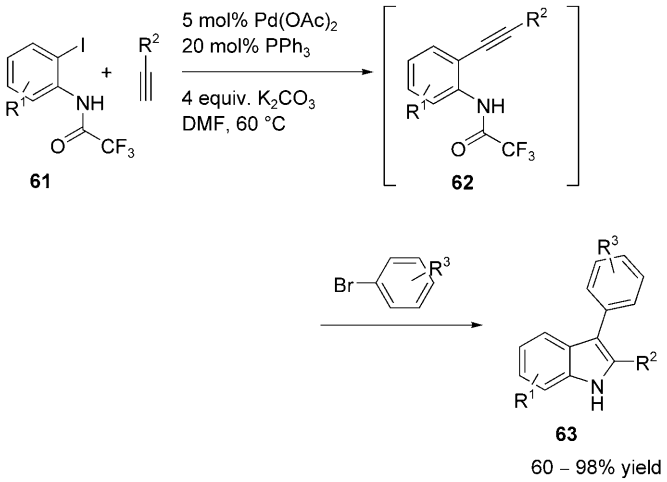
Scheme 19. Reaction of *o*-alkynyltrifluoroacetanilides with aryl chlorides.

Best results are obtained with $Pd_2(dba)_3$ and 2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl (Xphos) as ligand to give 2,3-disubstituted indoles **60** in moderate to excellent yields.



Scheme 17. $Hg(OTf)_2$-catalyzed indole cyclization.

Lu and Senanayake also reported a one-pot, three-component domino Sonogashira-cyclization reaction of 2,3-disubstituted indoles **63**.[32] This sequential process involved the *in situ* formation of the *o*-alkynyltrifluoroacetanilide **62** by Sonogashira coupling, followed by cyclization *via* aminopalladation, and coupling with aryl bromides (Scheme 20).



Scheme 20. *In situ* formation of *o*-alkynyltrifluoroacetanilides and cyclization.

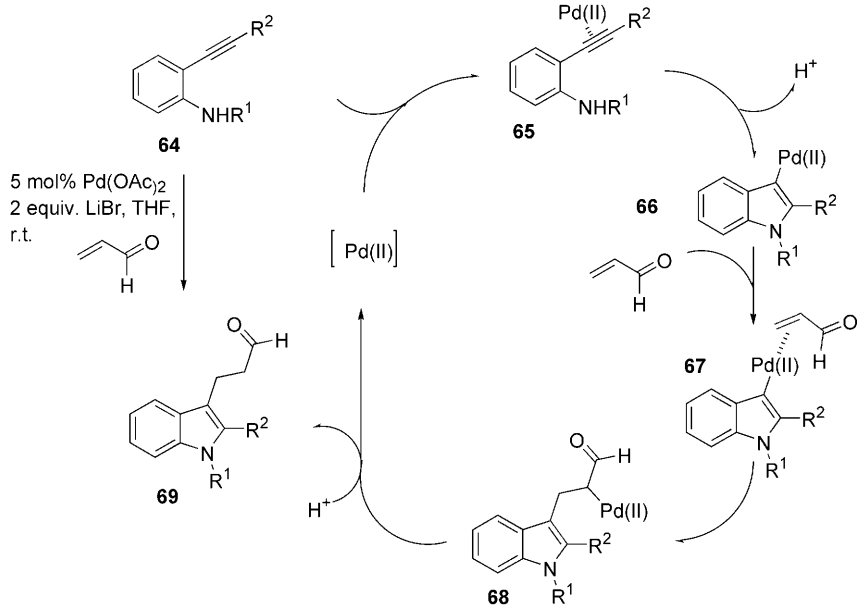
A combination of palladium-catalyzed cyclization and subsequent Heck reaction was reported by Yasuhara and Sakamoto. Here, 2-substituted 3-alkenylindoles are obtained through the reaction of *N*-protected 2-alkynylanilines with electron-deficient alkenes in the presence of palladium and copper dichloride as an oxidant.[33] Domino cyclization and Heck reaction resulted in 2-substituted 3-alkenylindoles through β-hydride elimination.

Based on this concept, Lu and co-workers published the palladium(II)-catalyzed reaction of *N*-protected 2-alkynylanilines **64** with α,β-unsaturated carbonyl compounds for the synthesis of 2-substituted 3-alkylindoles **69**. In the presence of LiBr β-hydride elimination did not occur (Scheme 21).[34] From a mechanistic viewpoint, activation of the alkyne took place by coordination of Pd(II). Aminopalladation of **65** gave the Pd intermediate **66** followed by insertion of the double bond of the olefin to **68**. Finally, protonolysis of the newly formed carbon-palladium bond yielded indole **69** in the presence of halide ions (Scheme 21). A similar reaction type was also reported by Arcadi and co-workers using an Au(III) catalyst.[35]

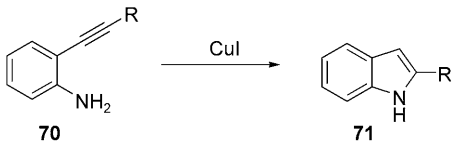
Campagne and co-workers published the use of a catalytic combination of $FeCl_3$-$PdCl_2$ in dichloroethane for the synthesis of 2,3-substituted indoles.[36] They proposed that the role of iron could be the facilitation of the *in situ* reoxidation of Pd(0) to Pd(II). If this is true such a principle might be used in other redox reactions involving Pd(0)/Pd(II), too.

Another attractive method for the cyclization of 2-alkynylanilines is based on economically attractive copper(I) salts, usually copper(I) iodide. This methodology is typically known as the Castro indole synthesis (Scheme 22). For example, reaction of *o*-alkynylaniline derivatives **70** led to 2-substituted indoles **71**.[37]

Based on the successful application of CuI/*N*,*N*-dimethylglycine in the catalytic coupling reactions of aryl bromides,[38] Ma and co-worker reported a



Scheme 21. Palladium-catalyzed reaction for the synthesis of 2-substituted 3-alkylindoles.



70 71

Scheme 22. Castro indole synthesis.

domino coupling/cyclization process of terminal alkynes **73** and 2-bromotrifluoroacetanilides **72** (Scheme 23).[39] This reaction sequence involves a CuI/L-proline-catalyzed coupling between the alkyne and the aryl bromide and then a CuI-catalyzed cyclization towards the indole **74**.

72 73 74

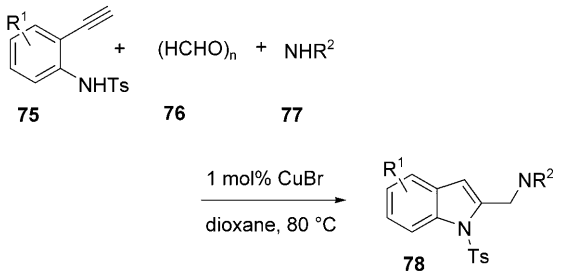
68 – 94% yield

Scheme 23. Copper iodide-catalyzed domino coupling/cyclization process.

The coupling reaction proceeded under mild conditions through the *ortho*-substituent effect directed by $NHCOCF_3$.

In 2007, Ohno and Fujii developed a domino three-component coupling and cyclization reaction for the synthesis of 2-(aminomethyl)indoles **78** (Scheme 24).[40] In the presence of copper(I) bromide *N*-protected alkynylanilines **75** were treated with paraformaldehyde **76** and secondary amines **77** to give **78**. Most likely this reaction proceeds through Mannich-type multicomponent coupling reaction (MCR) followed by indole cyclization.

As mentioned before Au(III) is also known as a catalyst for this type of cyclization to afford 2-substituted indoles.[41] Hence, Marinelli and co-workers reported last year the cyclization of *o*-alkynylanilines in

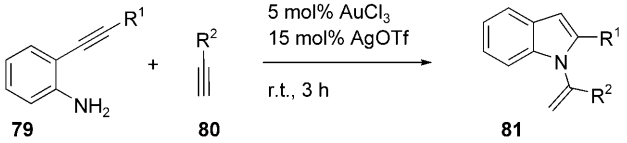


75 76 77 78

61 – 89% yield

Scheme 24. Domino three-component coupling and cyclization reaction for the synthesis of 2-(aminomethyl)indoles.

the presence of $NaAuCl_4 \cdot H_2O$ using the ionic liquid $[bmim]BF_4$ as a potential environmentally benign reaction medium.[42] With respect to gold catalysts, it is noteworthy that Li and co-workers developed a double-hydroamination reaction of *o*-alkynylanilines **79** with terminal alkynes **80** leading to *N*-vinylindoles **81** (Scheme 25).[43] After optimization, the best result is obtained at room temperature without any solvent in the presence of an $AuCl_3$/AgOTf mixture.



79 80 81

2 equiv 42 – 82% yield

Scheme 25. Gold-catalyzed synthesis of *N*-vinylindoles.

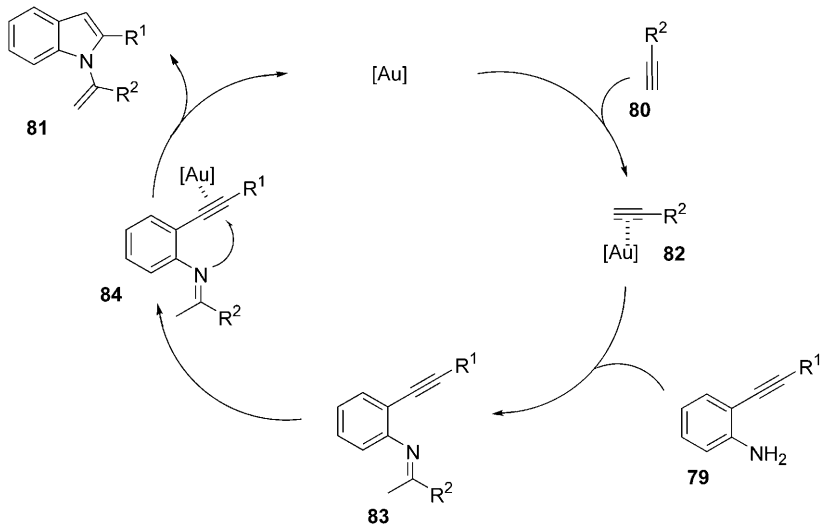
The proposed mechanism for the Au(III)-catalyzed double hydroamination is shown in Scheme 26. It is claimed that initially the terminal alkyne **80** is activated by Au(III) to generate intermediate **82**. This reacts further with **79** to yield the first hydroamination product **83**. Subsequently, the alkyne is again activated by Au(III) and produces intermediate **84** *via* nucleophilic addition of the imine nitrogen. After protonation at the C-3 position of the indole the final product **81** is formed and the catalyst is regenerated.

Besides Au(III) catalysts also AgOTf was reported by Rutjes and co-workers to catalyze the cyclization of *o*-alkynylanilines to give isotryptophan derivatives.[44]

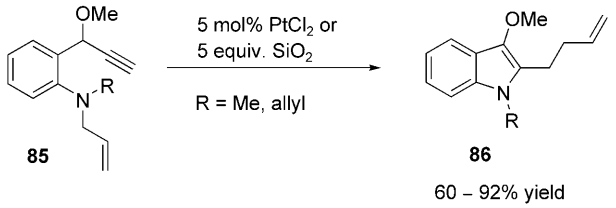
In addition to the numerous known metal-catalyzed cyclizations of 2-alkynylaniline derivatives, a transition metal-free electrophilic cyclization for the synthesis of 2,3-substituted indoles in the presence of iodine is known.[45] This strategy constitutes a convenient and general method for the synthesis of 3-iodoindoles.

Very recently, Fensterbank and Malacria published an alternative 5-*exo*-*dig* isomerization to the 5-*endo*-dig cyclization.[46] In their approach, 2,3-functionalized indoles and especially 3-alkoxyindoles **86** (Scheme 27) are prepared in the presence of $PtCl_2$ or simple acids. The *N,N*-diallyl precursor underwent transfer of an allyl group from the nitrogen to the terminal alkyne carbon. Formally, this constitutes an aminoallylation of the triple bond followed by isomerization of the unsaturated bond.

Finally, Doye and co-workers reported a one-pot procedure for 2-substituted indoles from (2-chloroaryl)alkynes. Combination of the titanium-catalyzed hydroamination of *ortho*-chloro-substituted 1-phenyl-2-alkylalkynes **87** with a Pd-catalyzed *N*-arylation of



Scheme 26. Mechanistic proposal for the synthesis of *N*-vinylindoles by gold catalysis.



Scheme 27. Synthesis of 3-alkoxyindoles through 5-*exo*-*dig* isomerization.

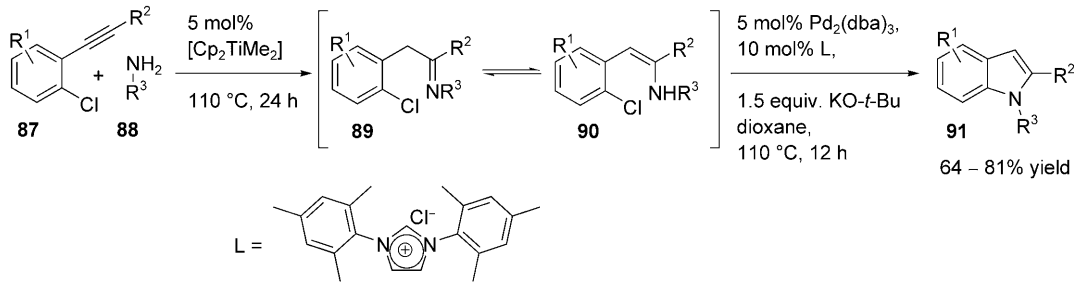
imines resulted in a novel method for the synthesis of indoles **91** (Scheme 28).[47]

3.3 Reaction of Anilines with Propargyl Alcohol Derivatives

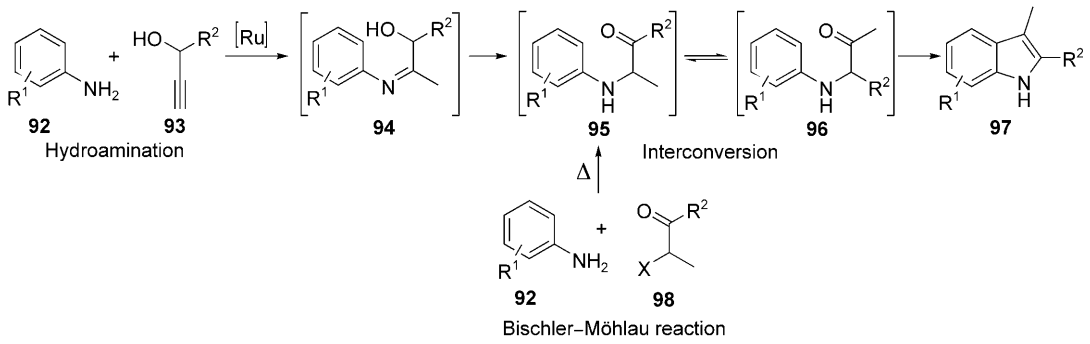
Most of the previously shown examples rely on qualified combinations of transition metal-catalyzed reactions with the classical Fischer indole synthesis.[48] Without doubt, this strategy can be applied to other well-known indole syntheses, too. As an example the Bischler–Möhlau indole synthesis starts from anilines **92** and α-halo ketones **98**.[49] A more recent and practical halogen-free process was developed by Wakatsuki and co-workers.[50]

Based on their results in ruthenium-catalyzed hydroamination reactions,[51] they provided a one-pot synthesis of 2-substituted 3-methylindoles **97** using anilines **92** and propargyl alcohol derivatives **93** as starting materials (Scheme 29). In the presence of $Ru_3(CO)_{12}$ and aniline hydrochloride as additive hydroamination of the C–C triple bond occurred followed by an isomerization of the resulting amino alcohol **94** to give amino ketone **95** (Bischler–Möhlau-type intermediate). In the presence of aniline hydrochloride there is fast interconversion between the regioisomers **95** and **96**. Also catalyzed by the additive these two intermediates underwent cyclization to the corresponding indole, wherein the 1,2-nitrogen migration product **97** cyclized from **96** is the major indole product.

Based on this methodology Liu and co-workers published a $Zn(OTf)_2$-catalyzed synthesis of these 2-substituted 3-methylindoles.[52] Herein, $Zn(OTf)_2$ is responsible for the hydroamination of the propargyl al-



Scheme 28. Titanium-catalyzed hydroamination followed by palladium-catalyzed *N*-arylation/cyclization reported by Doye et al.



Scheme 29. One-pot synthesis of 2-substituted 3-methylindoles *via* ruthenium-catalyzed hydroamination/cyclization.

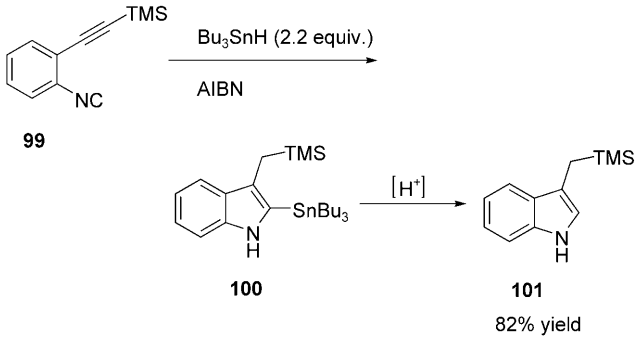
cohol, the isomerization as well as for the cyclization step.

After optimization of the reaction conditions, toluene was found to be the best solvent where only one regioisomeric product **97a** is observed (Table 1). Thus, 2-substituted 3-methylindoles can be synthesized by this methodology.

4 Indoles from Isocyanides

Isocyanides provide an additional nitrogen source as starting material for the synthesis of the indole skeleton.[53] Due to their high selective reactivity, these compounds are applied in a broad number of organic reactions.[54] In general, the reaction characteristics of isocyanides are distinguished by α-additions, α-metallations, and radical reactions. Based on the Fukayama isonitrile-alkene free-radical coupling reaction,[55] the group of Rainier developed an analogous alkyne-isonitrile free-radical reaction for the synthesis of indoles (Scheme 30).[56]

Starting from aryl isocyanides having a suitably positioned alkyne, 5-*exo*-dig radical cyclization provided the indolenine intermediate **100**. The resulting 2-stannylindole can be destannylated by acidic work-up to afford the 3-substituted indole **101**. For the synthesis of 2,3-disubstituted indoles, **100** can be applied directly in palladium-catalyzed coupling reactions



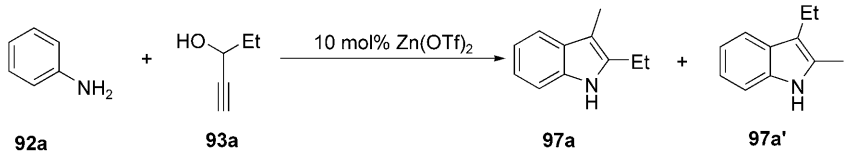
Scheme 30. Synthesis of indoles from *o*-alkynylaryl isocyanides *via* radical cyclization.

(Stille reaction) or oxidation of the tin-carbon bond with iodine resulting in 2-iodoindoles which further underwent palladium-catalyzed coupling reactions.[57]

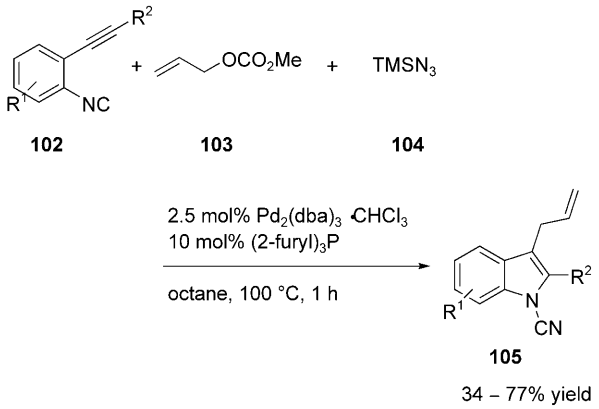
Moreover, *o*-alkynylphenyl isocyanides have been employed for the synthesis of various substituted *N*-cyanoindoles **105** *via* coupling of aryl isocyanides **102**, allylmethyl carbonate **103**, and trimethylsilyl azide **104** (Scheme 31).[58] In this reaction a wide range of functional groups is tolerated at the *p*-, *m*- and *o*-positions of the aromatic ring.

The proposed mechanism for this multicomponent coupling reaction is shown in Scheme 32. Initially, π-allylpalladium azide **106** is formed through the reac-

Table 1. $Zn(OTf)_2$-catalyzed regioselective synthesis of indole derivatives.



Entry	Solvent	Temperature [°C]	Time [h]	Product (Yield [%])
1		130	4	**97a**/**97a′** = 4.5 (95)
2	benzene	100	14	**97a** (89)
3	toluene	100	8	**97a** (97)

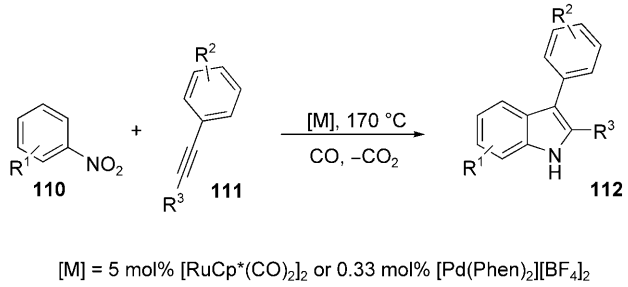


Scheme 31. Multicomponent coupling reaction for the synthesis of *N*-cyanoindoles.

tion of Pd(0) with allyl methyl carbonate **103** and $TMSN_3$ **104**. Then, reaction with the isocyanide **102** generates the π-allylpalladium intermediate **107**. Release of N_2 followed by 1,2-migration provides the palladium-carbodiimide complex **108** *via* a π-allylpalladium mimic of the Curtius rearrangement. The palladium-carbodiimide complex **108** is in equilibrium with the palladium-cyanamide complex **109**. Finally, the *N*-cyanoindoles **105** are formed through insertion of the alkyne moiety into the Pd–N bond of **109** followed by reductive elimination of Pd(0).

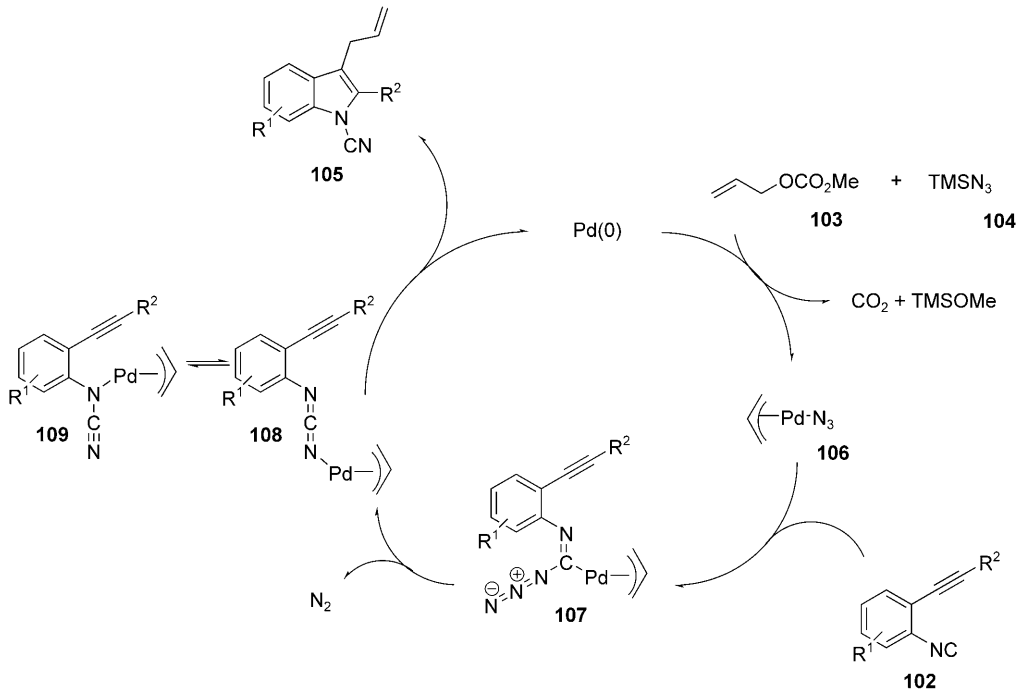
5 Cycloaddition of Nitro- and Nitrosoarenes with Alkynes

In 2002, Nicholas and Penoni reported a $[RuCp^*(CO)_2]_2$-catalyzed reaction of nitroarenes **110** with alkynes **111** to give indoles **112** at high temperature (Scheme 33).[59] Although the reaction proceeded with excellent regioselectivity, the yields of the corresponding indoles were only moderate.

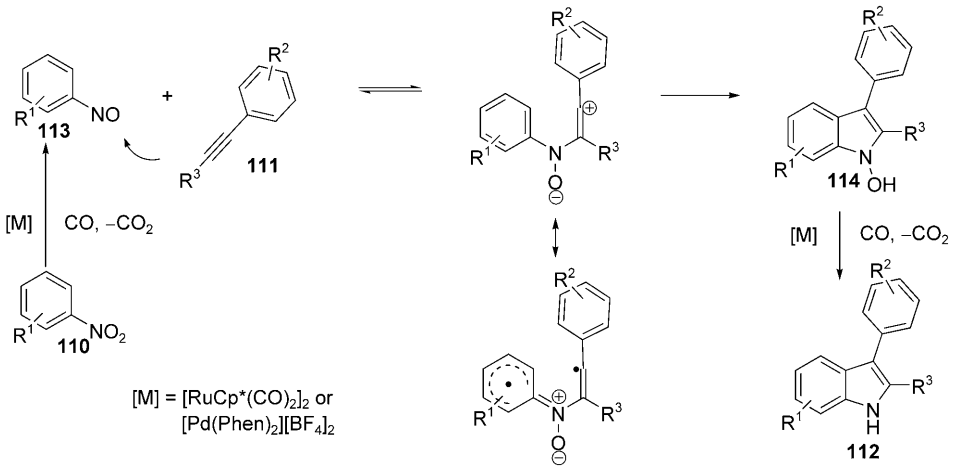


Scheme 33. Ruthenium- and palladium-catalyzed reaction of nitroarenes with alkynes.

A more active palladium catalyst for this reaction was published in 2006 by Ragaini and co-workers.[60] More specifically, palladium-phenanthroline complexes $[Pd(Phen)_2][BF_4]_2$ catalyze the reaction of nitroarenes with arylalkynes and CO towards 3-arylindoles. Notably, $[RuCp^*(CO)_2]_2$ and $[Pd(Phen)_2][BF_4]_2$



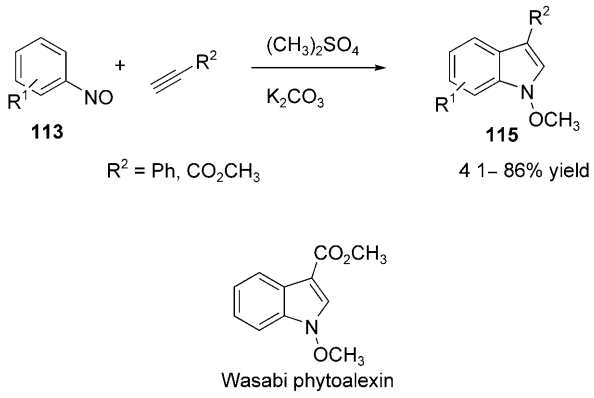
Scheme 32. Proposed mechanism for the synthesis of *N*-cyanoindoles.



Scheme 34. Mechanism for the reaction of alkynes with nitrosoarenes generated from nitroarenes.

represent active catalysts for the reductive carbonylation of nitroarenes.[61] Hence, it is not surprising that the catalytic reduction of nitroarenes **110** with CO initially produces nitrosoarenes **113**, which further react with the alkyne **111**. The latter reaction is expected to take place outside the coordination sphere of the metal. As shown in Scheme 34 the nitrosoarene interacts reversibly with the alkyne. Cyclization gives the corresponding *N*-hydroxyindole **114** which is reduced in a last step to the indole **112** in the presence of CO and the catalyst. The radical character of the intermediate adduct explains the need for an aryl group on the alkyne, wherein the aryl ring stabilizes charges or a radical in the α-position.

It is important to note that the stoichiometric reaction of nitrosoarenes with alkynes to give *N*-hydroxyindoles **114** in refluxing benzene was already observed by Nicholas and co-workers.[62] Hydrogenation with Pd/C or reductive carbonylation catalyzed by $[RuCp^*(CO)_2]_2$ of **114** resulted in **112**. Recently, the same group published the synthesis of the more stable *N*-methoxyindoles **115** (Scheme 35).[63] In the presence of $K_2CO_3/(CH_3)_2SO_4$ the reaction of nitrosoarenes with terminal alkynes formed the 3-substituted *N*-methoxyindoles in good yields. The analogous reaction with methyl propiolate provided a one-pot preparation of Wasabi's phytoalexin analogues.[64]



Scheme 35. Synthesis of 3-substituted *N*-methoxyindoles.

6 Conclusion

In the past decade alkynes have become attractive starting materials for the synthesis of a variety of indole derivatives. Diverse catalytic methods using different N nucleophiles have been developed or improved. Especially, the combination of known indole syntheses, e.g., Fischer indole synthesis, with modern catalytic coupling reactions has been a fruitful approach for the creation of novel, efficient and flexible domino sequences. Among the developed methods so far, the intermolecular addition of arylhydrazines to alkynes and the intramolecular cyclization of (2-aminoaryl)alkynes constitute the most frequently applied reaction types. In addition, aryl isonitriles and nitro- and nitrosoarenes are interesting building blocks for short and convenient synthetic approaches towards biologically interesting indoles. Special advantages of these methods are the tolerance of functional groups and the availability of the starting materials. Nevertheless, despite the versatility of all these reactions, there is still room for improvement. For example, with respect to green chemistry it would be even more appealing to synthesize indoles from olefins and anilines or nitroarenes. Future studies will hopefully allow for an even better access of this important class of biologically active compounds.

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