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Recent advances in the application of the Sonogashira method in the synthesis of heterocyclic compounds

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1. Introduction

Heterocyclic compounds are worthy of attention for many reasons, chief among which are their biological activities, which many important drugs being heterocycles. Therefore, organic chemists have been making extensive efforts to produce heterocyclic compounds by developing new and efficient synthetic transformations.[1]

Over the past few years, palladium-catalyzed coupling reactions have been extensively studied and the names of Heck, Stille, Suzuki and Sonogashira are well known for their contribution to this kind of catalyzed reactions.[2]

Palladium has found such wide utility because it affects an extraordinary number of very different reactions, including many carbon–carbon bond-forming reactions under relatively mild conditions. Furthermore, palladium can usually be used in only catalytic amounts and tolerates a wide variety of functional groups, thus avoiding protecting-group chemistry. Most palladium-based methodology proceeds stereo- and regioselectively in excellent yields.[3]

Another achievement in this field is the possibility offered by the methodology to access heterocyclic compounds either through a direct construction of the heterocyclic ring or by a two-step procedure (coupling followed by a heteroannulation).[2] In the following sections, these various routes for the preparation of heterocyclic compounds will be discussed.

2. Sonogashira coupling reaction: general comments

Among the variety of transition-metal-catalyzed coupling reactions, the Sonogashira coupling reaction of aryl halides with terminal acetylenes provides an effective route for C–C bond formation, and has become useful method for the preparation of arylalkynes and conjugated enynes,[4] having been widely applied as a key step in natural product synthesis and in the preparation of molecular organic materials.[5] Initially, the most common catalytic system for the Sonogashira reaction was palladium–phosphine complexes with CuI as the co-catalyst in an excess of amines.[6] In recent years, however, significant progress has been made in this reaction and an efficient copper-free catalyst system has been developed, which avoids the homocoupling.[7]

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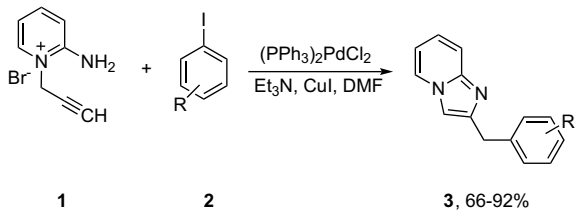
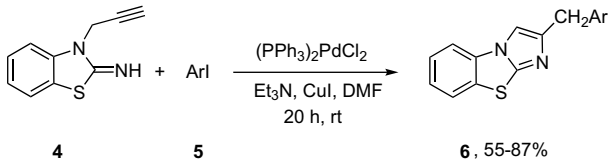
3. Synthesis of aza heterocyclic compounds

Bakherad et al. have developed a successful Pd/Cu-catalyzed heterocyclization involving Sonogashira coupling for the synthesis of 2-aryl-substituted imidazo[1,2-*a*]pyridines **3** from the reaction of 2-amino-1-(2-propynyl)pyridinium bromide **1** with various iodobenzenes **2** (Scheme 1).[8]



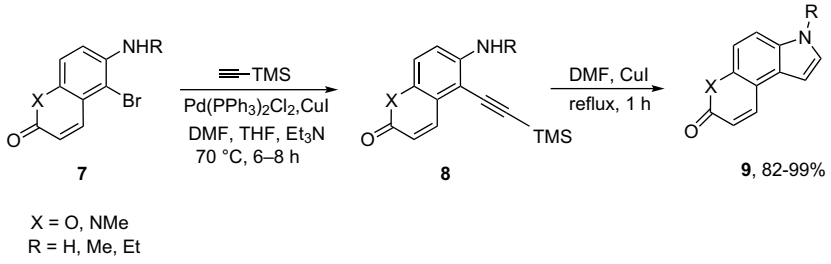
Scheme 1.

The reaction of 2-imino-3-(2-propynyl)-1,3-benzothiazole **4** with various iodobenzenes **5** in the presence of a palladium catalyst led to the production of 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles **6** (Scheme 2).[9]



Scheme 2.

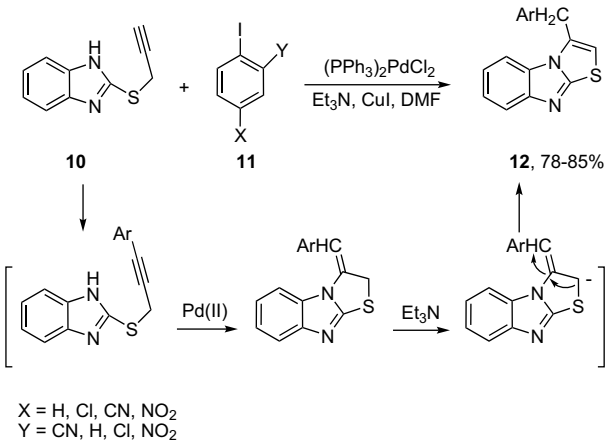
The sequential coupling and cyclization reactions between aryl bromides **7** and (trimethylsilyl)acetylene (TMSA), with concurrent elimination of the TMS substituent from **8**, allowed a straightforward synthesis of substituted pyrano[3,2-*e*]indolone and pyrrolo[3,2-*f*]quinolone derivatives **9** in excellent yields (Scheme 3).[10]



Scheme 3.

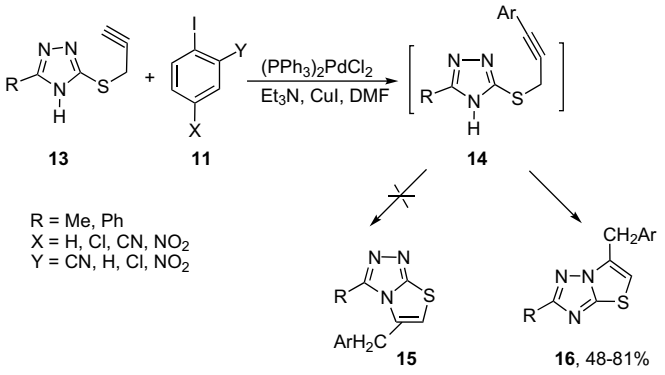
Our group has reported that the reaction of 2-mercaptopropargyl-benzimidazole **10** with various iodobenzenes **11** catalyzed by Pd–Cu leads to the formation of 3-benzylthiazolo[3,2-*a*]benzimidazoles **12** (Scheme 4).[11] The mechanism of the reaction is illustrated in Scheme 4. Most probably, a two-step process occurs involving a standard Sonogashira coupling and known Pd(II)-catalyzed intermolecular cyclization of the nucleophilic nitrogen moiety onto the triple bond, followed by a base-induced aromatization. The presence of electron-withdrawing groups such as $-NO_2$, –Cl, and –CN on the aryl iodide seems to be essential.

We have also reported the reaction of 3-mercaptopropargyl-1,2,4-triazoles **13** with various iodobenzenes **11** catalyzed by Pd–Cu



Scheme 4.

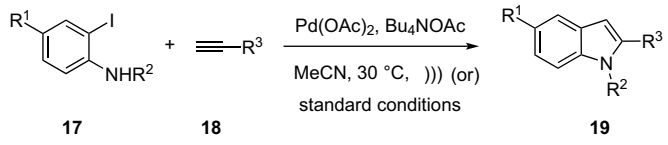
(Scheme 5).[12] Mechanistically, either thiazolo-1,2,4-triazines **15** or **16** were possible products (via **14**), as illustrated in Scheme 5. The reaction led to the regioselective formation of 6-benzylthiazolo[3,2-*b*]1,2,4-triazoles **16**.



Scheme 5.

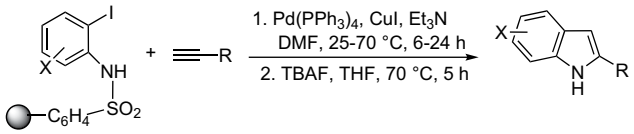
A general one-pot synthesis of 2-substituted indoles **19** via a palladium acetate-catalyzed tandem Sonogashira coupling 5-*endo-dig* cyclization at room temperature under ultrasonic irradiation and standard stirred conditions in the absence of any ligand, copper, and amine, Bu_4NOAc as the base, in acetonitrile was described by Srinivasan et al. Electron-donating and -withdrawing groups present in both coupling partners **17** and **18** were well tolerated under these mild conditions (Scheme 6).[13]

Applications of palladium-assisted cyclization of terminal alkynes to the solid phase to prepare indole derivatives have been described by Zhang et al. (Scheme 7).[14] Substituted indoles **22** were obtained in excellent yields by the palladium-catalyzed coupling of



R^1 = H, Me, COOMe, COMe
R^2 = Ts, Ms
R^3 = Ph, 3-FC_6H_4, 4-$MeOC_6H_4$, $C_{10}H_7$

Scheme 6.

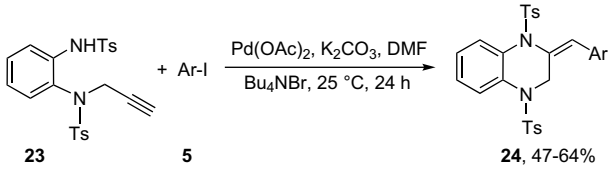


R = Ph, *o*-MeC_6H_4, *o*-FC_6H_4, *o*-$MeOC_6H_4$, *o*-$NO_2C_6H_4$, 2-pyridyl, $PhSCH_2$, *n*-Bu, $MeOCH_2$, X = H, 3-F, 3-OMe, 4-CO_2Me

Scheme 7.

resin-bound sulfonamides **20** with the terminal alkynes **21**, followed by cleavage of the sulfonamide linkage. The best system for this cyclization was found to be a catalytic amount of $PdCl_2(PPh)_2$ and CuI, plus Et_3N in DMF.

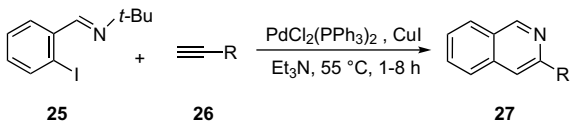
Kundu and co-worker showed that (*E*)-tetrahydroquinoxalines **24** were formed through a regio- and stereoselective palladium-catalyzed heterocyclization of tosylamide **23** and aryl iodides **5** (Scheme 8).[15] The cyclization takes place in good yields using $Pd(OAc)_2$ as the catalyst in the presence of Bu_4NBr and K_2CO_3. The reaction exhibited high stereoselectivity with the sole formation of the *E* product, instead of the usually expected *Z* configuration.



Ar = Ph, *m*-ClC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-$MeOCC_6H_4$, *o*-$NO_2C_6H_4$ 1-naphthyl, 2-thienyl

Scheme 8.

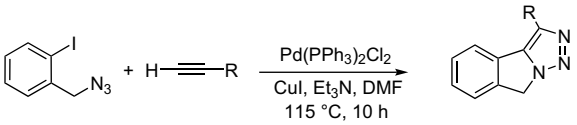
Larock et al. have described the use of *tert*-butylimine nucleophiles in the palladium-catalyzed annulation of terminal alkynes to prepare isoquinolines (Scheme 9).[16] Thus, a one-pot reaction of the aryl-, alkenyl-, and alkyl-substituted terminal alkynes **26** with the *tert*-butylimine of *o*-iodobenzaldehyde **25**, in the presence of $PdCl_2(PPh_3)_2$ and CuI, gave the *N*-heterocycles **27** in excellent yields.



R = Ph, $(CH_2)_2OTHP$, $CH(OEt)_2$, $(CH_2)_3CN$, *n*-Bu, C_6H_{11}

Scheme 9.

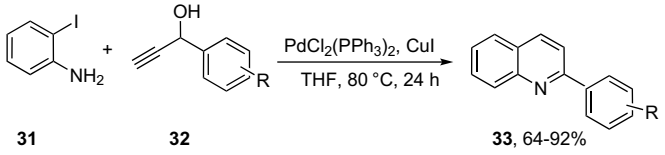
A convenient and general method for the synthesis of isoindoline fused with triazoles **30** from *ortho*-iodobenzyl azide **28** and acetylenes **29** through palladium–copper catalysis was described by Chowdhury et al. (Scheme 10).[17]



R = Ar, Alk

Scheme 10.

2-Iodoaniline **31** reacted with terminal acetylenic carbinols **32** in THF at 80 °C in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ and CuI along with aqueous tetrabutylammonium hydroxide to afford the corresponding 2-arylquinolines **33** in good yields (Scheme 11).[18]



R = H, 2-Me, 3-Me,4-Me, 2-OMe, 3-OMe, 4-OMe, 4-F, 4-Cl, 2,3-$(OMe)_2$

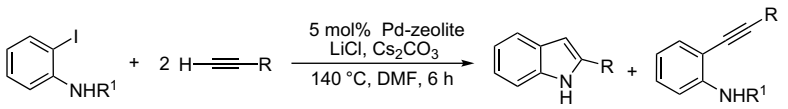
Scheme 11.

Various 2-substituted indoles **36** were prepared by heteroannulation of *o*-iodoanilines **34** and terminal alkynes **35** in a one-pot reaction with a Pd(II)–NaY zeolite catalyst. The product formation largely depended on the solvent, base, and reaction temperature. The recycled catalyst showed good reusability in the heteroannulation reaction (Scheme 12).[19]

An *o*-iodoaniline linked through an amide to the resin **37** was coupled and cyclized with 1-methyl-2-(trimethylsilyl)acetylene **38**, giving 2-(trimethylsilyl)-3-methylindole **39**. Deprotection from the resin was achieved under strongly acidic conditions (TFA) (Scheme 13).[20]

A novel and efficient strategy for the synthesis of 2-substituted 4-azaindoles **43** from 2-chloro-3-nitropyridine **40** through Pd-catalyzed Sonogashira cross coupling, giving **41**, followed by reduction to form **42** and heteroannulation on *t*-BuOK, was reported by Sun and Wang (Scheme 14).[21]

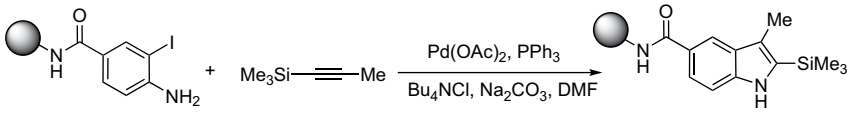
Palladium-catalyzed tandem Sonogashira coupling-5-*endo*-*dig* cyclization of *o*-iodoanilide derivative **44** with terminal alkyne **45** proceeded smoothly in acetonitrile by using $Pd(OAc)_2$ as the pre-catalyst, and Bu_4NOAc as the base under ligand-, copper-, and amine-free conditions to give the 2-substituted 4-azaindole **46** in good yield (80%) (Scheme 15).[22]



34 **35** **36**, 40-82%

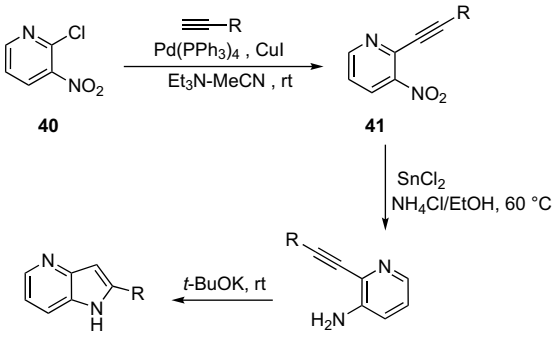
R^1 = Ac, Bn, Ts
R = H, Ar, Alk, etc.

Scheme 12.



37 **38** **39**

Scheme 13.



40 **41** **42** **43**, 70-85%

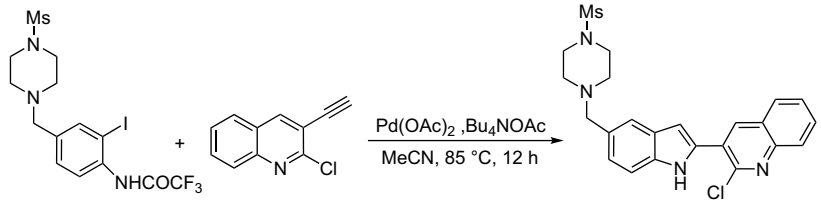
R = Ph, TMS, *n*-Pr, $(CH_2)_3CN$, $(CH_2)_3OH$

Scheme 14.

An efficient and novel route for the synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-ones **53** via a palladium-catalyzed site-selective cross-coupling reaction and cyclization process was described by Wu et al. 3-Bromo-4-aryl-quinolin-2(1*H*)-ones **50** reacted with 2-ethynylaniline **51** via Pd-catalyzed Sonogashira coupling (to **52**) and CuI-mediated cyclization, leading to the desired 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-ones **53** in good yields (Scheme 17).[24]

A Sonogashira/copper(I)-catalyzed heteroannulation sequence was developed to convert 3,5-diamino-6-chloro-1,2,4-triazines **54** and alkynes or arynes **55** in to the corresponding 3-amino-5*H*-pyrrolo[2,3-*e*]-1,2,4-triazine derivatives **57** in good yields via **56** (Scheme 18).[25]

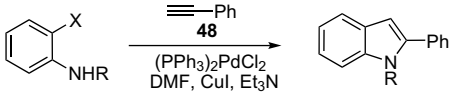
A variety of 3-substituted β- and γ-carbolines **61** and **64** have been synthesized from *N*-substituted 3-iodoindole-2-carboxaldehydes **58** and 2-bromoindole-3-carboxaldehydes **62**, respectively. The coupling of these aldehydes with various terminal acetylenes **59** using



44 **45** **46**

Scheme 15.

Our group has prepared 2-phenylindoles **49** by hetero-annulation of 2-haloaniline derivatives **47** and phenylacetylene **48** under mild conditions in a one-pot reaction catalyzed by $Pd(PPh_3)_2Cl_2$ (Scheme 16).[23]



47 **49**, 69-82%

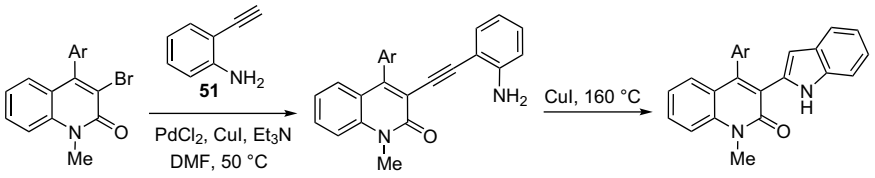
X = Br, I
R = H, Ac, Me, Bn, Ts

Scheme 16.

$PdCl_2(PPh_3)_2$/CuI readily affords the corresponding alkynylindole carboxaldehydes **60** and **63**, which have subsequently been converted in to the corresponding *tert*-butylimines, which have then been cyclized to β- and γ- carbolines **61** and **64** by either copper-catalyzed or thermal processes (Scheme 19).[26]

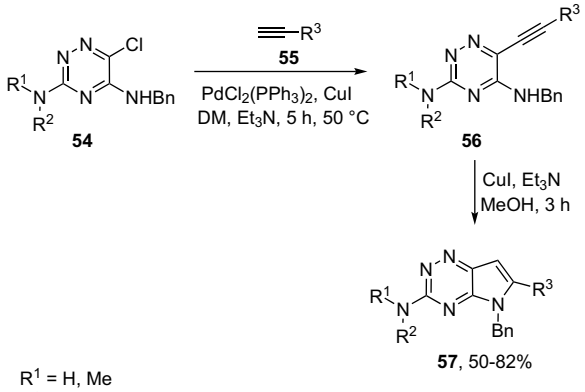
The preliminary results of an approach to 4-substituted-2-phenylimidazoles **67** starting from the readily available *N*-propargyl-benzamidine **65** and aryl halides **66** were reported by Abbiati et al. (Scheme 20).[27]

The derived *N*-substituted *o*-chloroarylamines **68** and terminal acetylenes **69** were converted via **70** into azaindoles or indoles **71** via one-pot processes comprising a novel combination of Sonogashira coupling and base-promoted indolization (Scheme 21).[28]



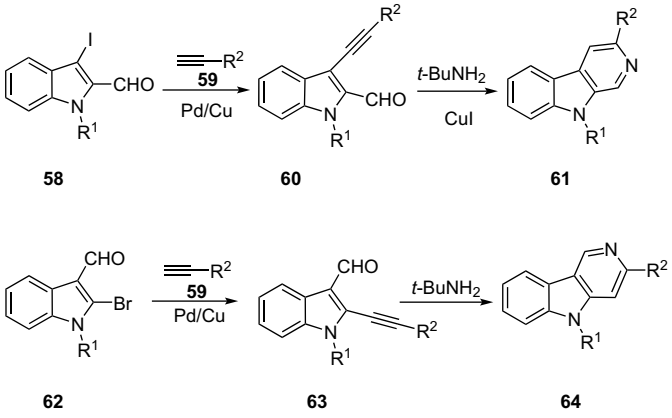
Ar = Ph, 4-CNC$_6$H$_4$, 3-CNC$_6$H$_4$, 3-COMeC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$

Scheme 17.



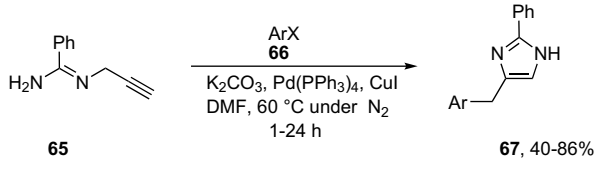
R^1 = H, Me
R^2 = Bn, Ph, c-Pr, 4-MeO-Ph
R^1,R^2 = -(CH$_2$)$_2$-O-(CH$_2$)$_2$-, -(CH$_2$)$_4$-,
R^3 = Pr, -CH$_2$-N(Me)$_2$, Ph, -CH$_2$-O-THP, SiMe$_3$

Scheme 18.



R^1 = Me, MOM; R^2 = Ph, C$_8$H$_{17}$, (CH$_2$)$_9$OH, (CH$_2$)$_8$CO$_2$Me

Scheme 19.



X = I, Br
Ar = Ph, 4-ClC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 4-COMeC$_6$H$_4$

Scheme 20.

A Pd-catalyzed, one-pot, two-step synthesis of 2-amidoindoles **74** from ynamides **73** and *o*-iodoanilines **72** was reported by Ruhland et al. (Scheme 22).[29]

o-Alkynylisocyanobenzenes **78** underwent nucleophile-induced intramolecular cyclization to give 2,3-disubstituted quinoline derivatives **79**.[30] *o*-Alkynylisocyanobenzenes **78** were prepared from *o*-iodoaniline **75** and terminal alkynes **76** via Sonogashira coupling (to give **77**) and N-formylation, followed by dehydration (Scheme 23).[31]

Larock et al. have developed an efficient method for the synthesis of 3-iodoindoles on a solid support which provides excellent yields and purities under very mild reaction conditions.[32] The Sonogashira reaction of **80** with terminal acetylenes **81** under standard reaction conditions [catalyst $PdCl_2(PPh_3)_2$, catalyst CuI, $HNEt_2$] afforded the immobilized alkynylanilines **82**.[33] The cyclization of **82** to the polymer-bound 3-iodoindoles **83** was carried out in CH_2Cl_2 using I_2 at room temperature for 24 h (Scheme 24).

Cu-assisted double pyrrolization of bis-alkynylpyrimidines to the 5-6-5 heteroaromatic core was demonstrated by Gevorgyan et al.[34]

Treatment of **84** with phosphorus oxybromide in benzene followed by Sonogashira coupling[4] of **85** with propyne proceeded to give bis-propynylpyrimidines **86**. The next step, a sequential double pyrrolization of **86**, gave 5-6-5 tricyclic bis-pyrrolopyrimidines **87** (Scheme 25).

A practical one-pot, regiospecific three-component process for the synthesis of 2,3-disubstituted indoles **91** from *o*-iodoanilide derivative **88** and terminal acetylenes **89** was developed via consecutive Pd-catalyzed Sonogashira coupling, amidopalladation, and reductive elimination via **90** (Scheme 26).[35]

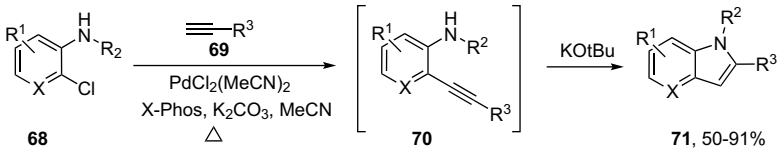
A straightforward approach to the intramolecular amidation of alkynes by a phenyliodine(III) bis(trifluoroacetate) (PIFA)-promoted cyclization reaction has been described by Tellitu et al. and applied to the synthesis of 5-substituted pyrrolidinone derivatives **94**.[36]

The substitution at the terminal position of the triple bond in amide **92** to form **93** was introduced by a Sonogashira cross-coupling reaction[37] using appropriately substituted iodides or bromides (RX) (Scheme 27).

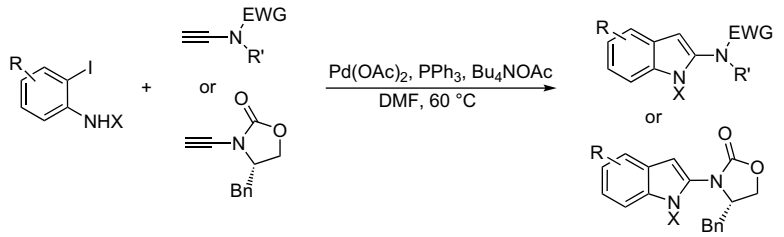
Stevens et al. have shown that Sonogashira coupling chemistry can be employed to construct a new series of indolyl quinols. Sulfonamides **95** undergo Sonogashira couplings under thermal or microwave (MW) conditions with the alkyne, 4-ethynyl-4-hydroxycyclohexa-2,5-dien-1-one **96** followed by cyclization to 4-[1-(arylsulfonyl-1*H*-indol-2-yl)]-4-hydroxycyclo-hexa-2,5-dien-1-ones **97** (Scheme 28).[38]

A three-component synthesis of substituted indoles **101** was accomplished starting from *ortho*-dihaloarenes **98** and terminal acetylenes **99** through the use of a multicatalytic system consisting of a palladium complex with ligand **100** and CuI. The corresponding indole derivatives were obtained as single regioisomers in high yields (Scheme 29).[39]

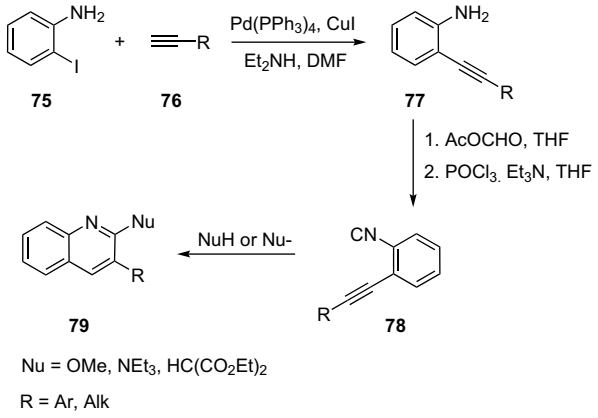
Majumdar et al. have developed a gold-catalyzed intramolecular cyclization of variously substituted acetylenic amines **104** and **107** under mild conditions, which yields, respectively, pyrrolopyridines and 2-substituted indoles **105** and **108**, quantitatively. The



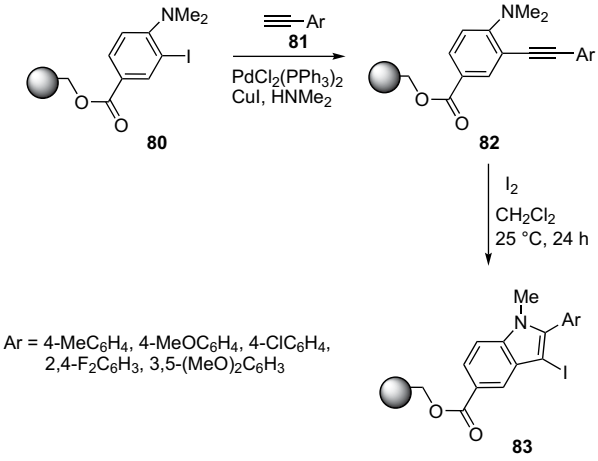
Scheme 21.



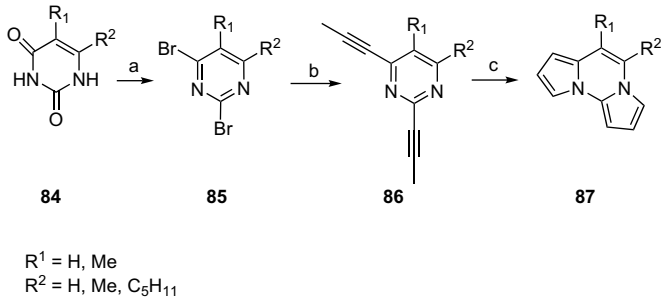
Scheme 22.



Scheme 23.



Scheme 24.



Scheme 25. (a) $PhN(Me)_2$, $POBr_3$, benzene; (b) CuI, $Pd(PPh_3)_2Cl_2$, propyne, Et_3N, 50 °C; (c) CuBr, Et_3N–DMA, 150 °C.

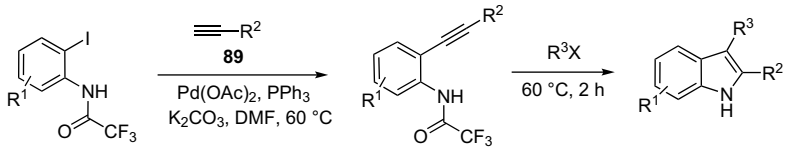
cycloisomerization of acetylenic amines was achieved with $AuCl_3$ as a catalyst without the use of base, acid or *N*-protecting groups.

The starting materials **104** and **107** were prepared in moderate- to -good yields by Sonogashira coupling of the respective free amines **103** and **106** with phenylacetylene **102** using $Pd(PPh_3)_2Cl_2$ as a catalyst and CuI as a co-catalyst in dry DMF–Et_3N (5:2) at 100 °C for 2 h (Scheme 30).[40]

Novel pyrrolopyridines **113** and **117** have been synthesized by an efficient, regioselective and catalytic method from 3-aminopyridine **109** or 2-aminopyridine **114**, respectively.

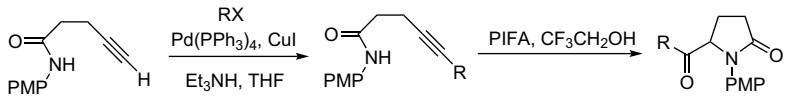
The required precursors **112** and **116** were synthesized in 95–98% yields by the acylation of **111** and **115** with trifluoroacetic anhydride.[41] The compounds **111** were prepared in good yields (70–75%) by the regioselective cross coupling of alkynes **110** with 3-amino-2,6-dibromopyridine **109** under Sonogashira coupling[42] conditions (Scheme 31). The compounds **115** were obtained by the same procedure (Scheme 32).[43]

Various alkynes **119** were introduced at the C-5 position of **118** under optimized Pd(0)-catalyzed Sonogashira cross-coupling alkynylation to yield **120**. The synthesis of their 8-aza-3-deazapurine analogues **121** was accomplished through the



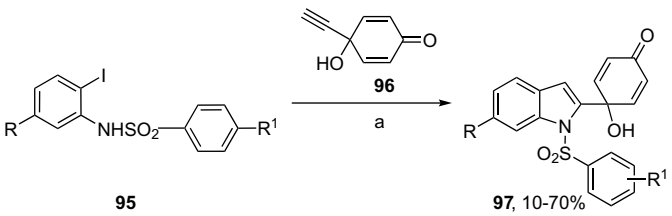
X = I, Br
R^1 = H, CN, CO_2Me
R^2 = Ph, *p*-Tol
R^3 = Ph, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$CO_2MeC_6H_4$

Scheme 26.



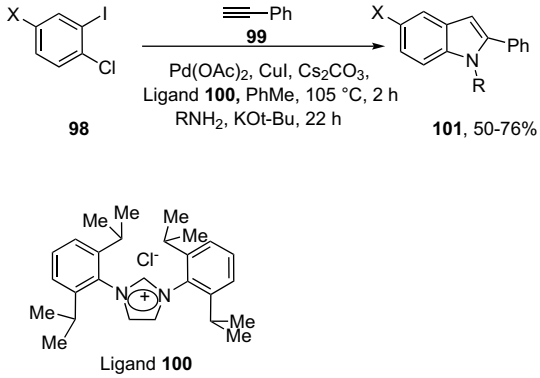
R = Ar, Het, Vinyl
PMP: *p*-Methoxyphenyl.

Scheme 27.



R^1 = H, Me, CN, NHAc, SO_2Me, $NHCO_2Et$
R = H, F

Scheme 28. (a) $Pd(PPh_3)_4$, CuI, DMAC, H_2O, 100 °C or 100 W MW; $(i\text{-}Pr)_2NH$.



R = *p*-Tol, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-FC_6H_4, 2-FC_6H_4
X = H, CF_3

Scheme 29.

heteroannulation of internal alkynes under aqueous dimethylamine (Scheme 33).[44]

2,4,6-Tri(hetero)aryl-substituted pyrimidines **126** were synthesized in a three-component, one-pot process based upon a coupling isomerization sequence of an electron-poor (hetero)aryl halide **122** and a terminal propargyl alcohol **123**, giving **124**, subsequently followed by a cyclocondensation with amidinium salts **125** (Scheme 34).[45]

4. Synthesis of oxygen-bearing heterocyclic compounds

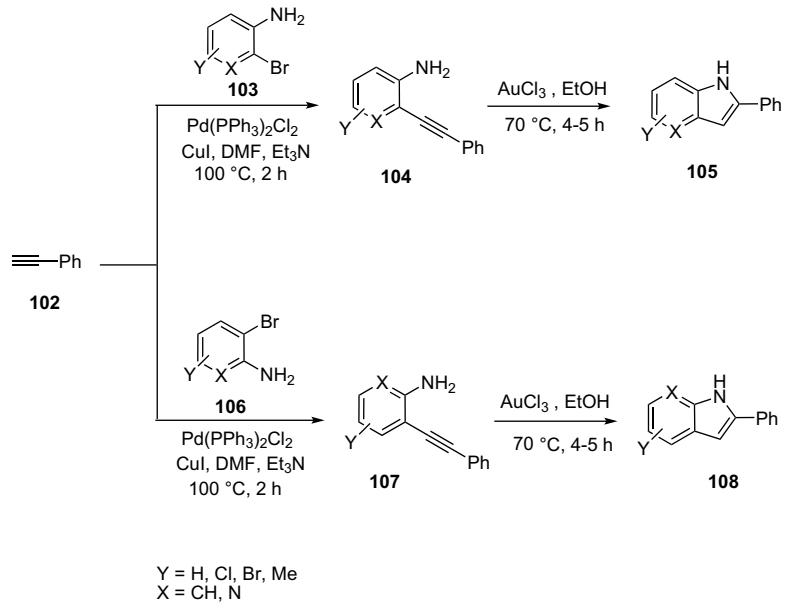
A wide variety of 3-iodobenzo[*b*]furans **131** were prepared by iodocyclization of 2-alkynyl-1-(1-ethoxyethoxy)benzenes **130** with a bis(2,4,6-collidine)iodonium hexafluorophosphate ($I(coll)_2PF_6$)-$BF_3{\cdot}OEt_2$ combination.[46] 2-Alkynyl-1-(1-ethoxyethoxy)benzenes **130**, the precursors for iodocyclization, were prepared by the conversion of 2-iodophenol **127** in to the ethoxyethyl ether, giving **128**[47] followed by Sonogashira coupling with terminal alkynes **129** (Scheme 35).[4]

Highly substituted 1*H*-isochromenes and pyranopyridines **133** and isobenzofurans **135** have been prepared by allowing *o*-(1-alkynyl)arenecarboxaldehydes **132** and ketones **134** to react with I_2, ICl, NIS, Br_2, NBS, *p*-$O_2NC_6H_4SCl$, or PhSeBr and various alcohols or carbon-based nucleophiles at room temperature.[48]

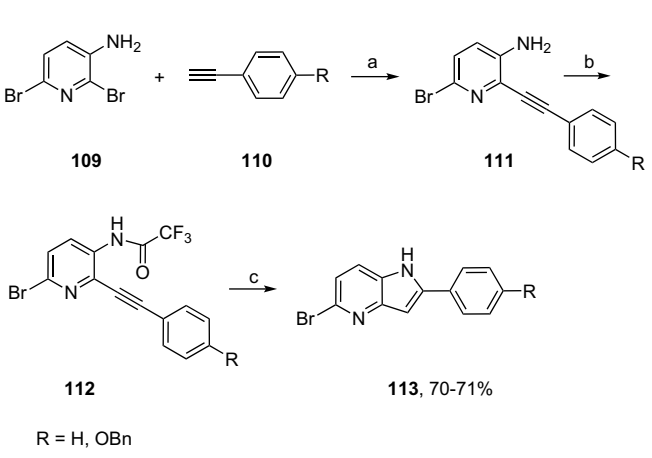
Acetylenic aldehydes bearing different substituents on the carbon–carbon triple bond were synthesized in high yields by palladium/copper-catalyzed coupling of the appropriate *o*-bromoarenecarboxaldehydes and the corresponding terminal alkynes.[4] The resulting acetylenic aldehydes were then allowed to react under electrophilic cyclization conditions to afford the corresponding products (Scheme 36).

An efficient one-pot protocol was developed by Kotschy et al. for the construction of the benzofuran **140** system from aryl halides **137** and protected iodophenols **138** using carbinol-based acetylene sources **136**. The sequence includes alternating palladium-catalyzed Sonogashira couplings and deprotection steps concluded by a ring closure via **139** (Scheme 37).[49]

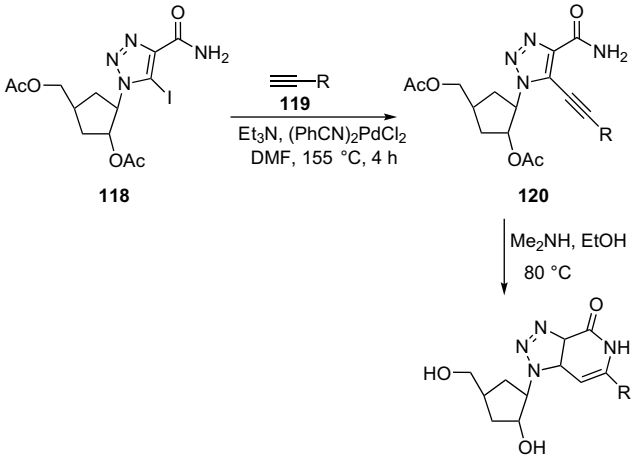
A simple one-pot procedure has been elaborated by Kotschy et al. for the preparation of substituted benzofurans **143** and **145** starting from halogenated phenols **141**. The precursors **142** and **144** were prepared by Sonogashira coupling of **141** with terminal alkyne. This method has been applied successfully to the total



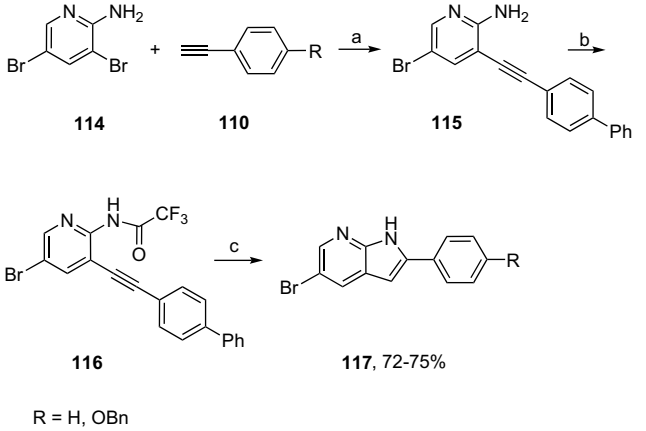
Scheme 30.



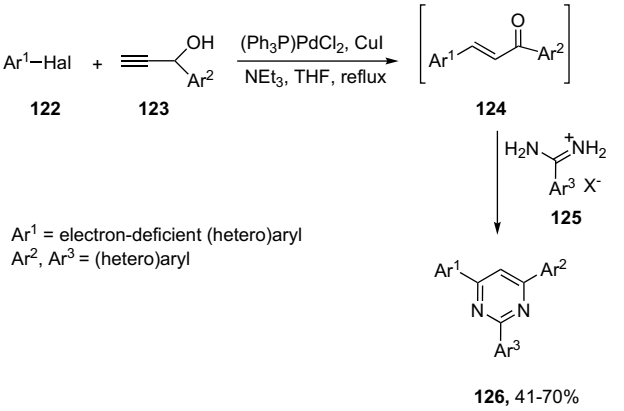
Scheme 31. (a) $Pd(PPh_3)_2Cl_2$, CuI, 5:2 DMF:Et_3N, 110 °C, 2 h. (b) trifluoroacetic anhydride, K_2CO_3, 1,4-dioxane, rt, 1–2 h. (c) DMF, 50 mol % Et_3N, 100 °C, 1 h.



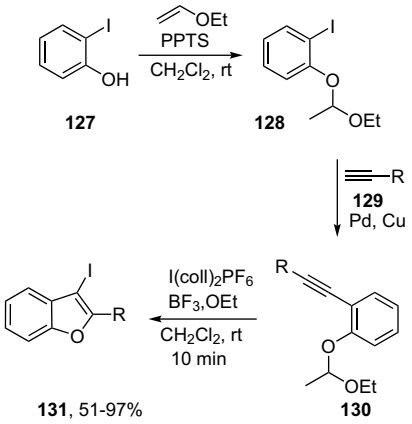
Scheme 33.



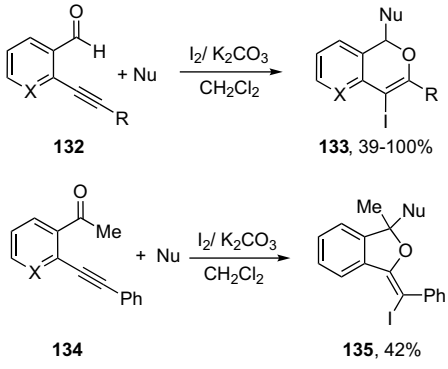
Scheme 32. (a) $Pd(PPh_3)_2Cl_2$, CuI, 5:2 DMF:Et_3N, 110 °C, 2 h. (b) trifluoroacetic anhydride, K_2CO_3, 1,4-dioxane, rt, 1–2 h. (c) DMF, 50 mol % Et_3N, 100 °C, 1 h.



Scheme 34.



Scheme 35.



Scheme 36.

An intramolecular Pd(II)-catalyzed cycloisomerization of a 2-(10-alkynyl)benzyl alcohol **155** via an apparent 6-*endo* diagonal pathway led to the 1*H*-isochromene ring system **156** (Scheme 40).[52] The functionalized cycloisomerization precursor **153** was prepared by a Sonogashira coupling, which linked the aryl bromide **151** and terminal acetylene **152**. The phenolic hydroxyls were then protected as TBS ethers **154**, and treatment of the latter compound with $NaBH_4$ in ethanol at 0 °C gave the corresponding benzyl alcohol **155**.

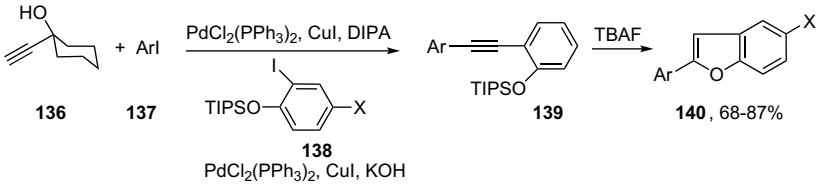
(*Z*)-2-Alkynyl-3-trifluoromethyl allylic alcohols **159**, available through $Pd(PPh_3)_4$-mediated coupling of (*Z*)-2-iodo-3-trifluoromethyl allylic alcohols **157** and terminal alkynes **158**, cyclized and subsequently isomerized to 3-trifluoroethylfurans **160** upon catalysis under $PdCl_2(MeCN)_2$ in THF at 5–10 °C (Scheme 41).[53]

A phosphine- and copper-free protocol for the synthesis of phthalides via a Pd/CNTs-catalyzed tandem coupling-cyclization process has been developed by Jiang et al. The palladium immobilized on CNTs showed a high catalytic activity, and the reactions with a variety of terminal alkynes **162** and *o*-iodobenoic acids **161** proceeded smoothly to give phthalides **163** in moderate- to -good yields catalyzed by 0.1 mol% Pd/CNTs (Scheme 42).[54]

The hydroboration of 2-[(2-ethynylphenyl)methoxy]-1-iodobenzene **164** with bis(pinacolato)diboron **165** in the presence of a palladium catalyst, gave **166**, and followed by consecutive oxidative addition, cis-cyclocarbopalladation, and cis-β-elimination gave highly stereoselective exocyclic alkenylboronate ester **167**. Cross coupling of the exocyclic alkenylboronate ester **167** with 2-bromo-*N*,*N*-dimethylacetamide **168** in the presence of a palladium catalyst, gave **169**, and followed by LAH reduction gave (*E*)-doxepin **170** (Scheme 43).[55]

An efficient synthesis of 2-alkyl/aryl-substituted benzo[*b*]furans/nitrobenzo[*b*]furans **173** and **176** in water has been accomplished via a Pd/C-catalyzed reaction of the respective *o*-iodophenols **171** and **174** with the terminal alkynes **172** and **175** in the presence of PPh_3, CuI and prolinol (Scheme 44).[56] The protocol does not require the use of a phase-transfer catalyst or water-soluble phosphine ligands and avoids the use of an organic co-solvent.

Dai and co-worker have reported that the reaction of the nitrophenols **177** and phenylacetylene **178** afforded the nitrobenzo[*b*]furans **179** when catalyzed by 10% $PdCl_2(PPh_3)_2$ and CuI in toluene as the solvent (Scheme 45).[57]

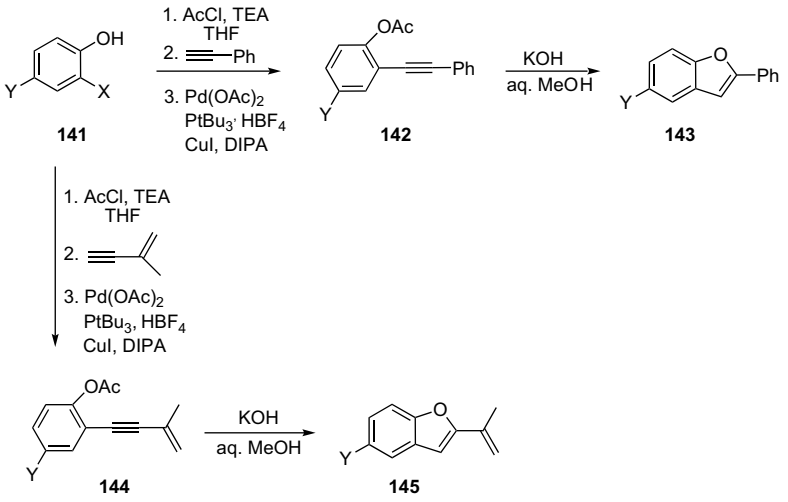


Scheme 37.

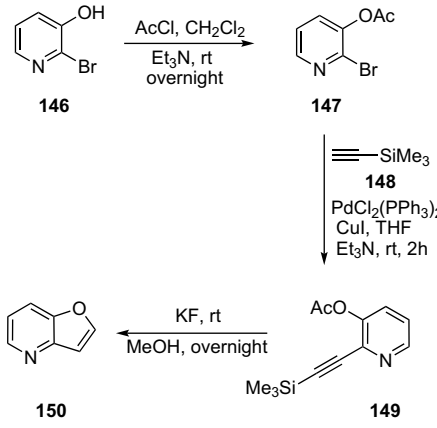
synthesis of dehydrotremetone, a natural product of White Snakeroot (Scheme 38).[50]

Fort et al. have described a convenient and efficient large-scale synthesis of furo[3,2-*b*]pyridine **150** starting from **146** in excellent overall yield using a tandem Sonogashira-coupling reaction of **147** and **148**, followed by heteroannulation of **149** as the main step (Scheme 39).[51]

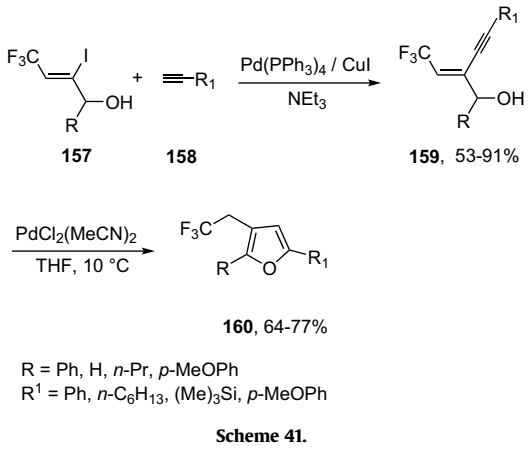
Balme and co-workers have described the synthesis of the furo[2,3-*b*]pyridones **183** in a single step through the sequential coupling of three starting materials: the 3-iodo-2-pyridones **180**, the terminal alkynes **181**, and the aryl bromides or iodides **182** (Scheme 46).[58] This one-pot procedure was optimized using a catalytic amount of $PdCl_2(PPh_3)_2$ and CuI in the presence of Et_3N and MeCN.



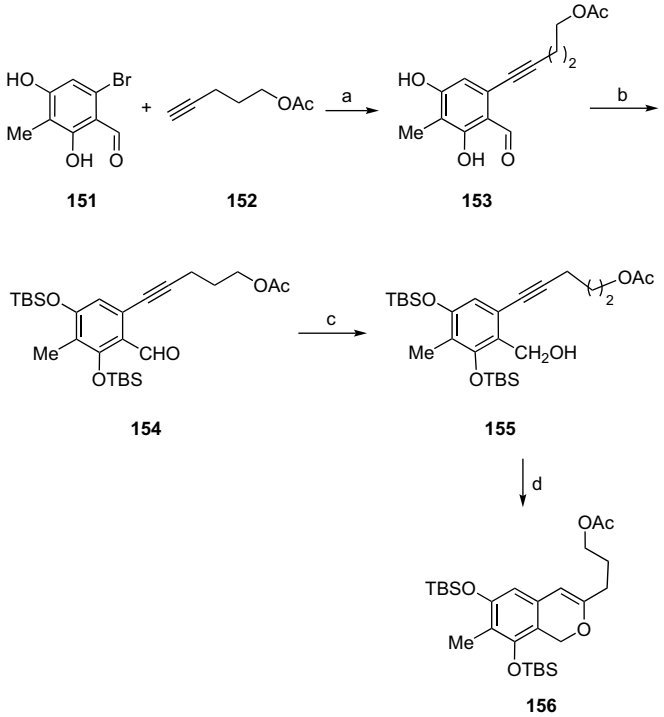
Scheme 38.



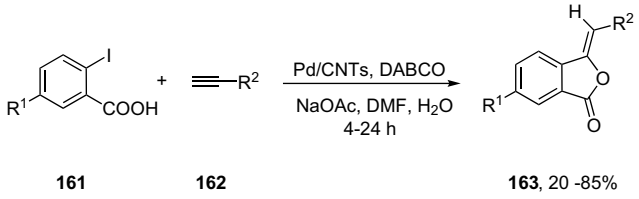
Scheme 39.



Scheme 41.



Scheme 40. (a) $Pd(PPh_3)_4$, CuI, 4-pentynyl acetate, Et_3N, DMF, 70 °C, 92%; (b) TBSCl, imidazole, DMF, 87%; (c) $NaBH_4$, EtOH, 0 °C, 5 min, 75%; (d) $PdCl_2(PPh_3)_2$, 1,4-dioxane, 85 °C, 72%.

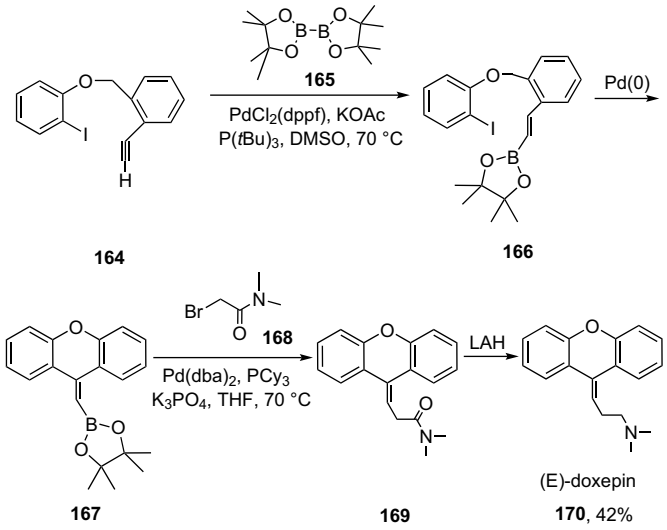


R^1 = H, NO_2
R^2 = Ph, CO_2Me, *p*-F-C_6H_4, *p*-Me-C_6H_4, $CH_2(CH_2)_4Me$, $SiMe_3$, $CH_2(CH_2)_4Me$ CH_2OH, CH_2CH_2OH, $CH_2(CH_2)_3OH$, $CH(OH)(CH_2)_2Me$, $C(Me)_2OH$

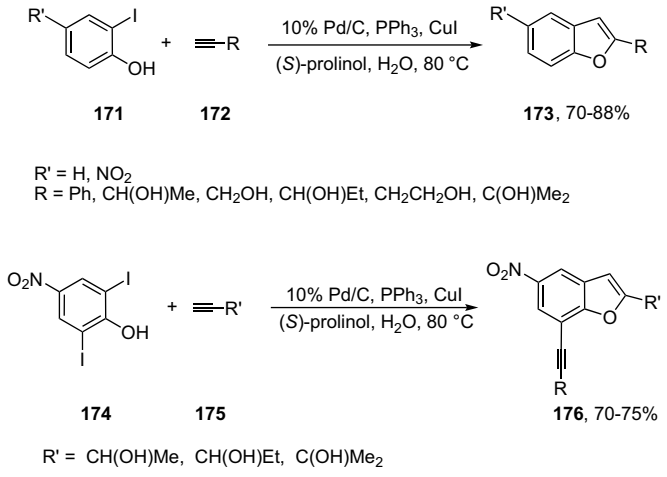
Scheme 42.

Fiandanese and co-workers have described the preparation of (*Z*)-γ-alkylidene butenolide **186** in good yield and high stereoselectivity from (*Z*)-3-iodo-2-propenoic acid **185** and the silylated polyunsaturated terminal alkyne **184** (Scheme 47).[59] The best results in this cyclization were obtained using $PdCl_2(PPh_3)_2$/CuI and Et_3N as the catalyst system.

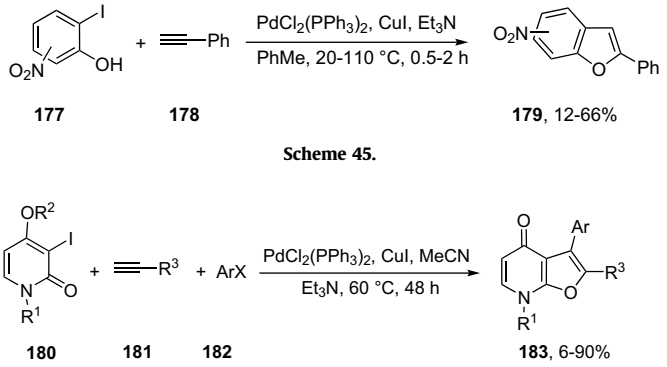
The Cacchi group has also shown that *N*-propargylamides readily underwent palladium-catalyzed cyclization with aryl iodides, affording the disubstituted oxazoles (Scheme 48).[60] The reaction of aryl iodides **188** with the *N*-propargylamides **187**, using a catalytic amount of $Pd_2(dba)_3$/P(2-furyl)$_3$, in the presence of NaO-*t*-Bu and MeCN, gave the 2,3-disubstituted oxazoles **189** in good yields. Other solvents, such as DMF and THF, and other bases, such as K_2CO_3, gave



Scheme 43.

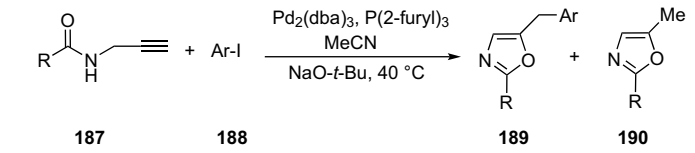


Scheme 44.



Scheme 45.

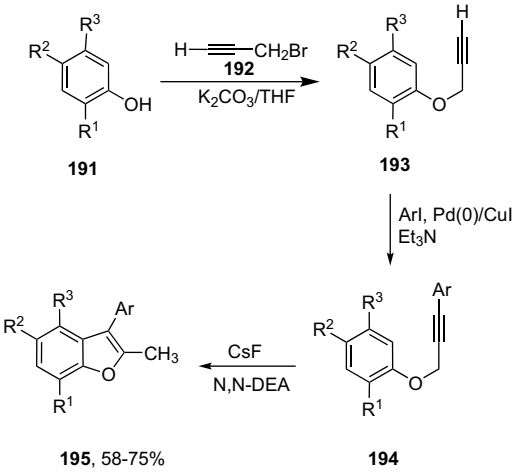
Scheme 46.



Scheme 48.

lower yields of the desired oxazoles. In some cases, the oxazoles **190** were observed as minor products.

A variety of mono- and disubstituted phenols **191** were alkylated with propargyl bromide **192** to give phenyl 2-propynyl ethers **193**, which were further coupled with aryl iodides under Sonogashira reaction conditions to give 3-phenoxy-1-aryl-1-propyne derivatives **194**. The latter compounds underwent an initial Claisen rearrangement followed by ring closure to give functionalized benzo[*b*]furans **195** in moderate- to -good yields (Scheme 49).[61]



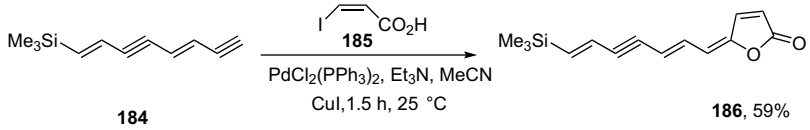
Scheme 49.

Sonagashira coupling of propargyl alcohol **197** to the arene **196** in the presence of $ZnCl_2$ provided only the isophthalide product **199** from 5-*exo dig* cyclization via **198** (Scheme 50).[62]

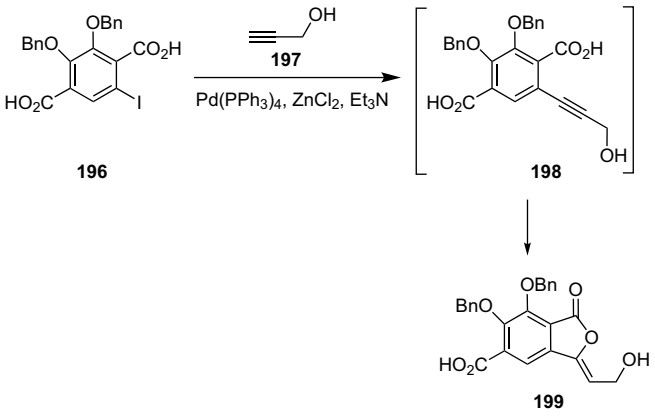
Ku et al. reported an efficient and convergent process for the preparation of a potent and selective H_3 receptor antagonist, ABT-239 (**202**). The key step in the synthesis was a Sonogashira coupling/cyclization reaction of 1-but-3-ynyl-2-(*R*)-methylpyrrolidine **200** with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **201** (Scheme 51).[63]

(*E*)-*O*-Protected-2-trifluoromethyl-1-bromo-1-substituted allylic alcohols **203** reacted with terminal alkynes **204** under Sonogashira reaction conditions to give the corresponding (*E*)-2-en-4-ynoic alcohol derivatives **205**, which were further converted in to the corresponding 4-trifluoromethylfuran derivatives **206** via a sequential deprotection-annulation reaction in moderate- to -excellent yields (Scheme 52).[64]

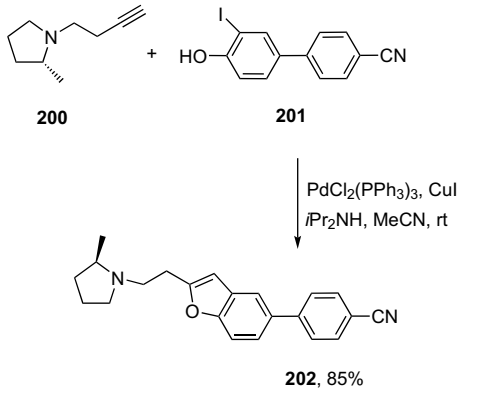
Monteiro et al. have shown that various 3-iodo-4-methoxypyridin-2-ones and related pyrone and coumarin derivatives **207** and terminal alkynes **208** can give easy access to 2-substituted furan derivatives **210** through in situ sequential Sonogashira-



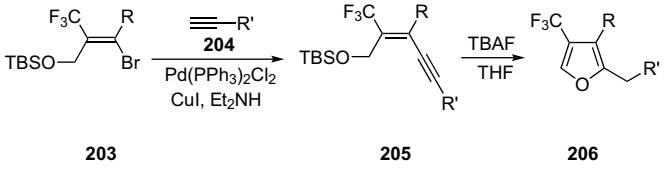
Scheme 47.



Scheme 50.

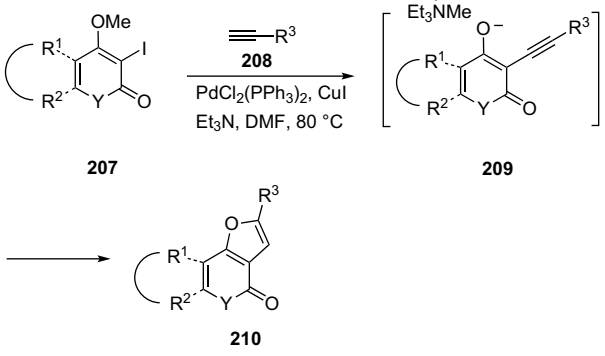


Scheme 51.



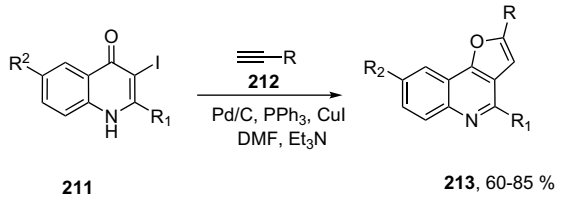
R = H, Bn, Me
R' = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, CH$_2$OBn, *n*-Pentyl

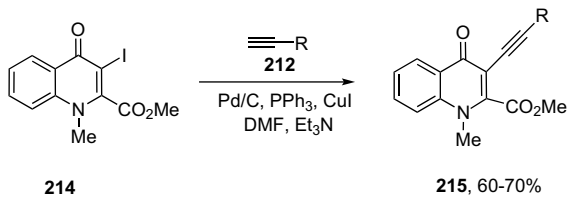
Scheme 52.



R^1 = Ph, *p*-MeOC$_6$H$_4$, *p*-CO$_2$MeC$_6$H$_4$
R^2 = H, Me
R^1-R^2= Ph
R^3 = Ph, SiMe$_3$, *p*-MeOC$_6$H$_4$, *p*-CO$_2$MeC$_6$H$_4$
Y = O, NR; R = Me, Bn

Scheme 53.





R^2 = H, F
R^1 = Ph, CO$_2$Me
R = Ph, C(OH)Me$_2$, CH(OH)Me, CH(OH)Et, CH$_2$OH

Scheme 54.

acetylide coupling, dealkylation, and furan annulation reactions via **209** (Scheme 53).[65]

Pd/C–Cu-catalyzed coupling reactions of 3-iodo-1*H*-quinolin-4-ones **211** with a variety of terminal alkynes **212** afforded furo[3,2-*c*]quinolines **213** regioselectively in good- to -excellent yields (Scheme 54).[66] 3-Alkynylquinolones **215** were isolated under the same reaction conditions when the nitrogen of 3-iodo-1*H*-quinolin-4-one was substituted with an alkyl group (**214**).

5. Synthesis of heterocyclic compounds containing sulfur

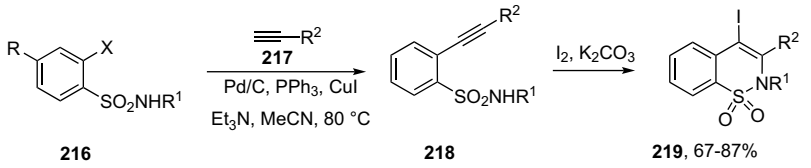
A variety of 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides **219** were prepared with high regioselectivity via a two-step process involving Pd/C-mediated C–C coupling of *o*-halobenzenesulfonamides **216** with terminal alkynes **217**, followed by iodocyclization of the resulting *o*-(1-alkynyl)-arenesulfonamides **218** using elemental iodine in acetonitrile (Scheme 55).[67]

The reaction of *S*-2-bromophenyl-*S*-methylsulfoximine **220** with terminal alkynes **221** in the presence of a palladium catalyst resulted in the formation of both 1,2-benzothiazines **222** and 1,2-benzoisothiazoles **223**. A preference for the former class was seen with alkylalkynes, while the latter compounds were preferentially formed with alkynylarenes (Scheme 56).[68]

Raju et al. have described the reaction between 3-iodothiophene-2-carboxylic acid **224** and terminal alkynes **225** to afford the 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones **226** in good yields and **227** as minor products (Scheme 57).[69]

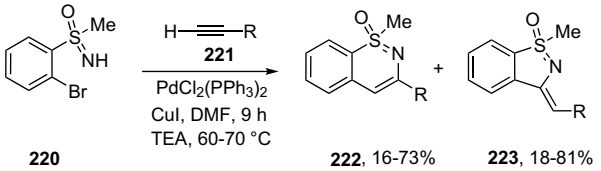
Flexible, convergent access to 2,3-disubstituted benzo[*b*]-thiophenes has been developed by Flynn et al. The most concise approach involved sequential coupling of *o*-bromoiodobenzenes **228** with benzylmercaptan and zinc acetylides **229** to give benzyl *o*-ethynylphenyl sulfides **230**, which reacted with iodine to give 3-iodobenzo[*b*]thiophenes **231** in a 5-*endo*-*dig* iodocyclization (Scheme 58).[70]

2,3-Dihydrothiopyran-4-one derivatives **234** were readily prepared by Pd/Cu-catalyzed reactions between α,β-unsaturated



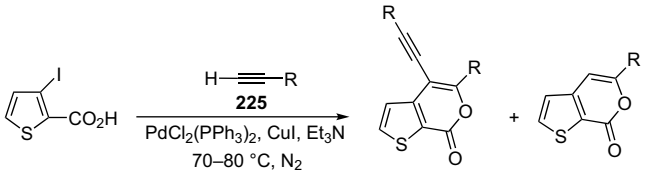
R = H, Me, Et, OMe
R^1 = Me, Et
R^2 = Alk, Ar
X = I, Br

Scheme 55.



R = Ar, Alk

Scheme 56.

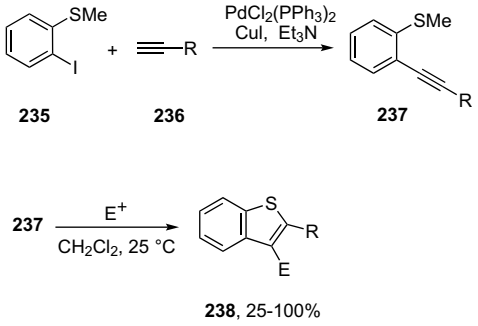


R = –C(Me)$_2$OH, –(CH$_2$)$_2$OH, –(CH$_2$)$_3$OH, –CH(OH)Me, –Bu
–(CH$_2$)$_5$Me, –Ph, –C$_6$H$_4$Me-*p*, –C$_6$H$_4$C$_5$H$_{11}$-*p*, –CH$_2$OPh

Scheme 57.

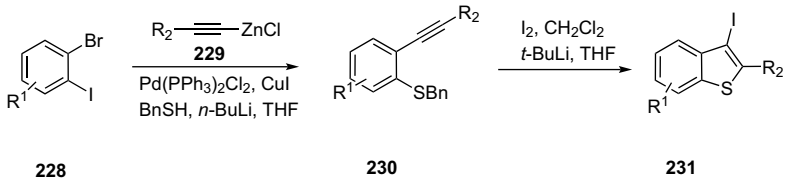
thioesters **232** and propargyl alcohols **233** in the presence of bases (Scheme 59).[71]

2,3-Disubstituted benzo[*b*]thiophenes **238** have been prepared via coupling of terminal acetylenes **236** with *o*-iodothioanisole **235** in the presence of a palladium catalyst and subsequent electrophilic cyclization of the resulting *o*-(1-alkynyl)thioanisole **237** derivatives, with I$_2$, Br$_2$, NBS, *p*-O$_2$NC$_6$H$_4$SCl, and PhSeCl being utilized as electrophiles (Scheme 60).[72]



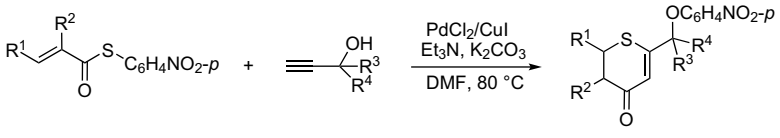
R = Ar, Alk, Vinyl, TMS, etc
E^+ = I$_2$, Br$_2$, NBS, *p*-O$_2$NC$_6$H$_4$SCl, PhSeCl

Scheme 60.



R^1 = 4-OMe, 3-OMe
R^2 = 4-MeOC$_6$H$_4$

Scheme 58.



R^1 = H, Ph, Me; R^2 = H, Me, *i*-Pr, 4-NO$_2$C$_6$H$_4$
R^3 = H, Me; R^4 = H, Me, Ph, *n*-Pen
R^3, R^4 = -(CH$_2$)$_5$-, -(CH$_2$)$_4$-

Scheme 59.

6. Conclusions

In this review, we have presented numerous very useful processes for the synthesis of heterocycles, which involve palladium-catalyzed coupling followed by heteroannulation reactions, reported in recent years. The reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups. Most palladium-based methodologies proceed stereo- and regioselectively in excellent yields. We hope this review will generate strong interest among the general readership of this journal.

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