PERSPECTIVE

Recent advances in indole syntheses: New routes for a classic target

Rubén Vicente*

Indoles are the most abundant heterocycles in biologically active natural products, pharmaceuticals, agrochemicals, and are relevant substructures in functional materials. As a result, the development of methodologies that enable the synthesis of these compounds is continuously demanded. This review summarizes most recent and relevant approaches towards the preparation of this prevalent structural motif.

Introduction

The indole ring is one of the most widely distributed heterocycles in nature. Although indole was isolated for the first time by Baeyer from the treatment of indigo with oleum,[1] its importance in chemistry grew impressively from the 1950s, when several structurally diverse indole derivatives were found to have significant biological activities. As a result, the indole moiety appears as a

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al CSIC, Universidad de Oviedo, Julián Clavería 8, 33006, Oviedo, Spain. E-mail: vicenteruben@uniovi.es; Fax: +34 985103450; Tel: +34 985103450

substructure of numerous pharmaceuticals (Fig. 1). Moreover, indole has become a privileged structure in other research areas relevant for life such as agrochemistry or materials science.[2]
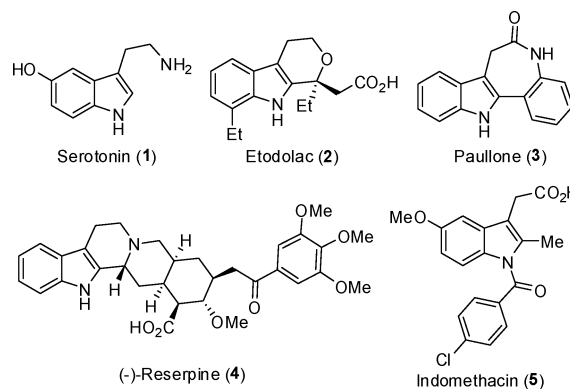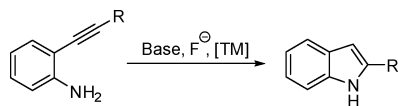

Fig. 1 Selected examples of relevant indole derivatives.

The great attention in organic chemistry that indole preparation has attracted, has turned into a large number of different synthetic approaches. Thus, while traditional approaches are based on condensation and cyclization sequences,[3] transition metal-catalyzed C–C- and C–N-bond formation reactions have recently enabled the development of alternative methodologies towards modular indole syntheses.[4,5] Despite the plentiful collection of available protocols to prepare indoles, the enormous interest in the indole structure results in this research area being continuously active. This review summarizes the most relevant achievements of the last five years in this important research area and emphasizes processes which involve a conceptual novelty in the synthesis of indoles.

Indole syntheses from *o*-alkynylanilines and derivatives

Indole syntheses from *o*-alkynylaniline derivatives have become very popular during the last decade. These reactions included base-[6] or ammonium fluoride-mediated cyclizations[7] and

Rubén Vicente

Rubén Vicente (Guadalajara, Spain, 1977) received his degree in Chemistry in 2000 (Complutense University of Madrid, UCM-Spain). Then, he worked on β-lactam chemistry with Prof. M. A. Sierra (UCM) and in industry. In 2002 he moved to the University of Oviedo (Spain) where he obtained his Ph. D. (with honors) in 2006 working on synthetic applications of Fischer–carbene complexes, under the guidance of Prof. J. Barluenga.
He complemented his formation with research stays at the University of Bonn (Prof. K. Muñiz) and Boston College (Prof. M. L. Snapper). He was a post-doctoral fellow (Humboldt Foundation) in the group of Prof. L. Ackermann (Georg-August-University, Göttingen, Germany, 2007–2009), where his research was focused on C–H-bond functionalizations. Since 2010, he has been a "Juan de la Cierva" fellow at the University of Oviedo. Among others, his research interests include the discovery of new reactivity patterns and the functionalization of inert bonds via transition metal catalysis.*

Scheme 1 Indole synthesis *via* cyclization of *o*-alkynylanilines.

transition metal-catalyzed reactions (Scheme 1). Simple cyclization reactions of *o*-alkynylaniline proved feasible by using a variety of metal catalysts,[8] however these reactions often led to unsubstituted indoles at position C-3.

In this section, relevant selected examples, which include the functionalization at position C-3 are presented. Thus, an electrophilic iodonium-mediated cyclization which led to N–H-free 3-iodoindole derivatives was reported by Barluenga using IPy_2BF_4 as an iodonium source (Scheme 2).[9,10] The formation of indole **8** was proposed to occur through an initial interaction of electrophilic iodine with alkyne **6**, which led to intermediate **7**. A nucleophilic attack by nitrogen would lead to indole **8**. HBF_4 likely activated the reagent in this reaction, while pyridine would facilitate proton abstraction during the transformation of **7** into indole **8**.
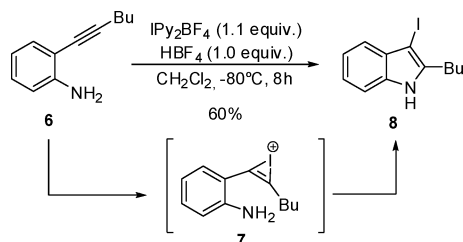
Scheme 2 IPy_2BF_4-promoted synthesis of 3-iodoindole **8**.

These valuable compounds could subsequently be functionalized into complex molecules using well-known organometallic chemistry. Related cyclizations which made use of copper halides enabled the preparation of 3-bromo- or 3-chloro-indoles; however, a large excess of the metal salt was required.[11]

In recent years, a variety of palladium-catalyzed cyclizations of *o*-alkynylaniline derivatives which permitted the preparation of 3-substituted indoles was reported. For instance, Cacchi reported the preparation of 3-arylindole **13** from aniline **9** in a straightforward manner through a sequence comprising an aminopalladation and reductive elimination.[12] The process would be initiated by an oxidative addition to aryl halides or arenediazonium salts such as **10** (Scheme 3).[13] Coordination of the arylpalladium to the alkyne
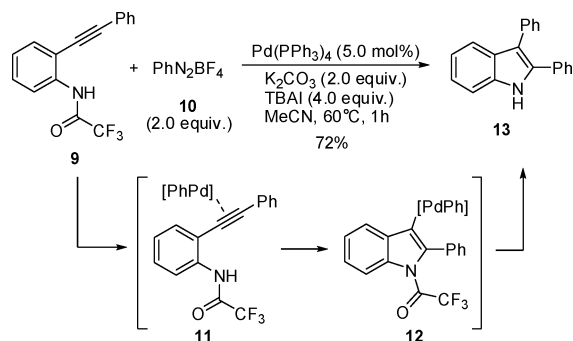
Scheme 3 Palladium-catalyzed synthesis of 3-arylindole **13** using arenediazonium salt **10**.

likely triggered a nucleophilic attack and a subsequent reductive elimination led to the corresponding N–H-free indole.

Formation of 3-indolylpalladium intermediates similar to **11** has been further exploited in order to introduce other valuable functionalities.[14] In this sense, de Lera reported very recently the preparation of alkenyl-substituted indoles combining a palladium-catalyzed cyclization with an oxidative Heck-coupling.[15] Thus, in the presence of acrylate **15**, aniline **14** could be converted into 3-alkenylindole **18** in good yield under aerobic reaction conditions using $PdCl_2$ as catalyst (Scheme 4). A plausible mechanism could start with an aminopalladation, followed by an alkene insertion to generate intermediate **17**. Indole **18** was obtained after β-hydride elimination. The presence of O_2 likely enabled the regeneration of an active PdX_2 species through oxidation. Interestingly, β-hydride elimination in intermediates such as **17** could be avoided using LiBr, affording the corresponding 3-alkylindoles.[16]
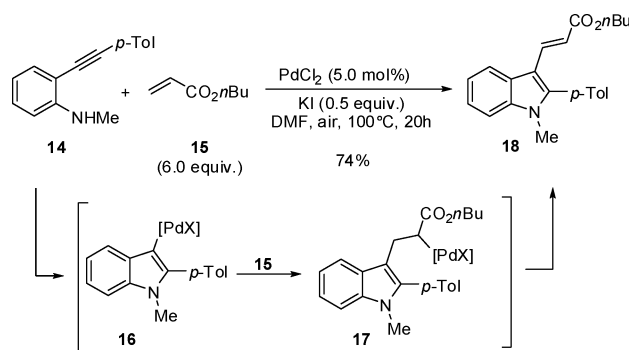
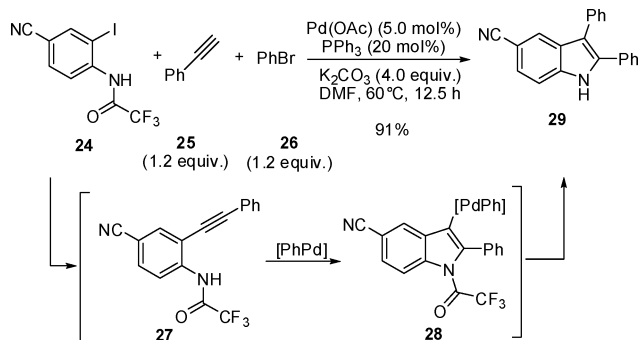**Scheme 4** Palladium-catalyzed synthesis of 3-alkenylindole **18**.

The replacement of an olefin by an aldehyde was further developed by Lu.[17] In this case, a cationic palladium catalyst allowed an efficient preparation of 3-hydroxymethylindole **23** using tosyl-protected aniline **19** and ethylglyoxalate (**20**) (Scheme 5). It is noteworthy that this protocol tolerated the presence of a C–Cl-bond, which could be further manipulated. This tandem reaction involved an addition of intermediate **21** to the carbonyl group to generate palladium alkoxide **22**. A simple protonolysis afforded indole **23** and regenerated a catalytically competent Pd(II) species, avoiding the necessity of additional oxidants.
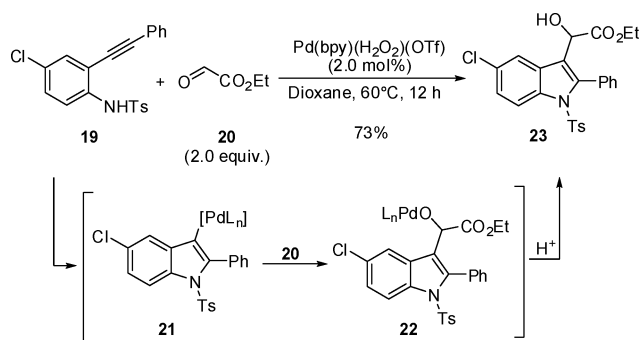
Scheme 5 Palladium-catalyzed synthesis of 3-hydroxymethylindole **23**.

An important drawback of the above mentioned methodologies lies in the preparation of the *o*-alkynylanilines. A practical protocol which circumvents this inconvenience was reported by Lu.[18] Hence, 2,3-disubstituted indole **29** was prepared in excellent

6470 | *Org. Biomol. Chem.*, 2011, **9**, 6469–6480

This journal is © The Royal Society of Chemistry 2011

yield through a one-pot three-component domino Sonogashira–cyclization–coupling sequence starting from *o*-iodoaniline **24**, which did not require the isolation of the *o*-alkynylaniline **27** (Scheme 6).

Scheme 6 Palladium-catalyzed multicomponent synthesis of 2,3-disubstituted indole **29**.

An interesting cascade multicomponent synthesis of 2-(aminomethyl)indoles was recently described by Ohno.[19] This protocol made use of *N*-protected *o*-alkynylanilines, aldehydes and secondary amines, which were selectively coupled using inexpensive CuBr as catalyst. In this manner, indole **35** was prepared in very good yield (Scheme 7). The reaction likely proceeded *via* Mannich-type coupling followed by a copper-catalyzed cyclization.
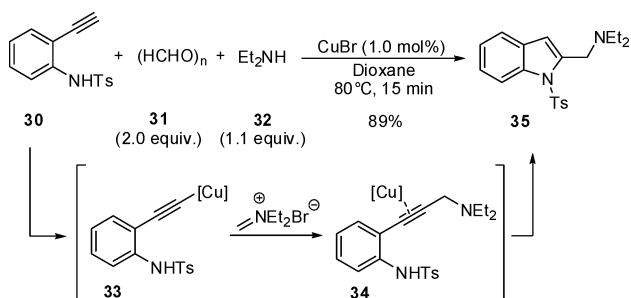

Scheme 7 Copper-catalyzed multicomponent synthesis of 2-(aminomethyl)indole **35**.

Biologically relevant 3-(2-aminoethyl)-1*H*-indol-2-amine derivatives were prepared by Wu through a copper-catalyzed three-component reaction of *o*-alkynylanilines, sulfonyl azide and nitroalkenes (Scheme 8).[20] Hence, Boc-protected *o*-alkynylaniline **36** was converted into substituted indole **41** under mild reaction conditions. The process was proposed to start with the formation of a triazolyl-copper species **38**, which evolved into intermediate **39** *via* N$_2$ extrusion and copper migration. A subsequent intramolecular cyclization led to 2-aminoindole **40**. Finally, an intermolecular Michael addition to alkene **37** and tautomerization would afford indole **41**.

N-(2-Alkynylphenyl)lactams could easily be converted into fused indoles as reported by Zhang (Scheme 9).[21] Thus, the thermal treatment of lactam **42** with PtCl$_4$ as catalyst under an atmosphere of O$_2$ selectively yielded indole **45**. The reaction was initiated by an aminometallation which led to metal-ammonium ylide **43**. Then, two consecutive migration reactions took place. Firstly, a 1,2-acyl migration gave rise to platinum–carbene intermediate **44**, which
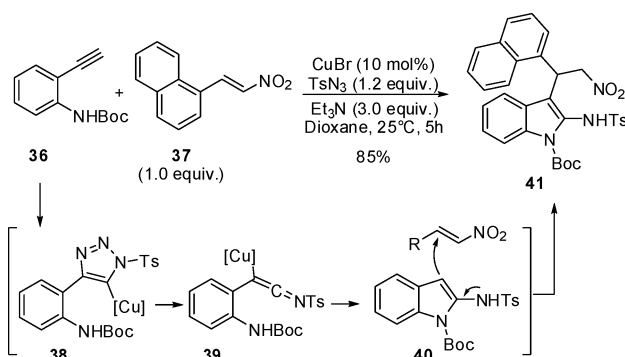

Scheme 8 Copper-catalyzed multicomponent synthesis of indole **41**.
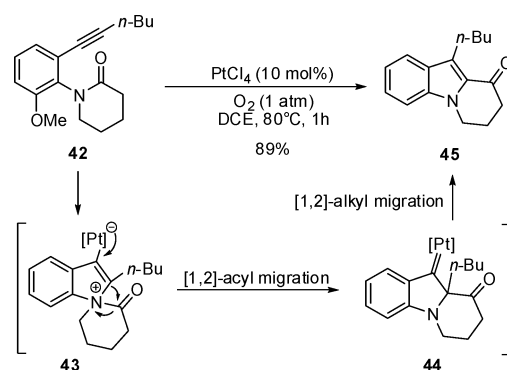
Scheme 9 Platinum-catalyzed synthesis of fused indole **45**.

finally underwent 1,2-alkyl migration to yield the corresponding indole **45**. A related process occurred when employing amines instead of amides as starting materials and rhenium or tungsten complexes as catalysts.[22]

A related platinum carbene was generated *in situ* from progargyl ether **46** through an alkyne activation as described by Iwasawa (Scheme 10).[23] Here, platinum carbene species **49** resulted from a cyclization/elimination sequence through intermediate **48**, and was subsequently trapped in the presence of an excess of vinyl ether **47**. Thus, this protocol enabled the preparation of fused indole **51** in good yield.
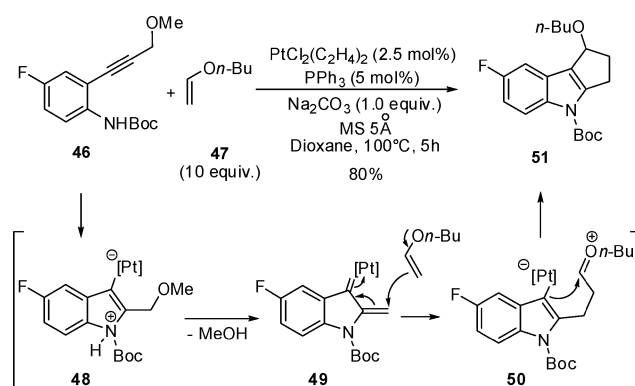

Scheme 10 Platinum-catalyzed synthesis of fused indole **51**.

## Indole syntheses from *o*-haloanilines

Since its first report in 1991, the Larock indole synthesis has become one of the most attractive and practical method for

the preparation of 2,3-disubstituted indoles,[24] and it has been extensively studied.[4g,h] This protocol consists of a palladium-catalyzed[25] heteroannulation of internal alkynes with *N*-protected *o*-iodoanilines (Scheme 11), however, alternatives which enable the use of *o*-bromo- or *o*-chloroanilines as well as halobenzoic acids as precursors have been developed.[26] A major drawback of this protocol arises in the control of the regioselectivity when unsymmetrical alkynes are used. Normally, the more sterically hindered group is attached at position C-2. Nevertheless, with similarly substituted alkynes, mixtures of regioisomers are obtained.
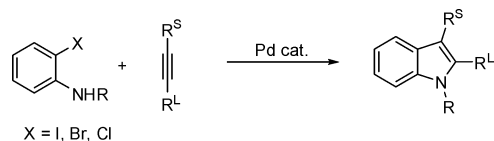

Scheme 11 Larock indole synthesis.

On the contrary, intramolecular versions of the Larock indole synthesis give rise to regioselectively substituted indoles.[27] The importance and validity of this approach becomes apparent in the next example. Here, Boger made use of the Larock's procedure to prepare complex indole **53** (Scheme 12), which is a key intermediate in the synthesis of relevant natural products such as chloropeptines.[28] Although a stoichiometric amount of Pd(OAc)$_2$ was required, the impressive yield obtained is noteworthy considering the dense functionalization of the starting aniline **52**.
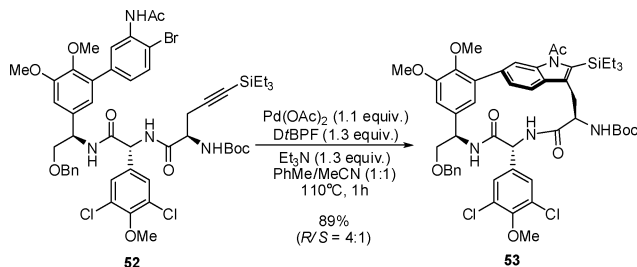
Scheme 12 Synthesis of densely functionalized indole **53** using Larock's procedure.

A different approach to indoles using *o*-chloroanilines and internal alkynes was described by Ackermann (Scheme 13).[29] This protocol comprised a multicatalytic sequence. For instance, indole **57** was obtained starting with a highly regioselective titanium-catalyzed hydroamination of unsymmetrical alkyne **55**
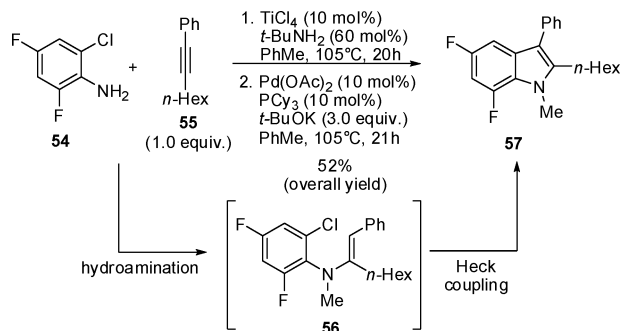
Scheme 13 Synthesis of indole **57** *via* titanium-catalyzed hydroamination/palladium-catalyzed Heck-coupling.

with aniline **54**, followed by a subsequent palladium-catalyzed intramolecular Heck-coupling in intermediate **56**. The best results for the Heck reaction were obtained when using electron-rich PCy$_3$ or sterically hindered imidazolium salts as preligands. Moreover, this sequential procedure could be achieved using ruthenium-catalyzed hydroaminations as well.[30]

Barluenga described an alternative approach to regioselectively access indoles from *o*-haloanilines using alkenyl bromides as coupling partners.[31] Here, a catalytic system comprising Pd$_2$(dba)$_3$ and electron-rich phosphine DavePhos enabled the synthesis of 2-substituted indole **61** from aniline **58** and *α*-bromostyrene (**59**) (Scheme 14). Interestingly, the reaction proceeded exclusively through the cleavage of the C–Br-bond, while the C–Cl-bond remained unaltered. This cascade reaction started with a Buchwald–Hartwig-type C–N-bond formation giving rise to intermediate **60**, which underwent an intramolecular Heck-coupling. Alternatively, the use of *trans*-1,2-bromoalkene derivatives afforded the corresponding 3-substituted indoles.
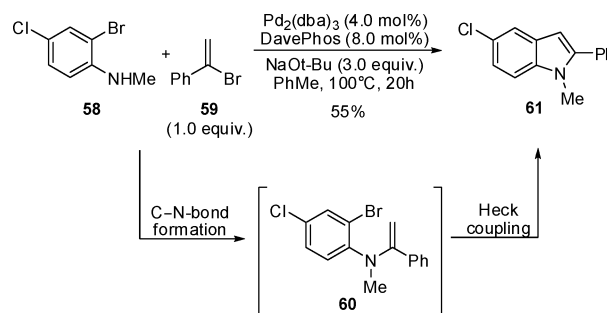

Scheme 14 Palladium-catalyzed synthesis of indole **61** *via* C–N-bond formation/Heck coupling sequence.

Indole syntheses from *o*-alkynylhaloarenes or *o*-dihaloarenes

In contrast to well studied approaches to indole syntheses from aniline derivatives, the use of dihaloarenes has received far less attention. However, the development of efficient and versatile transition metal-catalyzed C–N-bond formation processes through Buchwald–Hartwig- or Ullman–Goldberg-type couplings has enabled the establishment of new methodologies to prepare indoles from *o*-alkynylhaloarenes or dihaloarenes and amines. The most relevant examples regarding the use of these starting materials are discussed in this section.

A catalytic two-step one-pot procedure for the synthesis of 2-substituted indoles using *o*-alkynylchloroarenes was described by Doye.[32] The combination of a titanium-catalyzed hydroamination of alkyne **62** with sterically hindered amine **63**, followed by a subsequent palladium-catalyzed *N*-arylation of the enamine **65** afforded indole **66** in good yield (Scheme 15). Interestingly, fused indoles could be assembled with an intramolecular version of this protocol.

Remarkably, this overall transformation could be achieved with a single catalyst, as reported by Ackermann.[33] Thus, the sole use of palladium or low-priced copper[33a,34] catalysts enabled the accomplishment of this transformation with superior efficiency in terms of yields and shortening reaction times. In some cases, milder bases such as K$_3$PO$_4$ could be employed,[35] thereby allowing
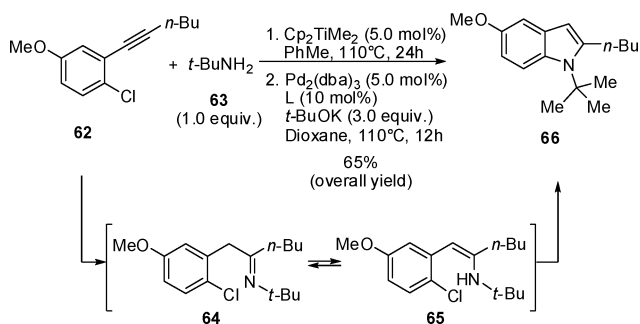
Scheme 15 One-pot hydroamination/C–N-bond formation synthesis of indole **66**. (L = 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride).

a better functional group tolerance. In addition, Ackermann found that a Sonogashira-coupling reaction was compatible with the hydroamination/amination sequence.[33] This overall transformation simplified the preparation of indole **69**, which could be accessed directly from o-dihaloarene **67** by a sequential treatment with alkyne **25** and p-toluidine (**68**) (Scheme 16).
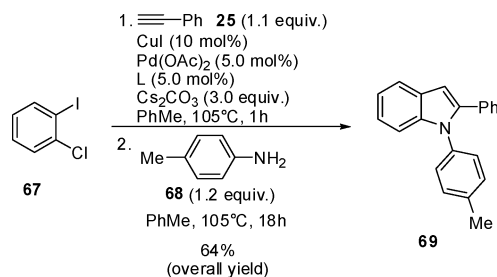
Scheme 16 One-pot synthesis of indole **69** from o-dihaloarene **67** (L = 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride).

A novel route to indole synthesis using o-dihaloarenes and imines was devised by Barluenga.[36] In this methodology an α-deprotonation of the imine set the stage to allow two consecutive palladium-catalyzed cross-coupling processes. Thus, under basic conditions, imine **71** was α-arylated with unsymmetric dihaloarene **70** to yield intermediate imine **72**, which tautomerized to the corresponding enamine **73**. A subsequent Buchwald–Hartwig amination gave rise to 2,3-disubstituted indole **74** in good yield (Scheme 17). Remarkably, the regioselectivity of the overall transformation could be controlled according to the preference of the oxidative addition to the C–Br- over the C–Cl-bond.
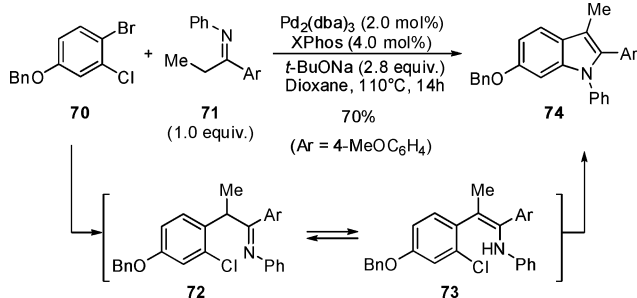
**Scheme 17** Synthesis of indole **74** via palladium-catalyzed imine α-arylation/N-arylation sequence.

This reaction was found to proceed regioselectively and with the same efficiency using o-chloroaryl sulfonates, which could be prepared from readily available inexpensive phenols.[37] Moreover, a convenient "on water" microwave-promoted protocol of this transformation was developed as well.[38] Similarly, Barluenga found that indoles could be built in a modular three-component cascade reaction employing simple starting materials such as bromoalkenes, primary amines and o-dihaloarenes.[36] In this manner, indole **79** was efficiently prepared from β-bromostyrene (**59**), aniline (**75**) and 1,2-dichlorobenzene (**76**) (Scheme 18). The overall transformation consisted of an alkenyl amination, an α-arylation of the imine and finally an intramolecular N-arylation, which were promoted by a single palladium catalyst. The selectivity of this process is noteworthy, since the three different cross-coupling events took place consecutively and with complete chemoselectivity.
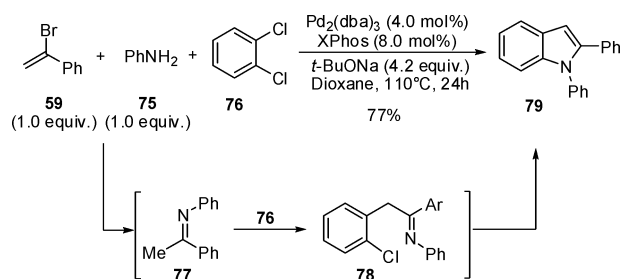
Scheme 18 Palladium-catalyzed three-component synthesis of indole **79**.

Jørgensen made use of well-established cross-coupling protocols to develop an elegant indole synthesis from o-dihaloarenes and allyl amines.[39] Here, a catalytic system comprising Pd(OAc)₂ and dppf as ligand enabled the regioselective synthesis of indole **83** from haloarene **80** and allyl amine (**81**) (Scheme 19). The sequence was proposed to start with an N-arylation. A Heck-coupling on intermediate **82** and an isomerization led to the indole in a good yield. Later, this protocol was extended to the use of chloroaryl triflates and Boc-protected allyl amines.[40]
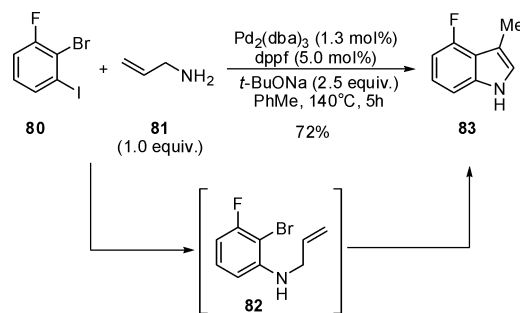
Scheme 19 Synthesis of indole **83** from o-dihaloarene **80** and allyl amine (**81**).

Indole syntheses from β-(pseudo)halostyrene derivatives

A variety of indole derivatives were prepared by Lautens and Alper when using ortho-gem-dihalovinylanilines as substrates.[41] This palladium-catalyzed reaction proceeded through an intramolecular Buchwald–Hartwig-coupling giving rise to 2-haloindoles. These valuable substrates could be further functionalized through

inter- or intramolecular C–C-couplings enabling the development of synthetically useful sequences. For instance, Florent recently developed a domino coupling reaction for the synthesis of 2-acylindole derivatives.[42] With this approach, indole **87** was efficiently prepared from aniline **84** and arylboronic acid **85** when the reaction was conducted under a high pressure of CO (Scheme 20). This one-pot palladium-catalyzed reaction occurred *via* sequential C–N-bond formation, carbonylation and Suzuki-coupling. A remarkable feature of this protocol resided in the use of a mild base. In this manner, sensitive moieties were well tolerated.
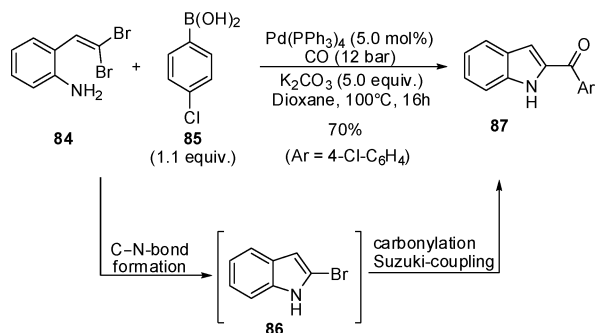
Scheme 20   Synthesis of 2-acylindole **87** from dihalovinylaniline **84**.

Alternatively, Willis reported a related palladium-catalyzed indole synthesis employing *o*-halostyryl triflates[43] or halides[44] as starting materials. In this approach, two consecutive C–N-bonds were formed and allowed for the introduction of functionalities at the N-atom. For instance, indole **91** bearing a bulky substituent at position 1, was synthesized from β-chlorostyrene **88** and *tert*-amylamine (**89**) in good yield. The low $Z:E$ ratio of the starting material, in contrast with the obtained yield, indicated that both geometrical isomers could be converted into the desired indole, thereby, simplifying the preparation of the starting substrate (Scheme 21).[44c]
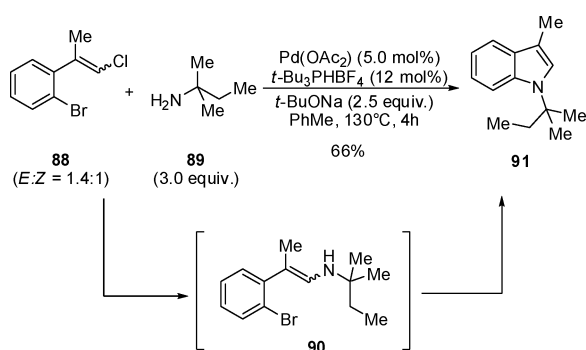

Scheme 21   Synthesis of indole **91** from *o*-bromo-β-chlorostyrene **88**.

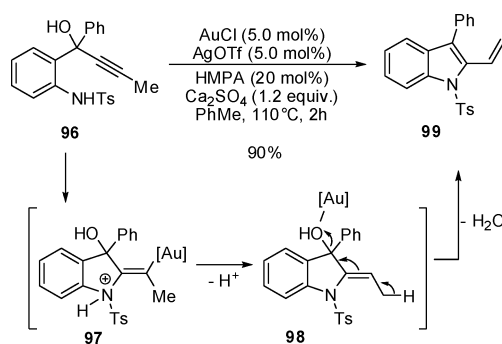## Indole syntheses from *o*-propargylanilines

As presented above, the indole core could be easily assembled through metal-catalyzed 5-*endo*-dig cyclizations from *o*-alkynylanilines. On the contrary, Malacria studied the feasibility to prepare indole derivatives *via* a 5-*exo*-dig cyclization using *o*-propargylanilines as substrates.[45] Thus, a straightforward preparation of 3-alkoxyindole **95** was achieved from aniline **92** using PtCl₂

as catalyst. Moreover, it was found that an excess of simple acids such as SiO₂ or *p*-toluenesulfonic acid promoted the transformation as well (Scheme 22). A mechanistic proposal for the Brønsted acid-promoted reaction would start with an alkyne activation by the acid, which triggered the cyclization to generate ammonium intermediate **93**. Then, a facilitated 3-aza-Cope rearrangement towards immonium species **94** and subsequent aromatization likely afforded the final product.
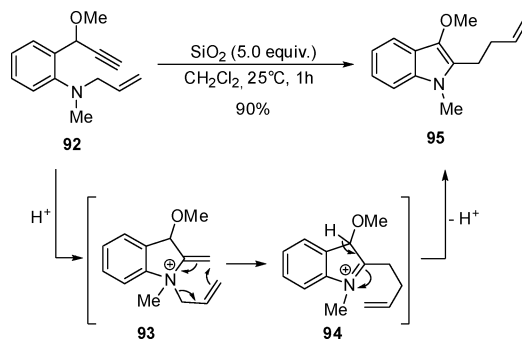
Scheme 22   Brønsted acid-promoted cyclization of aniline **92**.

In a related report, Chan described a gold-catalyzed 5-*exo*-dig cyclization of tertiary propargyl alcohols.[46] In this study, a variety of differently substituted indoles could be obtained, however, their structures had a strong dependence on the substrate. For example, alkynol **96** was converted into 2-vinylindole **99** in the presence of HMPA using an *in situ* generated cationic gold catalyst (Scheme 23). The formation of indole **99** took place through a gold-promoted cyclization, which afforded ammonium species **97**. Subsequent proton abstraction gave rise to alcohol **98**, which underwent a dehydration efficiently yielding indole **99**. Despite its beneficial influence, the role of the HPMA remained unclear at this stage.

Scheme 23   Gold-catalyzed cyclization of alkynol **96**.

Indole syntheses from acetophenone derivatives

As was shown in the previous sections, anilines or haloarenes bearing an alkenyl or alkynyl substituent at the *ortho* position have become the trendiest substrates for the synthesis of indoles. In contrast, Pei disclosed an attractive alternative to access 2-substituted indole derivatives using *o*-aminochloroacetophenones and Grignard reagents, which did not require the presence of transition metal catalysts.[47] In this manner, the treatment of chloroketone **100** with alkynyl Grignard **101** under very mild

reaction conditions afforded indole **104** in a reasonable yield (Scheme 24). The reaction was likely started with the addition of the organometallic reagent. Then, a key step consisting of a [1,2]-aryl migration in intermediate **102** took place, affording new ketone **103**, which gave rise to indole **104** through an intramolecular condensation.[48]
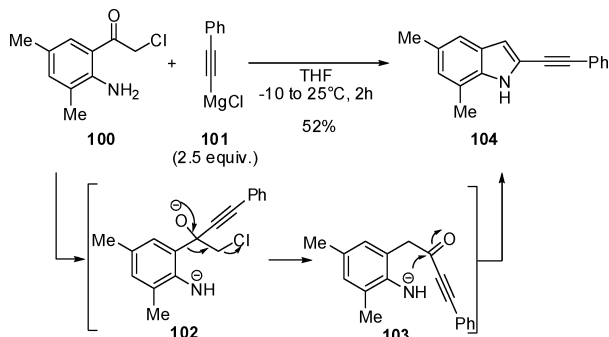
Scheme 24 Synthesis of indole **104** from chloroketone **100**.

A copper-catalyzed synthesis of indole-2-carboxylic acid esters from 2-haloarylketones and isocyanoacetates was reported by Cai.[49] Although the use of 2-bromoarenes yielded the desired indoles in good yields, it is remarkable that this ligand-free protocol could be efficiently achieved with less reactive 2-chloroketone **105** (Scheme 25). A sequence involving a condensation/intramolecular C–N-bond formation/deformylation likely operated to assemble the indole core.
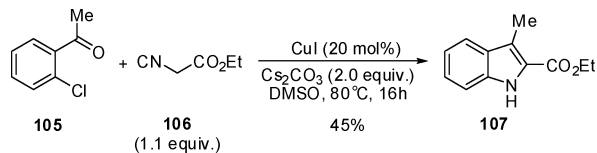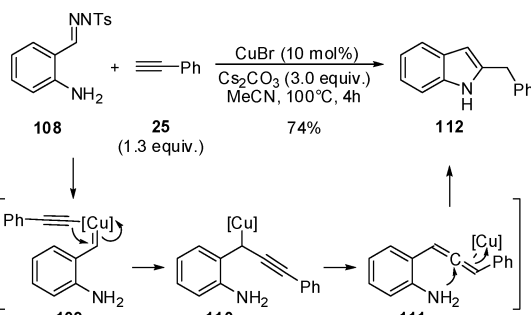

Scheme 25 Copper-catalyzed synthesis of indole **107**.

A different ligand-free copper-catalyzed indole synthesis comprising the use of terminal alkynes and hydrazones derived from 2-aminobenzaldehydes was very recently described by Wang.[50] Thus, 2-substituted indole **112** could be prepared from hydrazone **108** and alkyne **25**, using CuBr as catalyst and Cs_2CO_3 as a mild base (Scheme 26). A mechanistic proposal would involve a coupling of the alkyne with an *in situ* generated carbene to give rise to intermediate **110**, which could evolve *via* isomerization/cyclization to yield indole **112**. Unfortunately, the scope of this transformation seems still limited, since only very few examples have been reported.

Indole syntheses from arylhydrazines and related compounds

The Fischer indole synthesis has remained as one of the essential methodologies for the synthesis of indole derivatives. This approach consists of the condensation of an aromatic hydrazine with a ketone, followed by a [3,3]-sigmatropic rearrangement, subsequent ammonia elimination and aromatization (Fig. 2, a).[51] A mechanistically related process, which could be started with an alkyne hydroamination reaction constitutes an interesting alternative route to the indole scaffold (Fig. 2, b).

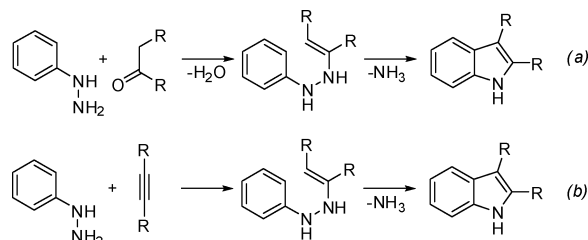**Scheme 26** Copper-catalyzed coupling of hydrazone **108** with alkyne **25**.

Fig. 2 Fischer indole synthesis *vs.* alkyne hydroamination-based indole synthesis.

Pioneering studies of this interesting approach were accomplished by Bergman, where zirconium-mediated domino hydroamination–Fischer-type cyclizations were reported.[52] Later, catalytic procedures using titanium catalysts and zinc salts as additives were developed by Odom and others.[53] Despite the interest of this reaction, these protocols unfortunately presented some drawbacks in terms of the sensitivity of functional groups towards titanium, the necessity to protect the hydrazine or low regioselectivities.

Some of these disadvantages were elegantly overcome by Beller.[54] Thus, it was found that titanium was not required to promote the hydroamination step. Thereby, zinc acting as Lewis acid was apparently inducing both the hydroamination and the subsequent cyclization. This easy protocol enabled the preparation of a variety of indoles from readily available reagents. For instance, zinc-mediated reaction of commercially accessible hydrazine **113** with terminal alkyne **114** afforded hydroxy-functionalized indole **116** with complete Markovnikov regioselectivity (Scheme 27).
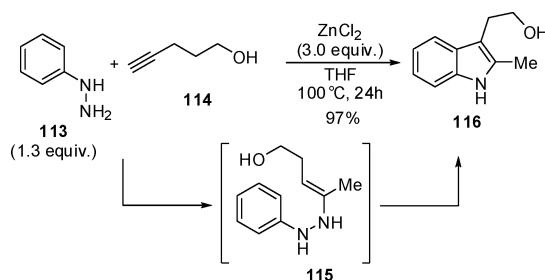
Scheme 27 Zinc-mediated hydroamination–Fischer cyclization.

A different pathway to access an enamine intermediate such as **115** in indole synthesis was shrewdly designed by Knochel.[55] In this approach hydrazines were replaced by aryldiazonium salts, which are readily available reagents. Moreover, the use of alkynes as coupling partners was substituted by alkylzinc reagents, which

conveniently tolerated a variety of valuable functional groups. As an example, functionalized indole **121** was prepared in excellent yield and with complete regioselectivity from diazonium salt **117** and alkylzinc complex **118** (Scheme 28). Thus, azo compound intermediate **119** was formed by coupling of substrates **117** and **118**. Then, an isomerization to enamine **120** took place, which was capable of undergoing cyclization as in the traditional Fischer indole protocol. Interestingly, this protocol was applied to the preparation of the anti-inflammatory drug indomethacin (**5**) (see Fig. 1).
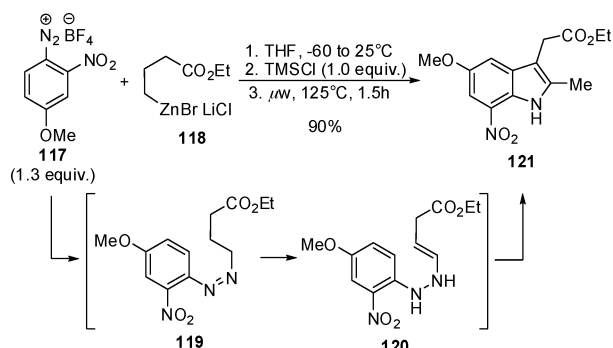

Scheme 28 Synthesis of indole **121** using diazonium salt **117** and organozinc **118**.

Indole syntheses *via* nitrene or carbene insertions

Modern developments towards indole syntheses make use of well-established C–N-bond formation protocols through cross-coupling reactions. These amination reactions are performed with aniline or amine derivatives. Nevertheless, less conventional sources of nitrogen, such as nitrenes have been successfully employed in indole synthesis.

Nitrenes can be generated *in situ* by rearrangement of 2*H*-azirines. When bearing an aryl substituent at position C-2, a nitrene intermediate could undergo an intramolecular C–H-insertion yielding the corresponding indole.[56] Thus, Zheng recently described the preparation of, among others, 2,3-disubstituted indole **125**.[57] This reaction took place through a ring opening of azirine **122** and the subsequent formation of iron–nitrene species **123**. Intramolecular[58] amination led to intermediate **124**, which finally evolved into indole **125** (Scheme 29).
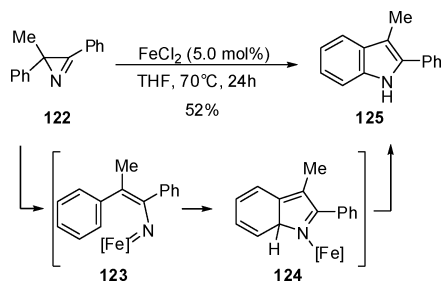
Scheme 29 Iron-catalyzed synthesis of indole **125** from azirine **122**.

Readily available azides proved to be convenient precursors of nitrenes as well. Accordingly, in a series of elegant studies, Driver developed complementary routes to indoles, which made

use of β-styrylazides or *o*-vinylarylazides as substrates.[59] These rhodium-catalyzed processes could be performed under mild reaction conditions,[60] avoiding undesired by-product formation. For instance, 2-indole carboxylate **127** was obtained almost quantitatively from vinylazide **126** (Scheme 30, a), while the preparation of 2-aryl substituted indole **129** was accomplished using aryl azide **128** (Scheme 30, b). The extrusion of N$_2$ followed by the formation of metal–nitrene intermediates **130** and **131** enabled regioselective intramolecular aminations to occur.
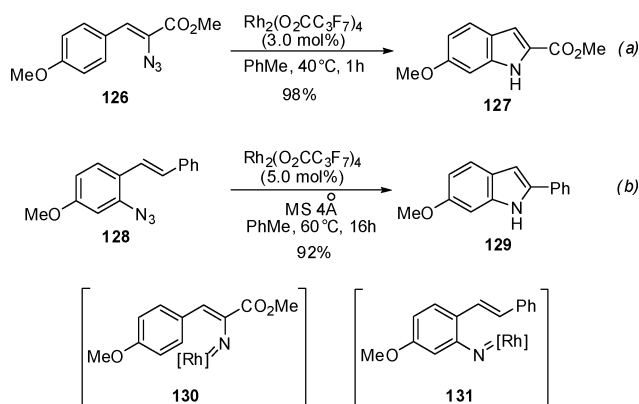
Scheme 30 Rhodium-catalyzed indole synthesis from azides.

Alternatively, Wang devised an indole synthesis from benzamides and EDA (ethyl diazoacetate, **133**), which proceeded through a formal carbene insertion.[61] This transformation was based on the electrophilic activation of the amide with Tf$_2$O in the presence of pyridine derivatives, while the diazo compound acted as nucleophile. In this manner, indole **137** was obtained in moderate yield by treatment of amide **132** with **133** and Tf$_2$O, in the presence of pyridine derivatives (Scheme 31). The utility of this procedure was limited to the availability of diazo compounds; however, the functional group tolerance was remarkable. For instance, the presence of a labile C–I-bond, which could be problematic when using cross-coupling methodologies, was tolerated. The mechanism of this domino reaction would start with the formation of pyridinium adduct **134**. A nucleophilic attack of the diazo compound could lead to intermediate **135**. Then, an electrophilic aromatic substitution could afford species **136**. Finally, an aromatization would lead to indole **137**.
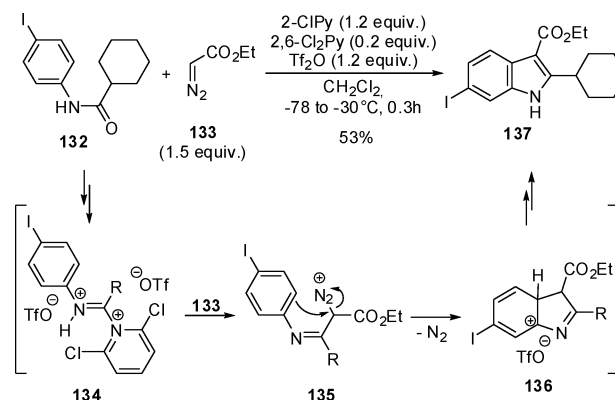
Scheme 31 Indole synthesis from benzamide **132** and EDA (**133**).

Indole syntheses *via* processes involving a C–C- or N–N-cleavage

Valuable intermediates for indole synthesis such as *o*-alkynylanilines can be accessed from other sources than *o*-haloanilines, such as benzamides or ketoximes. These protocols are based on domino reactions which involve the cleavage of a C–C-bond. For instance, Yanada reported a concise synthesis of *N*-carboxyl indoles from 2-alkynylbenzamides.[62] Hence, PhI(OAc)$_2$ promoted a Hofmann-type rearrangement of benzamide **138** to isocyanate **139**. A 5-*endo*-dig platinum-catalyzed cyclization and a final esterification, efficiently afforded indole **140** (Scheme 32). With the use of appropriate *bis*-amides, this reaction was further applied to the synthesis of macrocyclic *bis*-indoles.
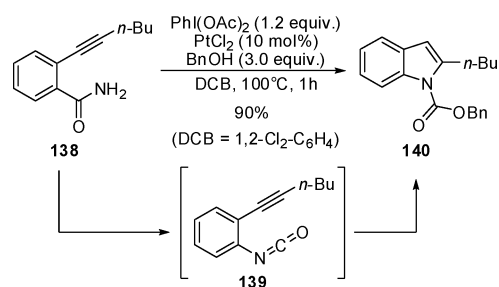

Scheme 32 Indole synthesis *via* Hofmann-rearrangement.

A multicatalytic one-pot reaction using 1-(2-alkynylphenyl) ketoxime derivatives to prepare *N*-acyl indoles was disclosed by Wu.[63] This protocol consisted of an indium and cyanuric chloride (CNC) co-catalyzed Beckmann-type rearrangement of a ketoxime such as **141**, which afforded non-isolated *o*-alkynyl aniline intermediate **142**. Subsequently, palladium-catalyzed cyclization in the presence of an excess of CuCl$_2$ led to 3-chlorosubstituted indole **143** (Scheme 33).
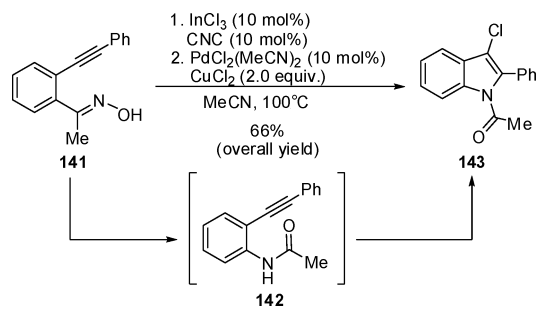
Scheme 33 Indole synthesis *via* Beckmann-rearrangement.

The use of *N*-acylbenzotriazole derivatives and internal alkynes was exploited by Nakamura to prepare 1,2,3-trisubstituted indoles.[64] In this interesting approach to indoles, the key step was the generation of a 2-aminobenzenediazonium species such as **146**, a reminiscent intermediate of the Larock indole synthesis (see Scheme 11). Thus, cleavage of the N–N-bond of benzotriazole **144** at high temperature afforded intermediate **146** and set the stage for oxidative addition to form the arylpalladium species **147**, which further inserted into the alkyne **145**, yielding indole **148** (Scheme 34).[65]
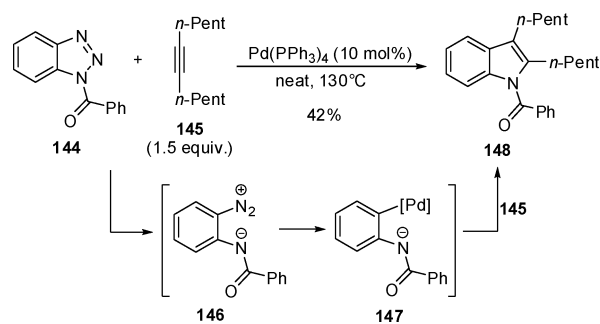

Scheme 34 Indole synthesis from benzotriazoles *via* N–N-bond cleavage.

Indole syntheses through C–H-bond functionalizations

Modern transition metal-catalyzed transformations for a fast assembly of the indole core require the use of *ortho*-substituted anilines or 1,2-dihaloarenes, which should be prefunctionalized, thereby lengthening synthetic sequences and restricting to some extent their availabilities. Other attractive alternatives comprise the use of stoichiometric amounts of organometallic reagents, or relatively dangerous starting materials such as azides, diazo compounds or diazonium salts. An approach starting from mono-functionalized arenes, which should involve a C–H-bond functionalization, would be highly desirable. In this way, a wider collection of starting materials would be accessible and synthetic routes would be shortened, presenting this strategy as an attractive alternative to prepare indoles in a more efficient manner. This section summarizes recent achievements in indole syntheses *via* C–H-bond functionalization.[66]

An intramolecular oxidative cyclization of *N*-aryl enamines was reported by Glorius.[67] This flexible procedure enabled the synthesis of, among others, functionalized indole **150** (Scheme 35). This palladium-catalyzed transformation made use of easy-to-prepare enamine **149** as starting material, however a large excess of a copper salt was required as terminal oxidant. Here, a large variety of anilines could be used since the transformation did not occur *via* electrophilic aromatic substitution, as was revealed by mechanistic studies, which supported a σ-bond metathesis or a deprotonation for the creation of the new C–C-bond.
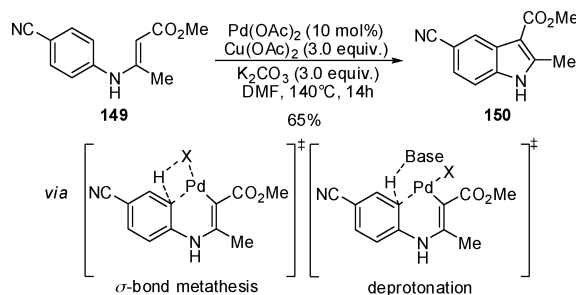
Scheme 35 Palladium-catalyzed oxidative cyclization of enamine **149**.

Interestingly, enamines could be generated *in situ via* condensation and further transformed into the corresponding indoles in comparable yields. Later, several variants of this protocol were reported. Thus, this oxidative cyclization could be accomplished using copper or iron catalysts[68] or was promoted by iodine(III) compounds.[69]

On the contrary, a C–N-bond formation *via* palladium-catalyzed intramolecular amination of an aromatic C–H-bond was the strategy employed by Hartwig to prepare indoles.[70] This attractive approach made use of *β*-aryl oxime ester derivatives, such as **151**, which was converted into indole **155** using a Pd(0) catalyst (Scheme 36). The neutral-redox conditions of this methodology should be noteworthy, since the use of external oxidants was suppressed. The proposed catalytic cycle likely started with a N–O-bond oxidative addition to oxime **151** to afford palladium species **152**, which after a tautomerization set the stage for the C–H-bond cleavage. Palladacycle intermediate **154** would lead to the final indole through a C–N-reductive elimination.
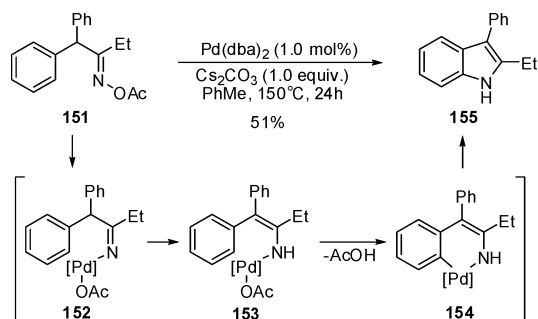
Scheme 36 Palladium-catalyzed amination with oxime ester **151**.

In terms of synthetic flexibility and operational simplicity, intermolecular oxidative couplings would be more convenient approaches to the indole core, as was cleverly devised by Fagnou.[71] Hence, in an evocation of the Larock indole synthesis, Fagnou developed a rhodium-catalyzed cyclization of protected anilines with alkynes. Extensive optimization studies allowed for the development of mild reaction conditions, which turned out in a remarkably ample scope and made possible the use of simple O_2 as terminal oxidant.[72] For example, using anilide **156** and alkyne **157**, 5-chloro-substituted indole **160** was obtained in good yield and with complete regioselectivity (Scheme 37). This remarkable transformation was proposed to occur through a sequence started with a C–H-bond cleavage. Rhodacycle intermediate **158** would undergo a carbo-rhodation into the alkyne to generate a new rhodacycle species **159**, which evolved *via* C–N-reductive elimination to produce the desired indole **160**.[73]
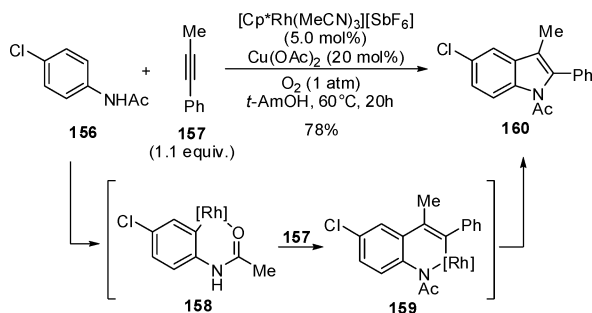
Scheme 37 Intermolecular rhodium-catalyzed oxidative cyclization.

Summary and outlook

Syntheses of indole derivatives represent an amazing area of research for organic chemists. In addition, due to the relevance of

indoles, efforts to develop their efficient syntheses influence other research areas, including biology, medicine and material science, thereby affecting our society and our life. The most recent and remarkable discoveries in the syntheses of indoles are presented in this review.

A plethora of versatile methodologies based on transition metal-catalyzed cyclizations, C–C- or C–N-bond formation cross-coupling reactions are currently available and allow for the assembly of functionalized indoles. While these protocols ensure the regioselective preparation of the desired indole derivative, they required a prefunctionalization of starting materials, which results in longer synthetic routes. In this sense, procedures involving functionalization of ubiquitous C–H-bonds have emerged as promising alternative routes to prepare indoles. However, the functionalization of strong C–H- or C–X-bonds involve, among others, the use of harsher reaction conditions or rather expensive catalysts, which proceed with low turnovers. Besides, synthetically elaborated substrates enable an easy access to specific indole-containing structures through transition metal-catalyzed cyclizations, particularly, when using noble metals such as palladium, gold or platinum. In contrast, inexpensive copper or iron catalysts still remain a challenge to perform these valuable transformations.

As shown in this review, many cleverly devised routes for the synthesis of indoles have been developed in recent years. This could give the impression to the reader that not many new goals remain unravelled in this field. However, new solutions necessarily provoke new questions, which should be addressed. Thus, for example, sustainability and efficiency criteria appear as mandatory requirements. These translate into the necessity to put into practice protocols which make use of ecologically benign media, in terms of energy and cleanliness, starting from readily available feedstocks. Likewise, cascade-domino reactions or multi-step one-pot procedures which enable the straightforward preparation of highly functionalized indoles are highly desirable. Moreover, the development of robust catalysts might be useful in terms of functional group tolerance or catalytic efficiency, which should be beneficial in the preparation of complex indole-containing structures or to accomplish large scale synthesis. As a consequence, new exciting and innovative achievements are expected to appear in this relevant research area.

Acknowledgements

Notes and references

1 A. Baeyer, *Justus Liebigs Ann. Chem.*, 1866, **140**, 295.
2 (*a*) R. J. Sundberg, in *The Chemistry of Indoles*, Academic Press, New York, 1970; (*b*) R. K. Brown, in *Indoles* (Ed.: W. J. Houlihan), Wiley-Interscience, New York, 1972.
3 *"Indole and its Derivatives"* J. A. Joule, in *Science of Synthesis (Houben-Weyl Methods of Molecular Transformations)*, Vol. 10 (Ed.: E. J. Thomas), Thieme, Stuttgart, 2000, chap. 10.13.
4 Selected recent reviews: (*a*) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641–652; (*b*) S. A. Patil, R. Patil and D. D. Miller, *Curr. Med. Chem.*, 2011, **18**, 615–637; (*c*) G. Palmisano,

A. Penoni, M. Sisti, F. Tibiletti, S. Tollari and K. M. Nicholas, *Curr. Org. Chem.*, 2010, **14**, 2409–2441; (*d*) J. Barluenga, F. Rodríguez and F. J. Fañanás, *Chem.–Asian J.*, 2009, **4**, 1036–1048; (*e*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442; (*f*) K. Krüger, A. Tillack and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2153–2167; (*g*) L. Ackermann, *Synlett*, 2007, 507–526; (*h*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911; (*i*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920; (*j*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285–2310.

5 For a recent review on indole functionalization, see: M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608–9644.

6 Selected examples: (*a*) H. Zhou, D. Zhu, Y. Xing and H. Huang, *Adv. Synth. Catal.*, 2010, **352**, 2127–2131; (*b*) A. H. Stoll and P. Knochel, *Org. Lett.*, 2008, **10**, 113–116; (*c*) A. L. Rodriguez, C. Koradin, W. Dohle and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488–2490.

7 A. Yasuhara, N. Suzuki, T. Yoshino, Y. Takeda and T. Sakamoto, *Tetrahedron Lett.*, 2002, **43**, 6579–6582.

8 Selected examples: (*a*) I. Nakamura, U. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2007, **46**, 2284–2287; (*b*) B. M. Trost and A. McClory, *Angew. Chem., Int. Ed.*, 2007, **46**, 2074–2077; (*c*) X. Li, A. R. Chianese, T. Vogel and R. H. Crabtree, *Org. Lett.*, 2005, **7**, 5437–5440; (*d*) N. Sakai, K. Annaka and T. Konakahara, *Org. Lett.*, 2004, **6**, 1527–1530; (*e*) B. C. J. van Esseveldt, F. L. van Delft, R. de Gelder and F. P. J. T. Rutjes, *Org. Lett.*, 2003, **5**, 1717–1720; (*f*) F. E. McDonald and A. K. Chatterjee, *Tetrahedron Lett.*, 1997, **38**, 7687–7690.

9 J. Barluenga, M. Trincado, E. Rubio and J. M. González, *Angew. Chem., Int. Ed.*, 2003, **42**, 2406–2409.

10 For related processes, see: (*a*) R. Halim, P. J. Scammells and B. L. Flynn, *Org. Lett.*, 2008, **10**, 1967–1970; (*b*) D. Yue and R. C. Larock, *Org. Lett.*, 2004, **6**, 1037–1040.

11 (*a*) Z. Shen and X. Lu, *Adv. Synth. Catal.*, 2009, **351**, 3107–3112; (*b*) S. Tang, Y.-X. Xie, J.-H. Li and N.-X. Wang, *Synthesis*, 2007, 1841–1847.

12 (*a*) S. Cacchi, G. Fabrizi and A. Goggiamani, *Adv. Synth. Catal.*, 2006, **348**, 1301–1305; (*b*) G. Battistuzzi, S. Cacchi and G. Fabrizi, *Eur. J. Org. Chem.*, 2002, 2671–2681.

13 For a related process which makes use of arenediazonium salts, see: S. Cacchi, G. Fabrizi, A. Goggiamani, A. Perboni, A. Sferrazza and P. Stabile, *Org. Lett.*, 2010, **12**, 3279–3281.

14 For representative pioneering studies, see: (*a*) L. S. Hegedus, G. F. Allen and D. J. Olsen, *J. Am. Chem. Soc.*, 1980, **102**, 3583–3587; (*b*) Y. Kondo, T. Sakamoto and H. Yamanaka, *Heterocycles*, 1989, **48**, 1013–1016; (*c*) A. Yasuhara, M. Kaneko and T. Sakamoto, *Heterocycles*, 1998, **48**, 1793–1799.

15 R. Álvarez, C. Martínez, Y. Madich, J. G. Denis, J. M. Aurrecoechea and Á. R. de Lera, *Chem.–Eur. J.*, 2010, **16**, 12746–12753.

16 (*a*) Z. Shen and X. Lu, *Tetrahedron*, 2006, **62**, 10896–10899. Gold- or rhodium-catalyzed processes: (*b*) M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi and F. Marinelli, *J. Org. Chem.*, 2005, **70**, 2265–2273; (*c*) N. Isono and M. Lautens, *Org. Lett.*, 2009, **11**, 1329–1331.

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

18 B. Z. Lu, W. Zhao, H.-X. Wei, M. Dufour, V. Farina and C. H. Senanayake, *Org. Lett.*, 2006, **8**, 3271–3274.

19 (*a*) H. Ohno, Y. Ohta, S. Oishi and N. Fujii, *Angew. Chem., Int. Ed.*, 2007, **46**, 2295–2298; (*b*) Y. Ohta, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2009, **74**, 7052–7058; (*c*) Y. Ohta, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2009, **11**, 1979–1982. For a Pd-catalyzed process which lead to the same indole derivatives, see: (*d*) I. Ambrogio, S. Cacchi and G. Fabrizi, *Org. Lett.*, 2006, **8**, 2083–2086.

20 Z. Chen, D. Zheng and J. Wu, *Org. Lett.*, 2011, **13**, 848–851.

21 G. Li, X. Huang and L. Zhang, *Angew. Chem., Int. Ed.*, 2008, **47**, 346–349.

22 J. Takaya, S. Udagawa, H. Kusama and N. Iwasawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 4906–4909.

23 (*a*) K. Saito, H. Sogou, T. Suga, H. Kusama and N. Iwasawa, *J. Am. Chem. Soc.*, 2011, **133**, 689–691. For a silver-catalyzed related process, see: (*b*) C. H. Oh, S. Karmakar, H. Park, Y. Ahn and J. W. Kim, *J. Am. Chem. Soc.*, 2010, **132**, 1792–1793.

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

25 For a copper-catalyzed cyclization with activated alkynes, see: D. Gao, M. Parvez and T. G. Back, *Chem.–Eur. J.*, 2010, **16**, 14281–14284.

26 (*a*) M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina and C. H. Senanayake, *Org. Lett.*, 2004, **6**, 4129–4132; (*b*) O. Leogane and H. Lebel, *Angew. Chem., Int. Ed.*, 2008, **47**, 350–352.

27 (*a*) J. Liu, M. Shen, Y. Zhang, G. Li, A. Khodabocus, S. Rodriguez, B. Qu, V. Farina, C. H. Senanayake and B. Z. Lu, *Org. Lett.*, 2006, **8**, 3573–3575; (*b*) J. Liu, Y. Zhang, G. Li, F. Roschangar, V. Farina, C. H. Senanayake and B. Z. Lu, *Adv. Synth. Catal.*, 2010, **352**, 2667–2671.

28 (*a*) J. Garfunkle, F. S. Kimball, J. D. Trzupek, S. Takizawa, H. Shimamura, M. Tomishima and D. L. Boger, *J. Am. Chem. Soc.*, 2009, **131**, 16036–16038; (*b*) H. Shimamura, S. P. Breazzano, J. Garfunkle, F. S. Kimball, J. D. Trzupek and D. L. Boger, *J. Am. Chem. Soc.*, 2010, **132**, 7776–7783.

29 (*a*) L. Ackermann, L. T. Kaspar and C. J. Gschrei, *Chem. Commun.*, 2004, 2824–2825; (*b*) L. Ackermann, R. Sandmann, A. Villar and L. T. Kaspar, *Tetrahedron*, 2008, **64**, 769–777.

30 L. Ackermann and A. Althammer, *Synlett*, 2006, 3125–3129.

31 (*a*) J. Barluenga, M. A. Fernández, F. Aznar and C. Valdés, *Chem.–Eur. J.*, 2005, **11**, 2276–2283. For related processes, see: (*b*) G. Shore, S. Morin, D. Mallik and M. G. Organ, *Chem.–Eur. J.*, 2008, **14**, 1351–1356; (*c*) Y. Liu, B. Yao, C.-L. Deng, R.-Y. Tang, X.-G. Zhang and J.-H. Li, *Org. Lett.*, 2011, **13**, 1126–1129.

32 H. Siebeneicher, I. Bytschkov and S. Doye, *Angew. Chem., Int. Ed.*, 2003, **42**, 3042–3044.

33 (*a*) L. Ackermann, *Org. Lett.*, 2005, **7**, 439–442; (*b*) L. Ackermann, R. Sandmann and M. V. Kondrashov, *Synlett*, 2009, 1219–1222; (*c*) L. Ackermann, R. Sandmann, M. Schinkel and M. V. Kondrashov, *Tetrahedron*, 2009, **65**, 8930–8939; (*d*) L. Ackermann, W. Song and R. Sandmann, *J. Organomet. Chem.*, 2011, **696**, 195–201.

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

35 For a related approach to 1-aminoindoles, see: N. Halland, M. Nazare, J. Alonso, O. R'Kyek and A. Lindenschmidt, *Chem. Commun.*, 2011, **47**, 1042–1044.

36 J. Barluenga, A. Jiménez-Aquino, C. Valdés and F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 1529–1532.

37 J. Barluenga, A. Jiménez-Aquino, C. Valdés and F. Aznar, *J. Am. Chem. Soc.*, 2009, **131**, 4031–4041.

38 (*a*) J. Barluenga, A. Jiménez-Aquino, F. Aznar and C. Valdés, *Chem.–Eur. J.*, 2010, **16**, 11707–11711. For a related cyclization based on the trapping of Blaise reaction intermediates, see: (*b*) J. H. Kim and S.-g. Lee, *Org. Lett.*, 2011, **13**, 1350–1353.

39 T. Jensen, H. Pedersen, B. Bang-Andersen, R. Madsen and M. Jørgensen, *Angew. Chem., Int. Ed.*, 2008, **47**, 888–890.

40 C. A. Baxter, E. Cleator, M. Alam, A. J. Davies, A. Goodyear and M. O'Hagan, *Org. Lett.*, 2010, **12**, 668–671.

41 (*a*) S. G. Newman and M. Lautens, *J. Am. Chem. Soc.*, 2010, **132**, 11416–11417; (*b*) N. Isono and M. Lautens, *Org. Lett.*, 2009, **11**, 1329–1331; (*c*) C. S. Bryan and M. Lautens, *Org. Lett.*, 2008, **10**, 4633–4636; (*d*) Y.-Q. Fang and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538–549; (*e*) A. Fayol, Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2006, **8**, 4203–4206; (*f*) Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2005, **7**, 3549–3552; (*g*) T. O. Vieira, L. A. Meaney, Y.-L. Shi and H. Alper, *Org. Lett.*, 2008, **10**, 4899–4901.

42 M. Arthuis, R. Pontikis and J.-C. Florent, *Org. Lett.*, 2009, **11**, 4608–4611.

43 M. C. Willis, G. N. Brace and I. P. Holmes, *Angew. Chem., Int. Ed.*, 2005, **44**, 403–406.

44 (*a*) L. C. Henderson, M. J. Lindon and M. C. Willis, *Tetrahedron*, 2010, **66**, 6632–6638; (*b*) R. C. Hodgkinson, J. Schulz and M. C. Willis, *Org. Biomol. Chem.*, 2009, **7**, 432–434; (*c*) A. J. Fletcher, M. N. Bax and M. C. Willis, *Chem. Commun.*, 2007, 4764–4766; (*d*) M. C. Willis, G. N. Brace, T. J. K. Findlay and I. P. Holmes, *Adv. Synth. Catal.*, 2006, **348**, 851–856.

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

46 (*a*) P. Kothandaraman, W. Rao, S. J. Foo and P. W. H. Chan, *Angew. Chem., Int. Ed.*, 2010, **49**, 4619–4623. For a related intermolecular reaction, see: (*b*) M. Tokunaga, M. Eckert and Y. Wakatsuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 3222–3225.

47 T. Pei, C. Chen, P. G. Dormer and I. W. Davies, *Angew. Chem., Int. Ed.*, 2008, **47**, 4231–4233.

48 For a related indole synthesis involving [1,2]-aryl migration, see: P. Levesque and P.-A. Fournier, *J. Org. Chem.*, 2010, **75**, 7033–7036.

49 Q. Cai, Z. Li, J. Wei, C. Ha, D. Pei and K. Ding, *Chem. Commun.*, 2009, 7581–7583.

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

This journal is © The Royal Society of Chemistry 2011

Org. Biomol. Chem., 2011, **9**, 6469–6480 | 6479

51 For two step route to indoles using Boc-protected hydrazines, see: M. Inman and C. J. Moody, *Chem. Commun.*, 2011, **47**, 788–790.

52 P. J. Walsh, M. J. Carney and R. G. Bergman, *J. Am. Chem. Soc.*, 1991, **113**, 6343–6345.

53 (*a*) C. Cao, Y. Shi and A. L. Odom, *Org. Lett.*, 2002, **4**, 2853–2856; (*b*) A. Tillack, H. Jiao, I. Garcia Castro, C. G. Hartung and M. Beller, *Chem.–Eur. J.*, 2004, **10**, 2409–2420; (*c*) L. Ackermann and R. Born, *Tetrahedron Lett.*, 2004, **45**, 9541–9544; (*d*) S. Banerjee, E. Barnea and A. L. Odom, *Organometallics*, 2008, **27**, 1005–1014.

54 (*a*) K. Alex, A. Tillack, N. Schwarz and M. Beller, *Angew. Chem., Int. Ed.*, 2008, **47**, 2304–2307. See also: (*b*) N. T. Patil and A. Konala, *Eur. J. Org. Chem.*, 2010, 6831–6839.

55 B. A. Haag, Z.-G. Zhang, J.-S. Li and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 9513–9516.

56 Thermal rearrangements: (*a*) K. Isomura, G.-I. Ayabe, S. Hatano and H. Taniguchi, *J. Chem. Soc., Chem. Commun.*, 1980, 1252–1253; (*b*) D. F. Taber and W. Tian, *J. Am. Chem. Soc.*, 2006, **128**, 1058–1059. Metal-catalyzed rearrangements: (*c*) K. Isomura, K. Uto and H. Taniguchi, *J. Chem. Soc., Chem. Commun.*, 1977, 664–665; (*d*) S. Chiba, G. Hattori and K. Narasaka, *Chem. Lett.*, 2007, **36**, 52–53; (*e*) X. Li, Y. Du, Z. Liang, X. Li, Y. Pan and Kang Zhao, *Org. Lett.*, 2009, **11**, 2643–2646.

57 S. Jana, M. D. Clements, B. K. Sharp and N. Zheng, *Org. Lett.*, 2010, **12**, 3736–3739.

58 For an intermolecular related reaction, see: D. A. Candito and M. Lautens, *Org. Lett.*, 2010, **12**, 3312–3315.

59 (*a*) K. Sun, S. Liu, P. M. Bec and T. G. Driver, *Angew. Chem., Int. Ed.*, 2011, **50**, 1702–1706; (*b*) B. J. Stokes, S. Liu and T. G. Driver, *J. Am. Chem. Soc.*, 2011, **133**, 4702–4705; (*c*) M. Shen, B. E. Leslie and T. G. Driver, *Angew. Chem., Int. Ed.*, 2008, **47**, 5056–5059; (*d*) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500–7501; (*e*) B. J. Stokes, K. J. Richert and T. G. Driver, *J. Org. Chem.*, 2009, **74**, 6442–6451. See also: (*f*) A. G. O'Brien, F. Levesque and P. H. Seeberger, *Chem. Commun.*, 2011, **47**, 2688–2690.

60 For an iron-catalyzed reaction, see: (*a*) J. Bonnamour and C. Bolm, *Org. Lett.*, 2011, **13**, 2012–2014; (*b*) Y. Liu, J. Wei and C.-M. Che, *Chem. Commun.*, 2010, **46**, 6926–6928.

61 S.-L. Cui, J. Wang and Y.-G. Wang, *J. Am. Chem. Soc.*, 2008, **130**, 13526–13527.

62 (*a*) N. Okamoto, Y. Miwa, H. Minami, K. Takeda and R. Yanada, *Angew. Chem., Int. Ed.*, 2009, **48**, 9693–9696; (*b*) N. Okamoto, K. Takeda and R. Yanada, *J. Org. Chem.*, 2010, **75**, 7615–7625.

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

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

65 A related nickel-catalyzed decarbonylative process: N. Maizuru, T. Inami, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2011, **13**, 1206–1209.

66 Pioneering findings: (*a*) B. Åkermark, L. Eberson, E. Jonsson and E. Pettersson, *J. Org. Chem.*, 1975, **40**, 1365–1367. Representative carbazole or fused indoles synthesis using this approach in: (*b*) M. Yagoubi, A. C. F. Cruz, P. L. Nichols, R. L. Elliott and M. C. Willis, *Angew. Chem., Int. Ed.*, 2010, **49**, 7958–7962; (*c*) L. Ackermann and A. Althammer, *Angew. Chem., Int. Ed.*, 2007, **46**, 1627–1629. For a recent review on indole synthesis through C–H-bond functionalization, see: (*d*) J. J. Song, J. T. Reeves, D. R. Fandrick, Z. Tan, N. K. Yee and C. H. Senanayake, *ARKIVOC*, 2010, **i**, 390–449.

67 S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230–7233.

68 (*a*) R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, *Angew. Chem., Int. Ed.*, 2009, **48**, 8078–8081; (*b*) Z.-H. Guan, Z.-Y. Yan, Z.-H. Ren, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2010, **46**, 2823–2825.

69 W. Yu, Y. Du and K. Zhao, *Org. Lett.*, 2009, **11**, 2417–2420.

70 Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676–3677.

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

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

73 For additional examples of rhodium-catalyzed oxidative coupling, see: (*a*) J. Chen, Q. Pang, Y. Sun and X. Li, *J. Org. Chem.*, 2011, **76**, 3523–3526; (*b*) J. Chen, G. Song, C.-L. Pan and X. Li, *Org. Lett.*, 2010, **12**, 5426–5429. For a palladium-catalyzed version of this reaction, see: (*c*) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572–4576.