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PERSPECTIVE

Copper catalysis in the construction of indole and benzo[*b*]furan rings

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This perspective reports on some of the main copper-catalyzed routes to the construction of the pyrrole and furan rings incorporated into the indole and benzo[*b*]furan systems, respectively. The first part illustrates the synthesis of indoles through cyclizations of 2-alkynylanilid(n)es, preformed or generated *in situ*, and cyclizations *via* intramolecular N-arylation, N-vinylation, and C–C bond forming reactions. The second part illustrates the synthesis of benzo[*b*]furans through cyclizations of preformed 2-alkynylphenols, domino synthesis of 2-alkynylphenols/cyclization processes, and cyclizations *via* intramolecular O-arylation reactions.

Introduction

Heterocycles are important structural motifs of a wide range of natural substances, compounds of pharmaceutical interest and commodity chemicals. Because of this, a large number of methods have been developed to provide access to almost every type of heterocyclic derivative. In this context, transition metal catalysis has played a remarkable and ever growing role. In the last 40 years or so transition-metal-catalyzed reactions have achieved an important place in the arsenal of the practising organic chemist revolutionizing the design of organic synthesis.[1] Heterocyclic chemistry is no exception to this trend. Transition metal-catalyzed reactions, particularly palladium-catalyzed reactions,[2] have been widely employed in the construction of heterocyclic rings providing increased functional group tolerance, simplified procedures and improved yields.

More recently, because of the economic advantages related to the use of copper catalysis (and hence because of its potential in large-scale reactions), a great deal of attention has been dedicated to the utilization of this metal in organic synthesis[3] and a variety of new practical and efficient methods based on copper-catalyzed reactions have been developed for the synthesis of heterocycles.

This perspective focuses on some of the main copper-based synthetic approaches to the construction of functionalized indoles and benzo[*b*]furans, two of the most diffused and important structural components of a vast number of biologically active natural and unnatural compounds.[4,5]

In general, methodologies based on the use of a stoichiometric amount of copper are not treated and only synthetic procedures where copper catalysis is involved in the indole or benzo[*b*]furan ring construction event are discussed herein. Even copper-catalyzed procedures producing indole or benzo[*b*]furan related compounds such as indolines, oxindoles, indazoles, benzofuranones, and related systems are not treated and neither are the reactions in which copper catalysis is involved in the cyclization to condensed polycyclic compounds such as pyrazoleindoles, benzofuro heterocycles, and related systems discussed. The literature has been surveyed up to the end of 2009.

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1. Copper and ligands

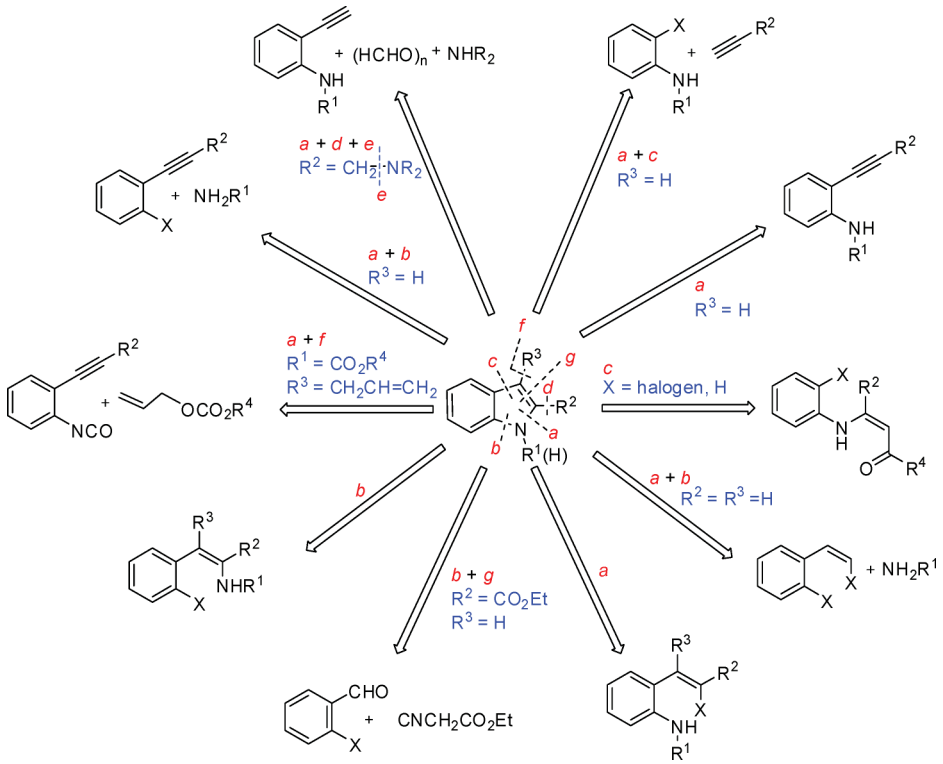
The most commonly used copper salts in general, and particularly in indole and benzofuran chemistry, are commercially available CuCl, CuBr, CuI, Cu(OAc), $Cu(OAc)_2$, $Cu(OBz)_2$, $Cu(OCOCF_3)_2 \cdot xH_2O$, $Cu(OTf)_2$ and CuTC (TC = thiophene-2-carboxylate). In some cases, they are employed as preformed complexes with phosphine ligands such as $[Cu(phen)(PPh_3)_2]NO_3$.[6] More frequently, copper complexes are formed *in situ* combining copper salts with suitable ligands such as PPh_3, 1,2-*trans*-cyclohexanediamine, *N*,*N*-dimethylethylenediamine, and L-proline.

2. Indoles

The copper-based construction of the indole system has been usually performed through the assembly of the functionalized pyrrole nucleus on a benzenoid scaffold. The main retrosynthetic approaches that are discussed in the present perspective are shown in Scheme 1. They include cyclization of 2-alkynylanilid(n)es, preformed or generated *in situ*, and cyclizations *via* intramolecular N-arylation, N-vinylation, and C–C bond forming reactions.

2.1 Indoles *via* cyclization of 2-alkynylanilid(n)es

The intramolecular hydroamination of arylalkynes bearing a nitrogen nucleophile *ortho* to the carbon–carbon triple bond is one of the most common and efficient approaches to indoles. The attractiveness of this cyclization protocol is largely due to the ready availability of this class of compounds. They are usually prepared through the arylation of terminal alkynes[7] under Sonogashira



Scheme 1 Retro-synthetic representation of the main copper-catalyzed routes to the construction of the pyrrole ring incorporated into the indole system.

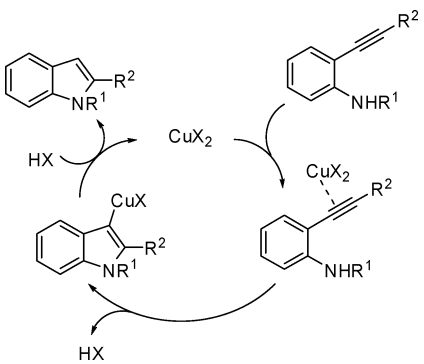
cross-coupling conditions[8,9] or copper-free palladium-catalyzed reactions.[10–12] They can also be generated and subjected to cyclization *in situ* so as to provide a route to domino syntheses of indoles.

Cyclization of preformed 2-alkynylanilid(n)es. The cyclization of *N*-methanesulfonyl-, *N*-ethoxycarbonyl-, *N*-tosyl-2-alkynylanilides in the presence of Cu(II) salts (Scheme 1, disconnection *a*) produces the corresponding *N*-protected indoles (Scheme 2a–c).[13a,b] *N*-Methanesulfonyl-2-alkynylanilides can also be converted to indoles in a mixture of H_2O and MeOH at room temperature in the presence of 1-ethylpiperidine (Scheme 2e).[13c] Using 2-alkynylanilines as the substrates (Scheme 2d)[13b] provides access to free N–H indoles. $Cu(OTf)_2$, $Cu(OBz)_2$ and $Cu(OCOCF_3)_2{\cdot}xH_2O$ proved to be efficient catalysts, with the latter producing the fastest and cleanest reaction. The application of this cyclization process to 2-alkynylanilines is particularly interesting in that the final target of many indole syntheses is the free N–H indole and the cleavage of the N-protecting substituent after cyclization adds one more step to the synthetic process.[14]

a	R^1 = Ms; R^2 = Ph $Cu(OAc)_2$, 18 h	CH_2Cl_2, reflux	94%
b	R^1 = COOEt, R^2 = Ph $Cu(OTf)_2$, 28 h	CH_2Cl_2, reflux	88%
c	R^1 = Ts, R^2 = Ph $Cu(OAc)_2$, 27 h	CH_2Cl_2, reflux	98%
d	R^1 = H; R^2 = Ph $Cu(OCOCF_3)_2{\cdot}xH_2O$, 2 h	CH_2Cl_2, reflux	72%
e	R^1 = Ms; R^2 = Ph $Cu(OCOCF_3)_2{\cdot}xH_2O$ 1-ethylpiperidine, 21 h	H_2O:MeOH rt	93%

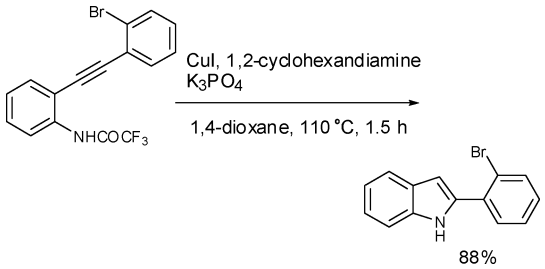
Scheme 2 Construction of the indole ring through copper-catalyzed intramolecular hydroamination of 2-alkynylanilides and anilines.

Very likely, the catalytic process starts from the coordination of the acetylene moiety to copper followed by the intramolecular nucleophilic attack of the nitrogen nucleophile onto the activated C–C triple bond to give an indolylcopper intermediate. The indole product is subsequently formed *via* substitution of the C–H bond for the C–Cu bond (Scheme 3).



Scheme 3 Suggested mechanism for the copper-catalyzed intramolecular hydroamination of 2-alkynylanilid(n)es.

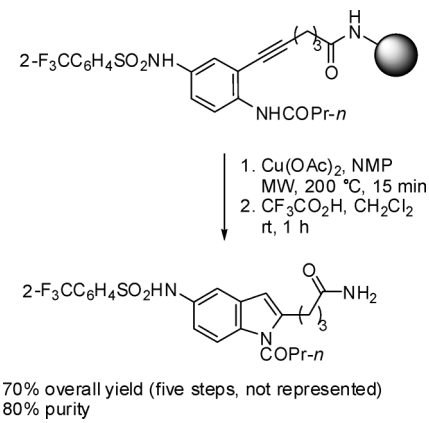
Free N–H indoles can also be obtained from 2-alkynyltrifluoroacetanilides in the presence of CuI and 1,2-*trans*-cyclohexanediamine or PPh_3 (Scheme 4).[15] As observed with the related palladium-catalyzed synthesis of indoles,[16] the



Scheme 4 Copper-catalyzed synthesis of free N–H indoles *via* intramolecular hydromination of 2-alkynyltrifluoroacetanilides.

trifluoroacetamido substituent plays a crucial role in promoting this transformation. Under the same conditions, moderate yields were obtained with 2-alkynylanilines or with the corresponding acetamido derivatives. Furthermore, the trifluoroacetamido group provides the additional advantage of being readily cleaved (the amide bond is broken during the reaction or/and the work-up) so as to allow for the formation of the free N–H pyrrole nuclei, avoiding troublesome and time-consuming deprotecting steps.[14]

The copper-catalyzed intramolecular hydroamination protocol has been exploited to develop microwave-assisted solid-phase syntheses of indoles. Under microwave irradiation,[17] *N*-acyl-2-alkyl-5-arenesulfamoylindoles have been obtained from resin-bound 2-alkynylanilides, after cleavage from the resin with trifluoroacetic acid in dichloromethane (Scheme 5).[18]



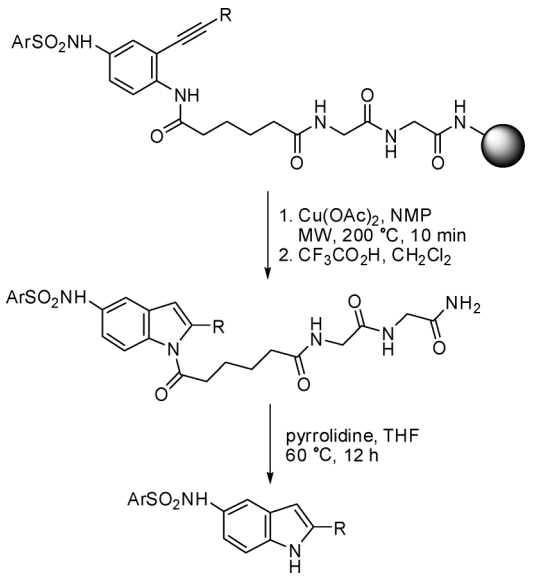
Scheme 5 The copper-catalyzed ring closing step of resin bound 2-alkynylanilides under microwave conditions.

More recently, a linker containing a tripeptide unit with dual functions for anchoring the 2-alkynylanilide fragment onto a solid support and for promoting a copper-mediated heterocyclization has been developed (Scheme 6).[19] *N*-Acyl chains contained in the indole derivative after cleavage can be easily removed upon exposure to pyrrolidine, which results in an indirect traceless[20] solid-phase synthesis.

The effect of the tripeptide unit on the cyclization step has been explained by a metal-catching (*via* formation of a Cu(II) complex through the amide carbonyl oxygen donors) and activation mechanism (*via* chelation of the copper ion with the neighboring alkyne fragment) (Fig. 1).

Domino synthesis of 2-alkynylanilid(n)es/cyclization. The observation that aryl iodides and 1-alkynes can give coupling products through copper-catalyzed reactions[21] set the stage to the development of a domino *alkynylation/cyclization* process in which free N–H 2-aryl- and 2-heteroarylindoles are directly prepared from 2-iodotrifluoroacetanilides and terminal alkynes in a single operative step, avoiding the isolation of the 2-alkynyltrifluoroacetanilide intermediates (Scheme 1, disconnection *a* + *c*). An example of this chemistry is shown in Scheme 7.[14] Both $[Cu(phen)(PPh_3)_2]NO_3$ and CuI/PPh_3 in toluene or dioxane serve as efficient catalysts. The reaction tolerates a wide range of functionalized terminal alkynes, including those containing ether, amide, aldehyde, ester, nitro, and heterocyclic groups. Only 1-hexyne, among the alkynes that were investigated, produced the desired indole product in low yield, very likely because of a sluggish coupling step. Using the same strategy, 2-aryl- and 2-heteroaryl pyrrolo[2,3-*b*]quinoxalines have been prepared through the reaction of terminal alkynes with 2-bromo-3-trifluoroacetamidoquinoxaline in the presence of catalytic amounts of CuI, PPh_3 and K_2CO_3 in dioxane at 110 °C.[22]

This domino copper-catalyzed *coupling/cyclization* process was also performed using a catalytic system made of a 1,10-phenanthroline immobilized on a polystyrene/divinylbenzene solid support and $Cu(PPh_3)NO_3$ as the copper source.[23] The cyclization step was not as efficient as with $[Cu(phen)(PPh_3)_2]NO_3$. The ratio between the coupling intermediate and the 2-substituted indole was slightly skewed toward the first one. However, the catalytic system could be reused three times.



Scheme 6 Microwave assisted solid-phase indole synthesis through copper-catalyzed intramolecular hydroamination promoted by a linker containing a tripetide unit.

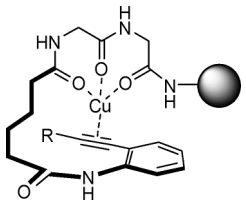
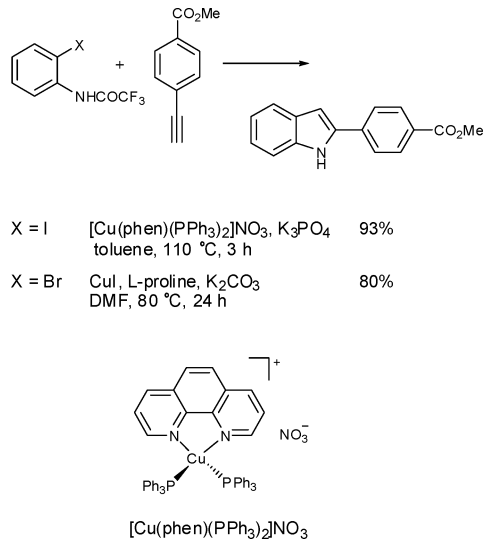


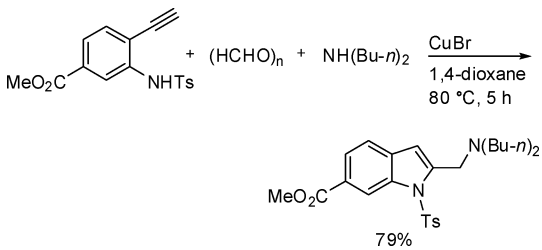
Fig. 1 The Cu(II) complex with the tripeptide linker through the amide carbonyl oxygen donors and with the neighboring alkyne fragment through coordination to the C–C triple bond.



Scheme 7 Synthesis of free N–H indoles through a domino *alkynylation/intramolecular* hydroamination process.

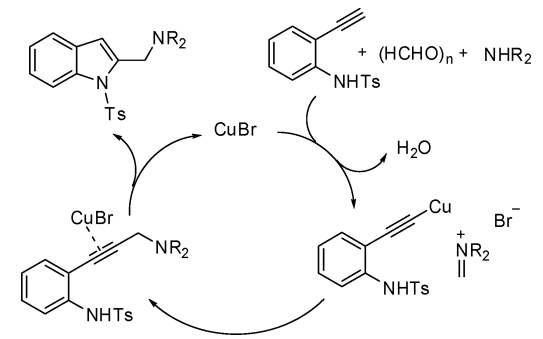
The procedure has been subsequently extended to 2-bromoalkynyltrifluoroacetanilides using CuI and L-proline as the ligand (Scheme 7).[24] Notably, despite the employment of the less reactive bromo derivatives, the amino acid ligand allows for running the reaction under conditions milder than those employed with 2-iodotrifluoroacetanilides. Analogously to the related reaction with 2-iodotrifluoroacetanilide, treatment of 2-bromotrifluoroacetanilide with 1-heptyne produced 2-n-pentylindole in low yield. However, when *O*-protected propargyl alcohols were employed, the desired indoles were obtained in satisfactory yields. Most probably, subtle changes in the electron density of the terminal alkynes can influence their reactivity in the coupling step.

2-Alkynylanilides have been prepared and cyclized *in situ* to indoles by treating readily available *N*-protected ethynylanilines with paraformaldehyde and secondary amines in the presence of CuBr (Scheme 1, disconnection $a + d + e$).[25] This three-component reaction provides a facile access to 2-(aminomethyl)indoles (Scheme 8) and has been rationalized in terms of a domino process that involves a Mannich type reaction of copper acetylides with iminium ions followed by a copper-catalyzed hydroamination of the resultant 2-alkynylanilide intermediates (Scheme 9).

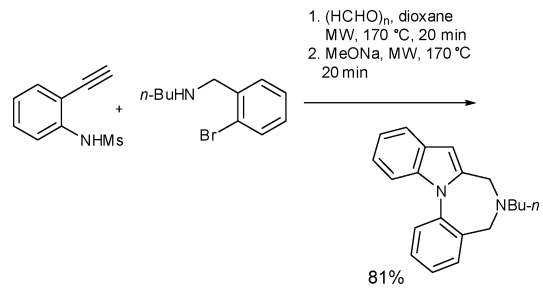


Scheme 8 Synthesis of 2-(aminomethyl)indoles through copper(I)-catalyzed domino three-component *coupling/cyclization* reactions.

With properly substituted amines, this strategy has been shown to be feasible for the synthesis of a variety of polycyclic indole derivatives combining the copper-catalyzed cyclization with a subsequent cyclization step. Indole-fused benzo-1,4-diazepines have been prepared by a copper-catalyzed domino three-component *coupling/indole formation/N-arylation* sequence under microwave irradiation starting from 2-ethynylanilines and *o*-bromobenzylamines (Scheme 10).[26] The reaction can be extended to the preparation of pyridine- and thiophene-fused tetracyclic compounds. 1,2,3,4-Tetrahydro-β-carbolines have been prepared in moderate to good yields by copper-catalyzed domino three-component *coupling/cyclization* of an appropriate ethynylaniline, aldehyde, and a secondary amine followed by the cyclization of the resultant indole intermediate upon treatment with KOBu-*t*/hexane or MsOH (Scheme 11).[27]



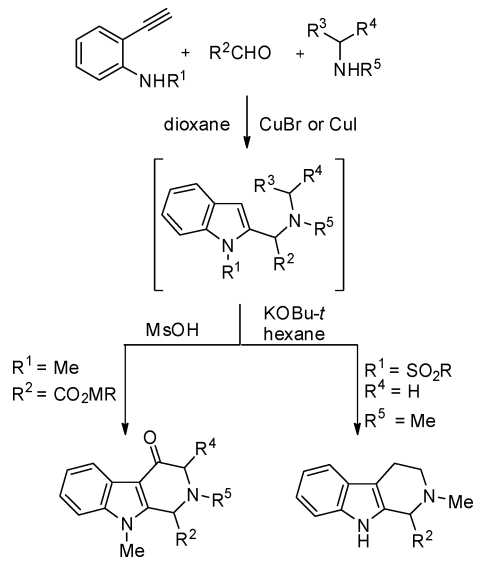
Scheme 9 Suggested mechanism for the three-component synthesis of 2-(aminomethyl)indoles from N-protected ethynylanilines, paraformaldehyde and secondary amines.



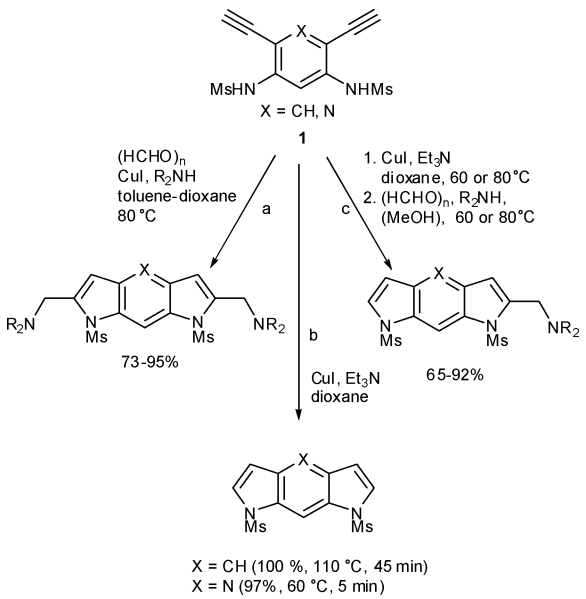
Scheme 10 Synthesis of indole-fused 1,4-diazepines through copper-catalyzed domino three-component *coupling/cyclization/N-arylation* under microwave irradiation.

Starting from diethynyl, diamino derivatives **1**, various pyrrole-fused indoles have been prepared *via* the three component chemistry (Scheme 12a), intramolecular hydroamination (Scheme 12b) and a sequential intramolecular hydroamination/three component coupling-cyclization reaction (Scheme 12c).[28]

The N-arylation of 2-haloarylalkynes represents an interesting alternative for generating 2-alkynylanilid(n)es *in situ*. This strategy has been successfully employed in the development of a domino *N-arylation/hydroamin(d)ation* process (Scheme 1, disconnection $a + b$). In this process 2-haloarylalkynes undergo a copper-catalyzed N-arylation with anilines, amides and carbamates followed by a copper-catalyzed cyclization *in situ* to the corresponding indole derivatives (Scheme 13).[29] The synthesis of *N*-arylindoles was performed under ligand-free conditions. KOBu-*t* is superior to related bases such as NaOBu-*t* or LiOBu-*t*. *ortho*-Substituents or more sterically hindered anilines are well tolerated. The optimized protocol for the synthesis of *N*-acylindoles has been shown to be applicable to the synthesis of 5-azaindoles. Taking advantage of this protocol, free N–H indoles can be prepared through



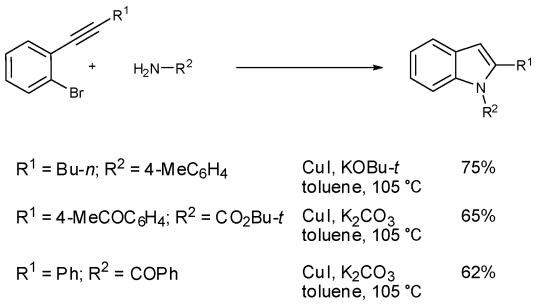
Scheme 11 Synthesis of 1,2,3,4-tetrahydro-β-carbolines by copper-catalyzed domino three-component *coupling/cyclization* of an appropriate ethynylaniline, aldehyde, and a secondary amine followed by treatment with *t*-BuOK/hexane or MsOH of the resultant indole intermediate.



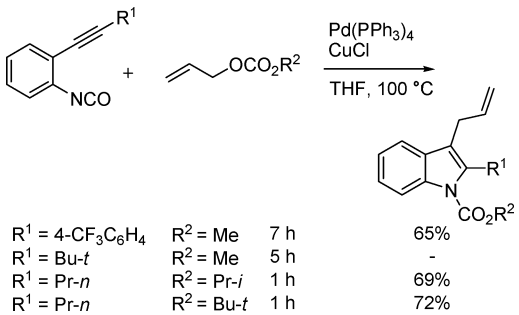
Scheme 12 Synthesis of pyrrole-fused indole derivatives through copper–catalyzed multicomponent coupling and bis-cyclization processes.

a one-pot process by using *tert*-butylcarbamate as nucleophile in the copper-catalyzed domino *N-arylation/hydroamin(d)ation* transformation, along with a subsequent simple treatment with trifluoroacetic acid.

Arylalkynes bearing a nitrogen nucleophile *ortho* to the carbon–carbon triple bond have also been generated from 2-(alkynyl)phenylisocyanates and allyl carbonates in the presence of $Pd(PPh_3)_4$ and CuCl bimetallic catalyst.[30] Using this reaction, a variety of 2-(alkynyl)phenylisocyanates have been converted into the corresponding 3-allyl-*N*-(alkoxycarbonyl)indoles (Scheme 1, disconnection *a* + *f*). Some examples of this cyclization reaction are shown in Scheme 14. CuCl was proved to give higher yields than CuBr and to be far superior to other copper salts such as



Scheme 13 Synthesis of indoles from 2-alkynylhaloarenes through a domino *N-arylation/intramolecular hydroamin(d)ation* process.



Scheme 14 Synthesis of *N*-(alkoxycarbonyl)indoles from 2-(alkynyl)-phenylisocyanates with a Pd(0)–Cu(I) bimetallic dual role catalyst.

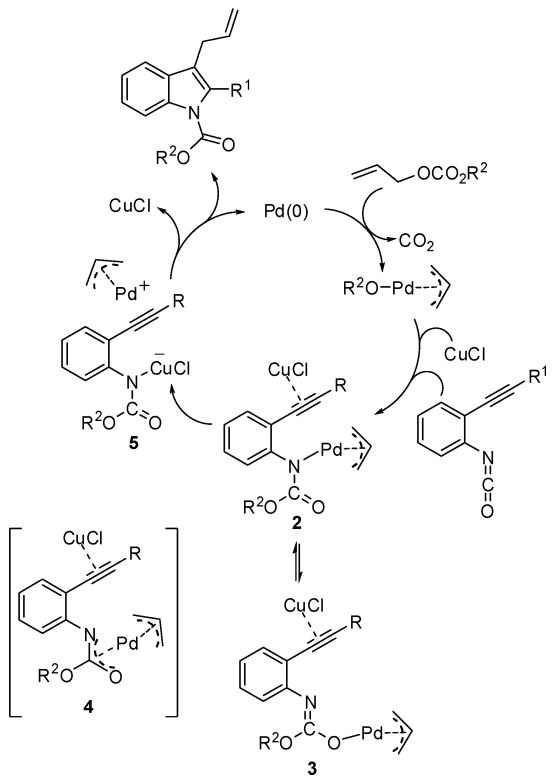
CuI, Cu(OAc), $(CuOTf)_2$·benzene, and $CuCl_2$. Longer reaction times are required when the substituent on the alkyne fragment (R^1) is a bulky substituent. With a *tert*-butyl group no allylindole was obtained and the sole product was the corresponding *N*-allylaniline derivative. Electronic effects of the *para* substituents on the aromatic ring as well as the bulkiness of the substituents R^2 of the allyl carbonates do not seem to exert a significant influence on the reaction outcome.

The proposed mechanism involves the following basic steps: a) the reaction of the isocyanate group with the π-allylpalladium alkoxide complex to give the π-allylpalladium complex **2** in equilibrium with **3** (most probably, it could be better represented as a heteroatom-containing bis-π-allylpalladium analogue **4**); b) a transmetalation step generating the intermediate **5**; c) a *trans*-aminopalladation followed by d) a reductive elimination (Scheme 15).

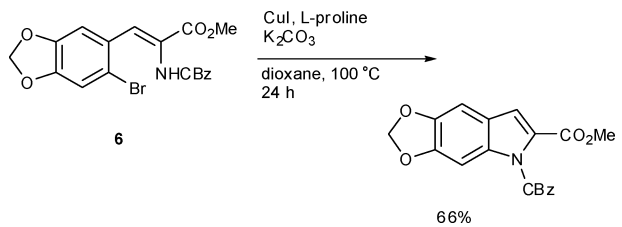
2.2 Intramolecular N-arylation and N-vinylation reactions

The application of copper catalysis to N-arylation and N-vinylation reactions has recently emerged as a powerful tool for assembling molecules either for fundamental[3a,31] or natural product[3b] synthesis. Not surprisingly this synthetic approach was quickly applied to the construction of the indole ring. Two main strategies have been developed: the cyclization of 2-haloarylenamid(n)es and the cyclization of 2-(bromovinyl)anilid(n)es.

Cyclization of preformed 2-haloarylenamid(n)es. Enecarbamates **6**, prepared in moderate to high yields by Horner–Wadsworth–Emmons condensation,[32] have been converted into the corresponding indole- (Scheme 16) or pyrrolo[2,3-*c*]pyridine-2-carboxylates through an intramolecular C–N bond forming reaction using a CuI/L-proline catalyst system (Scheme 1,



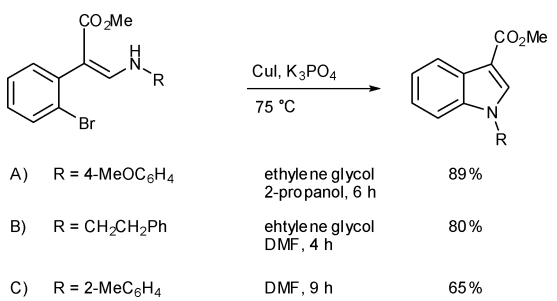
Scheme 15 Proposed mechanism for the synthesis of 3-allyl-*N*-(alkoxycarbonyl)indoles from 2-(alkynyl)phenylisocyanates.



Scheme 16 Synthesis of indole-2-carboxylates through an intramolecular C–N bond forming reaction.

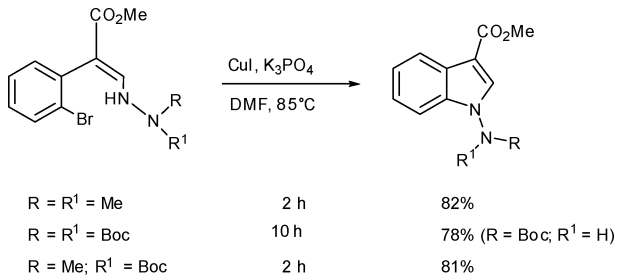
disconnection *b*).[33] Formation of significant amounts of the *N*-deprotected products was observed in some cases.

N-Substituted indole-3-carboxylates have been prepared *via* copper-catalyzed cyclization of *N*-substituted methyl 3-amino-2-(2-bromophenyl)acrylates (Scheme 17).[34] Three reaction conditions were developed: A) CuI, ethylene glycol, K_3PO_4, 2-propanol, 75 °C; B) CuI, ethylene glycol, K_3PO_4, DMF, 75 °C; C) CuI, K_3PO_4, DMF, 75 °C. Both aliphatic and aromatic amines can be used with the CuI–ethylene glycol combination. High yields have been obtained with unhindered amines. The reaction is sensitive to steric hindrance. α-Branched alkylamines and *ortho*-substituted anilines require longer reaction times. Occasionally, transesterification with ethylene glycol was observed. The use of ligandless conditions C may be a convenient alternative in these cases, although slightly longer reaction times are needed.

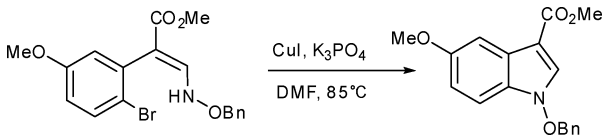


Scheme 17 Cyclization of *N*-substituted methyl 3-amino-2-(2-bromophenyl)acrylates to *N*-substituted indole-3-carboxylates.

Similarly, a route to various *N*-amino-indole-3-carboxylates by using a copper-catalyzed intramolecular *N*-arylation of enehydrazid(n)es has been developed (Scheme 18).[35] Deprotection of *N*-Boc-1-aminoindoles can be performed smoothly using trifluoroacetic acid in dichloromethane at reflux. Additionally, this copper-catalyzed cyclization process has been extended to the preparation of *N*-alkoxy derivatives (Scheme 19).[35]

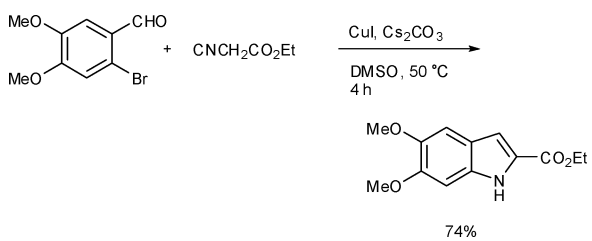


Scheme 18 Intramolecular *N*-arylation of enehydrazid(n)es.



Scheme 19 Synthesis of *N*-alkoxyindole-3-carboxylates.

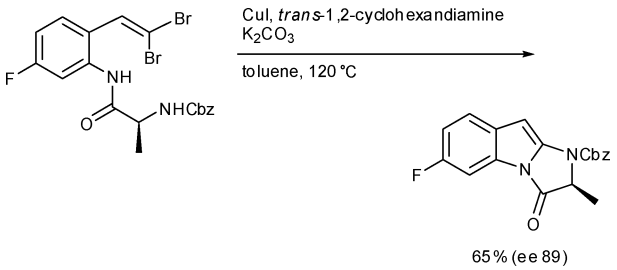
Domino synthesis of 2-haloarylenamid(n)es/cyclization. An example of a domino *synthesis of 2-haloaryl-enamid(n)es/cyclization* process (Scheme 1, disconnection *b* + *g*) is provided by the reaction of 2-halo aryl aldehydes or ketones with ethyl isocyanoacetate (Scheme 20).[36] Indole-2-carboxylates are formed through a ligand-free copper-catalyzed condensation/coupling/deformylation sequence carried out at room temperature or 50 °C with iodo- and bromo-substituted substrates. With chloride-substituted substrates a higher reaction temperature (80 °C) is required to obtain the desired indole derivative in satisfactory yields. Reactions were performed with



Scheme 20 Indole-2-carboxylates from 2-halo aryl aldehydes or ketones and ethyl isocyanoacetate through a ligand-free copper-catalyzed domino *condensation/coupling/deformylation* process.

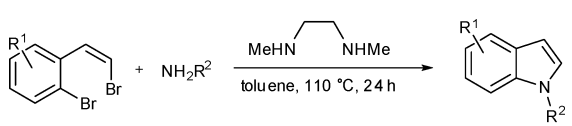
CuI. CuBr displayed a similar catalytic activity whereas CuCl, Cu_2O and $CuSO_4$ were less active.

Cyclization of 2-(*gem*-dibromovinyl)anilides. This strategy (Scheme 1, disconnection *a*) has been employed for the synthesis of substituted imidazoindolones from 2-(*gem*-dibromovinyl)anilides (Scheme 21),[37] readily available *via* amide coupling of 2-(*gem*-dibromovinyl)anilines with Cbz-aminoacids. The reaction proceeds through a double copper-catalyzed intramolecular C–N bond forming process. The preservation of the chiral center originating from the amino acid has been found to be very high with some substrates but highly variable in many cases.



Scheme 21 Synthesis of substituted imidazoindolones through Cu-catalyzed double intramolecular C–N bond forming reactions.

Domino *amination/cyclization* of 2-(2-bromoalkenyl)-bromoarenes. The copper-catalyzed domino *amination/cyclization* reactions of 2-(2-bromoalkenyl)bromoarenes with carbamates, amides and anilines allow the preparation of *N*-functionalized indoles (Scheme 1, disconnection *a* + *b*).[38] CuI in the presence of *N*,*N*-dimethylethylenediamine can be successfully employed (Scheme 22). Alternative Cu sources such as CuOAc and CuTC, in combination with *N*,*N*-dimethylethylenediamine, can also be used. K_2CO_3, K_3PO_4, and Cs_2CO_3 are effective bases. The range of N-coupling partners that can be used complements that achievable using Pd-catalysis, with the major advantage being the successful preparation of *N*-acyl indoles when employing the Cu-system. *N*-Acyl indoles could not be effectively prepared using the palladium-catalyzed process.[39] Conversely, couplings employing simple amines were less efficient when using the Cu-chemistry. In addition, two Br-substituents are needed to achieve efficient reactions. A significantly lower yield than the corresponding dibromo example was obtained using 2-(2-chlorovinyl)bromobenzene (56 instead of 88% yield) and 2-(2-bromovinyl)chlorobenzene was found to be unreactive.



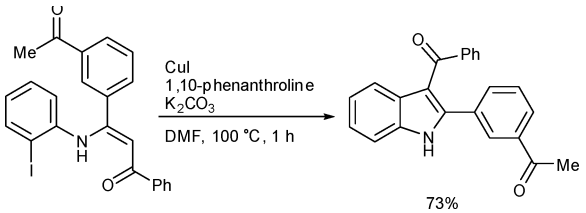
R^1 = H; R^2 = COEt	CuTC	K_2CO_3	89%
R^1 = H; R^2 = Ph	CuI	K_2CO_3	80%
R^1 = 4-F; R^2 = COOBu-*t*	CuOAc	K_3PO_4	80%

Scheme 22 Synthesis of *N*-functionalized indoles through domino *amination/cyclization* reactions of 2-(2-bromoalkenyl)bromoarenes with carbamates, amides and anilines.

2.3 Intramolecular C–C bond forming reactions

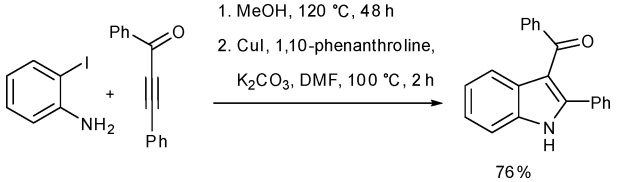
Taking advantage of the potential of copper in catalyzing the formation of C–C bonds,[40] some approaches to the construction of the indole skeleton have been based on this strategy. In particular, indoles have been prepared *via* C–C bond forming reactions from *N*-(2-iodoaryl)- and *N*-(aryl)enaminones.

Cyclization of *N*-(2-iodoaryl)enaminones. *N*-(2-Iodoaryl)-enaminones have been converted into the corresponding 3-acylindoles in the presence of catalytic amounts of CuI (Scheme 23).[41] *N*-(2-Iodoaryl)enaminones can be readily prepared through Sonogashira cross-coupling of terminal alkynes with aroyl chlorides,[42] followed by the conjugate addition of anilines with the resultant α,β-ynone.[43] The reaction (Scheme 1, disconnection *c*) proceeds through the copper-catalyzed substitution of the C–C bond for the C–I bond and tolerates a variety of useful functionalities including ether, keto, cyano, bromo, and chloro substituents.



Scheme 23 Synthesis of 3-acylindoles from *N*-(2-iodoaryl)enaminones.

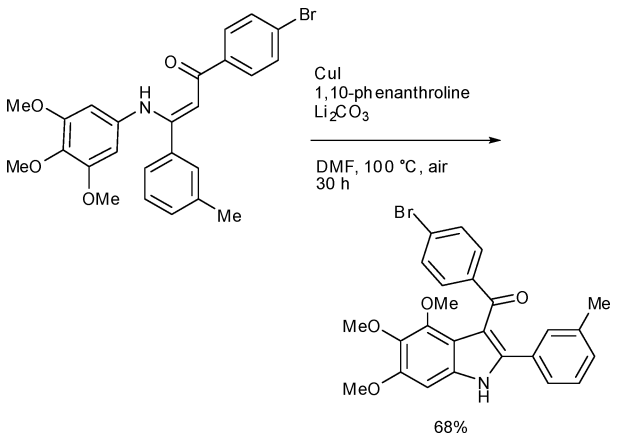
Indole products can also be prepared from α,β-ynones and primary amines by a sequential process that omits the isolation of the enaminone intermediates (Scheme 24).



Scheme 24 Synthesis of 3-acylindoles from iodoanilines and α,β-ynones omitting the isolation of enaminone intermediates.

Formation of C–C bond through C–H activation. Formation of C–C bonds through selective catalytic activation of aryl C–H bonds is a topic of intense current interest that, for the most part, has witnessed the use of palladium-, rhodium-, and ruthenium-based catalysts.[44] Recent reports have shown that copper catalysis can also be used in this chemistry through selective catalytic activation of aryl C–H bonds.[45] In this context, *N*-aryl enaminones have been proved to be useful substrates for the synthesis of multisubstituted indoles through a copper-catalyzed intramolecular C–C bond forming reaction (Scheme 25; Scheme 1, disconnection *c*).[46] Even in this case, indole products can also be prepared from α,β-ynones and primary amines by a sequential process, omitting the isolation of the enaminone intermediates.

The suggested mechanism for this indole synthesis is outlined in Scheme 26. The reaction of the starting enaminone with CuI under basic conditions presumably leads to the formation of the complex **7** that is converted into the ate complex **8** *via* nucleophilic



Scheme 25 Synthesis of multisubstituted indoles from *N*-aryl enaminones through a copper-catalyzed intramolecular C–C bond forming reaction.

attack of the *ortho* carbon of the aniline fragment to copper. This nucleophilic attack is promoted by the extraction of the hydrogen bound to the carbon α to the carbonyl group. Protonation of **8** followed by a rearomatization/tautomerization process leads to the formation of **9**. The latter undergoes a reductive elimination to give the indole product and CuH. The reaction of CuH with the conjugate acid of the base affords hydrogen and regenerates the active copper catalytic species.

3. Benzo[*b*]furans

As described for indole rings, even the copper-based construction of the benzo[*b*]furan system has been usually performed through the assembly of the functionalized furan nucleus on a benzenoid scaffold. The main retrosynthetic approaches that are discussed in the present perspective are shown in Scheme 27. They include cyclization of preformed 2-alkynylphenols, domino *synthesis of 2-alkynylphenols/cyclization*, and cyclizations *via* intramolecular O-arylation reactions.

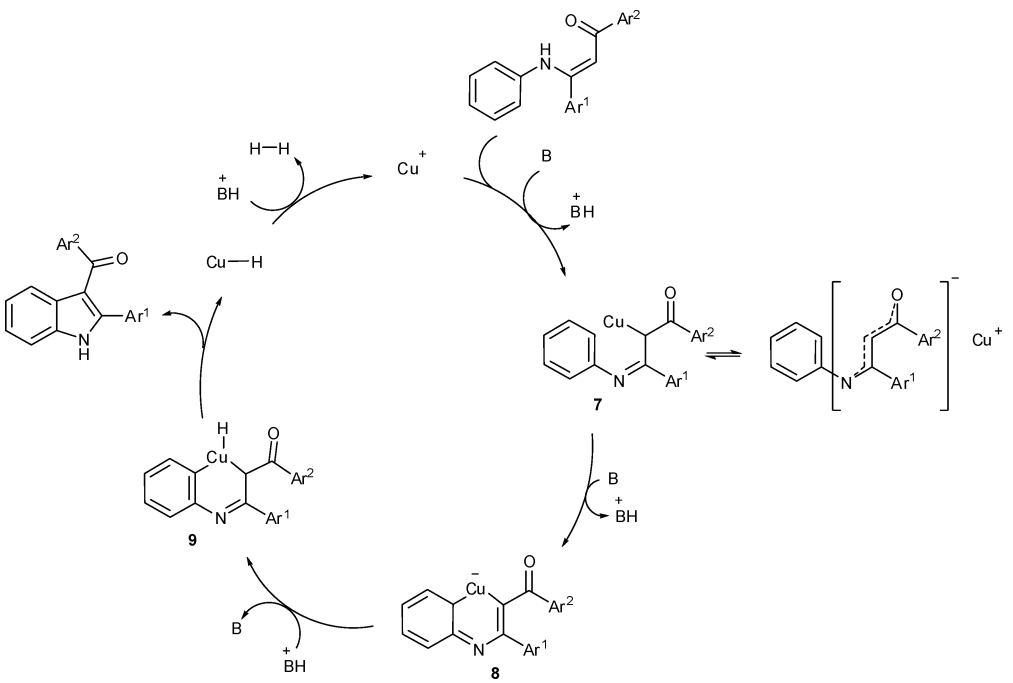
3.1 Cyclization of 2-alkynylphenols

Cyclization of preformed 2-alkynylphenols. This approach to the synthesis of benzo[*b*]furans (Scheme 27, disconnection *a*) is rarely used. The only example we found in literature is shown in Scheme 28.[13c]

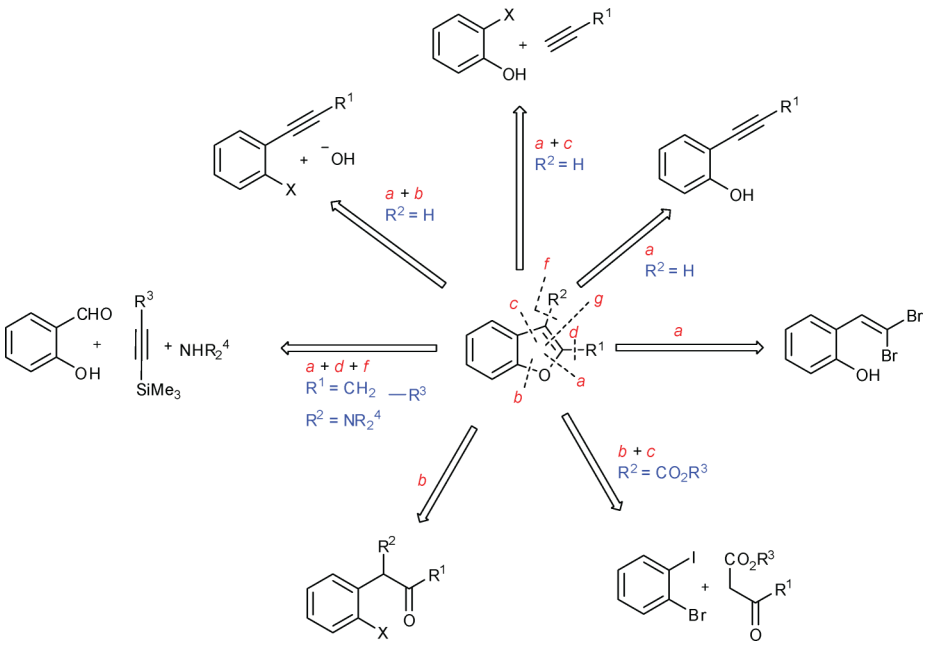
Domino synthesis of 2-alkynylphenols/cyclization. The reaction of *o*-iodophenols and aryl acetylenes in the presence of copper catalysts affords 2-alkynylphenols that are converted *in situ* into the corresponding 2-arylbenzo[*b*]furans (Scheme 27, disconnection *a* + *c*). This domino *alkynylation/cyclization* process has been performed by using $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst and Cs_2CO_3 as the base in toluene (Scheme 29).[6] Cs_2CO_3 was found to be the most effective base. Other bases such as K_2CO_3, K_3PO_4, NaOBu-*t*, and KOBu-*t* were less effective and Et_3N was ineffective. CuI, CuBr, or CuCl could not effectively catalyze the reaction.

An interesting alternative for generating 2-alkynylphenols *in situ* is represented by the hydroxylation coupling of 2-iodoarylalkynes. This strategy has been succesfully employed in the development of a domino *hydroxylation coupling/intramolecular hydroxyalkoxylation* process (Scheme 27, disconnection *a* + *b*) in which a 2-iodoarylalkyne is converted into a 2-phenylbenzo[*b*]furan in the presence of hydroxide anions (Scheme 30).[47]

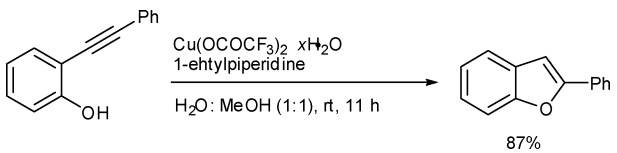
2-Alkynylphenols have been prepared and cyclized *in situ* to benzo[*b*]furans by treating readily available 2-hydroxybenzaldehydes with alkynylsilanes and secondary amines in the presence of $Cu(OTf)_2$, CuCl, and DMAP (Scheme 26, disconnection *a* + *d* + *f*).[48] This three-component reaction



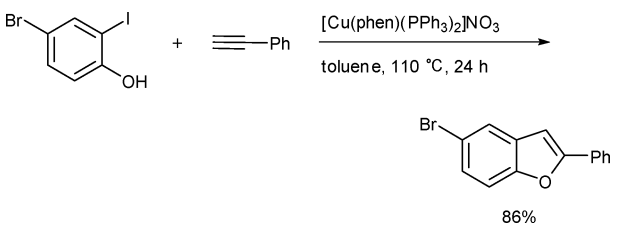
Scheme 26 Proposed reaction mechanism for the synthesis of multisubstituted indoles from *N*-aryl enaminones.



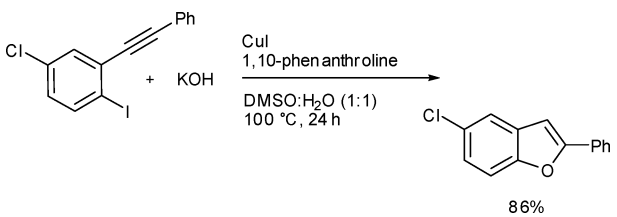
Scheme 27 Retro-synthetic representation of the main copper-catalyzed routes to the construction of the furan ring incorporated into the benzo[*b*]furan system.



Scheme 28 Construction of the benzo[*b*]furan ring through copper-catalyzed cyclization of 2-alkynylphenols.

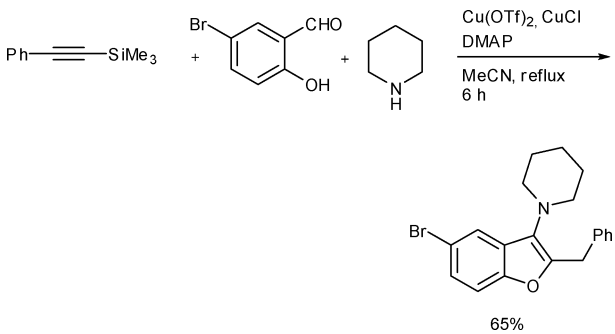


Scheme 29 Synthesis of 2-arylbenzo[*b*]furans through a domino *alkynylation/cyclization* process.



Scheme 30 Synthesis of benzo[*b*]furans from 2-iodoarylalkynes through a domino *hydroxylation coupling/intramolecular hydroxyalkoxylation* process.

provides a facile access to 2-substituted 3-aminobenzo[*b*]furans (Scheme 31). The proposed mechanism is shown in Scheme 32. Accordingly, the reaction takes advantage of a Cu(I)–Cu(II) cooperative catalytic effect. CuCl generates copper acetylides from alkynylsilanes and $Cu(OTf)_2$ has a dual role: (a) it behaves



Scheme 31 Synthesis of 2-substituted 3-aminobenzo[*b*]furans through a domino three-component *coupling/cyclization* reaction from alkynylsilanes, hydroxybenzaldehydes, and secondary amines.

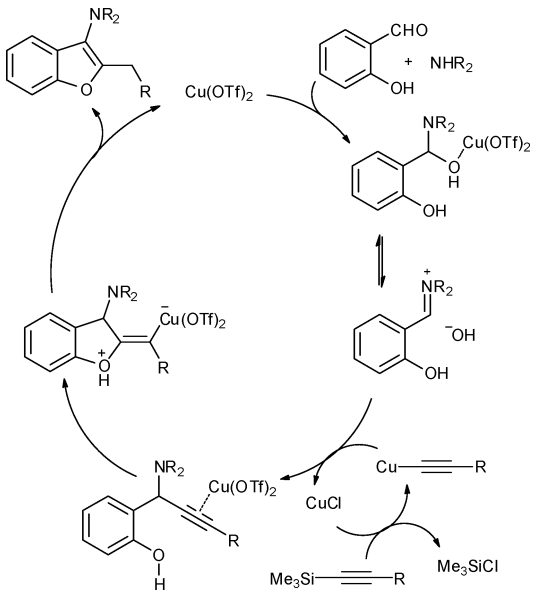
as a Lewis acid for *in situ* generation of iminium intermediates, which form from 2-hydroxybenzaldehydes and secondary amines, and (b) favors the intramolecular nucleophilic attack of the hydroxy group across the activated C–C triple bond.

A similar reaction has been performed using terminal alkynes instead of alkynylsylanes (Scheme 33).[49]

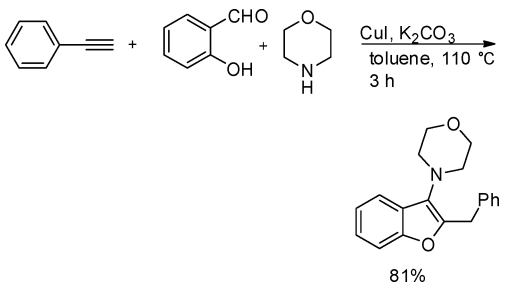
2.2 Intramolecular O-arylation and O-vinylation reactions

The copper-catalyzed O-arylation reaction has been widely used for assembling fundamental or natural products[3b] and the use of this protocol has not surprisingly found its way to the construction of the benzo[*b*]furan scaffold. Three main strategies have been developed: cyclization of 2-haloarylketones, domino *intermolecular C–C bond formation/intramolecular C–O bond formation* process, and cyclization of 2-(*gem*-dibromovinyl)phenols.

Cyclization of 2-haloarylketones. A variety of benzo[*b*]furans have been synthesized efficiently *via* copper-catalyzed ring closure of 2-haloarylketones (Scheme 27, disconnection *b*). In the first

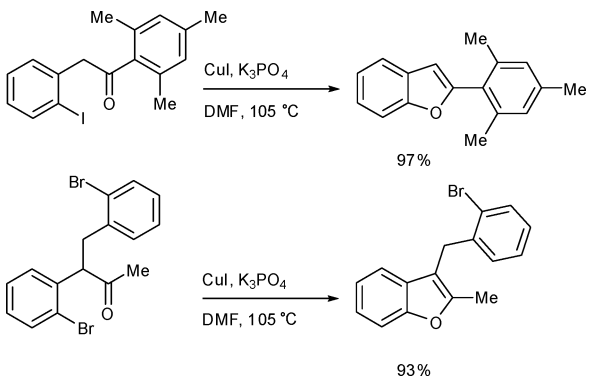


Scheme 32 Suggested mechanism for the three-component synthesis of 2-substituted 3-aminobenzo[*b*]furans.



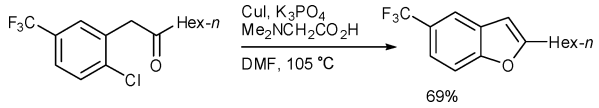
Scheme 33 Synthesis of 2-substituted 3-aminobenzo[*b*]furans through a domino three-component *coupling/cyclization* reaction from terminal alkynes, hydroxybenzaldehydes, and secondary amines.

example of this chemistry, benzo[*b*]furans have been prepared from 2-iodo- and 2-bromoarylketones using CuI as the catalyst (Scheme 34).[50] K_3PO_4 was proved to be best base. K_2CO_3 and Cs_2CO_3 could give similar results whereas Na_2CO_3 and DABCO were ineffective for the transformation.



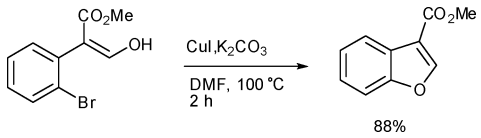
Scheme 34 Synthesis of benzo[*b*]furans *via* intramolecular O-arylation of 2-iodo- and bromoketones.

The reaction is believed to proceed *via* an intramolecular $S_{RN}1$ mechanism[51] involving the enolization of the ketone. As shown by one of the examples of Scheme 34, the formation of five-membered rings is preferred over the six-membered rings. This cyclization concept was also applied to less reactive 2-chloroketones.[52] In this case, most efficient catalysis was achieved with $Me_2NCH_2CO_2H$[53] as ligand (Scheme 35).



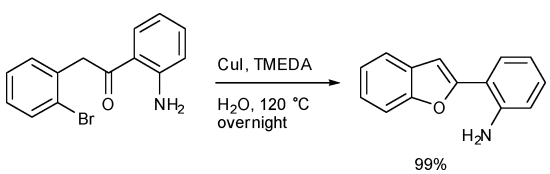
Scheme 35 Synthesis of benzo[*b*]furans *via* intramolecular O-arylation of 2-chloroketones.

The reaction has been subsequently extended to the synthesis of 2-unsubstituted methyl benzo[*b*]furan-3-carboxylates (Scheme 36).[54]



Scheme 36 Synthesis of 2-unsubstituted methyl benzo[*b*]furan-3-carboxylates *via* intramolecular O-arylation.

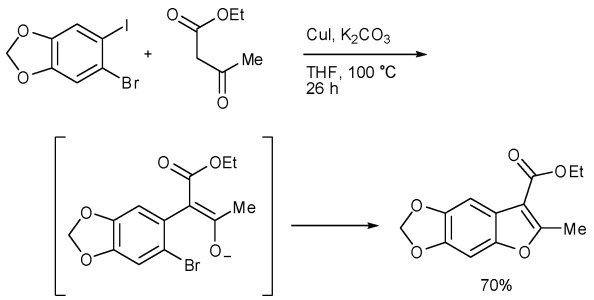
Following the current trend of using inexpensive, readily available, non toxic, non flammable water as the reaction medium in transition metal-catalyzed processes,[55] the reaction has also been performed in water. Indeed, there are remarkable advantages in using water instead of common organic solvents due to safety, economical, and environmental reasons.[56] In addition, the hydrophobic effect[57] often plays a beneficial role when reactions involving water-insoluble substrates are performed in water. Using water as the solvent, without organic cosolvents, 2-alkyl- or 2-arylbenzo[*b*]furans have been prepared from readily available ketone derivatives in the presence of CuI and TMEDA in good to excellent yields (Scheme 37).[58]



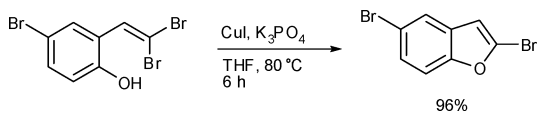
Scheme 37 Synthesis of 2-substituted benzo[*b*]furans *via* intramolecular O-arylation of 2-haloalketones in water.

Domino intermolecular C–C bond formation/intramolecular C–O bond formation process. This type of synthesis has been performed through an intermolecular C–C bond forming reaction between 1-bromo-2-iodobenzenes and β-keto esters followed by an *in situ* intramolecular C–O bond forming reaction of the resultant 2-bromoketones (Scheme 27, disconnection *b* + *c*).[59] The reaction has been carried out using CuI as the catalyst and K_2CO_3 as the base (Scheme 38).

Cyclization of 2-(*gem*-dibromovinyl)phenols. This strategy (Scheme 1, disconnection *a*) has been employed for the synthesis of 2-bromobenzo[*b*]furans from 2-(*gem*-dibromovinyl)phenols using CuI and K_3PO_4 at 80 °C in THF (Scheme 39).[60] The reactions works well with 2-(*gem*-dibromovinyl)phenols containing



Scheme 38 Synthesis of benzo[*b*]furans *via* a domino *intermolecular C–C bond formation/intramolecular C–O bond formation* process.



Scheme 39 Synthesis of 2-bromobenzo[*b*]furans from 2-(*gem*-dibromovinyl)phenols.

electron-withdrawing and -donating substituents. Halogen substituents on the aryl ring are tolerated, giving polyhalogenated benzofurans that may be useful for regioselective cross-coupling.[61] Optimization studies revealed that other copper species were effective catalysts, with good conversion being obtained with $CuCl_2$ and Cu(0) (powder). The base was found to play an important role, with organic bases such as Et_3N giving reduced reactivity, and Cs_2CO_3 complex reaction mixtures. The choice of solvent and temperature was also crucial. Several unidentified by-products were formed at higher temperatures, especially in non-polar solvents such as toluene. Interestingly, studies with palladium catalysis proved ineffective, often providing recovered starting material or a complex mixture of products.

Conclusions

The copper-catalyzed construction of indole and benzo[*b*]furan rings from acyclic precursors has received an ever growing attention in the last ten years or so. Although palladium catalysis, an obvious benchmark for evaluating the efficiency of copper-catalyzed methods, shows unique versatility, flexibility, and substrate scope, the impact of copper chemistry on indole and benzo[*b*]furan synthesis has been extraordinary. A variety of new practical and efficient synthetic methods based on copper catalysis has been developed. In addition to economic advantages due to the lower cost of the metal, they feature better results than palladium in some specific applications, synthetic routes that have not been explored using palladium, and/or bond-forming sequences that are different from those involved in palladium-catalyzed cyclizations. We believe that this brief summary can provide the reader with a helpful overview of the copper chemistry in this area and can be of value to chemists planning the construction of specific indole and benzo[*b*]furan derivatives.

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