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Synthesis of (iso)quinoline, (iso)coumarin and (iso)chromene derivatives from acetylene compounds

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Published data on the methods of synthesis of quinoline, isoquinoline, coumarin, isocoumarin, chromene and isochromene derivatives from acetylene compounds are summarized. The reactions catalyzed by metal complexes (Pd, Pt, Ru, Rh, Au, Ag, Ni, Cu, *etc.*) and transformations induced by various electrophilic reagents (Brønsted and Lewis acids) are considered. Moieties of the mentioned heterocyclic systems are present in many biologically active natural products and pharmaceutical agents. Besides, derivatives of these heterocycles are used in the manufacture of catalysts, dyes, perfumery and cosmetic products, corrosion inhibitors and so on.
The bibliography includes 211 references.

Contents

I. Introduction

Derivatives of quinoline, isoquinoline, coumarin, isocoumarin, chromene and isochromene have found wide practical application. These heterocyclic systems are key structural units of numerous biologically active natural compounds and drugs. The importance of investigations of these heterocycles is underscored by a recent series of reviews [1–3] on quinoline-based antimalarial agents. In addition, (iso)quinoline, (iso)coumarin and (iso)chromene derivatives are considered as promising anti-HIV agents and agents against Alzheimer's disease. These derivatives are also employed to prepare complex-forming agents, catalysts, dyes, preservatives, corrosion inhibitors and so on and are used in perfumery, cosmetics and in the design of organic light-emitting diodes.[4–13]

Numerous approaches have been developed for the synthesis of quinoline,[4,5] isoquinoline,[6] coumarin,[7–9] isocoumarin [10] and chromene [11–13] derivatives. However, a considerable amount of new data on the synthesis of these heterocycles from acetylene compounds were reported in the past 5–10 years due to a wide application of their complexes with different metals, primarily with Pd, Pt, Ru and Rh, as catalysts. In reactions of organic substrates, such complexes can not only activate carbon–hydrogen and carbon–heteroatom bonds but also simultaneously coordinate the substrate at the triple bond, thus facilitating various transformations involving this bond. On the whole, alkynes are widely applied in the synthesis of various carbo- and heterocyclic structures.[14–17]

As opposed to reviews,[4–13] which cover the synthesis of (iso)quinoline, (iso)coumarin and chromene derivatives from different classes of organic compounds, the present review is focused only on procedures for the synthesis of these heterocycles from acetylene compounds. In earlier publications,[5–13] the reactions of akynes are either not considered at all or only separate or sparse examples of these reactions are reported. The recent review [4] also

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includes data on the use of metal-catalyzed reactions of alkynes for the construction of the parent quinoline system. The present review not only considers the synthesis of the quinoline structure but also summarizes data on the preparation of di(tetra)hydro and 2(4)-oxo derivatives of the quinoline series.

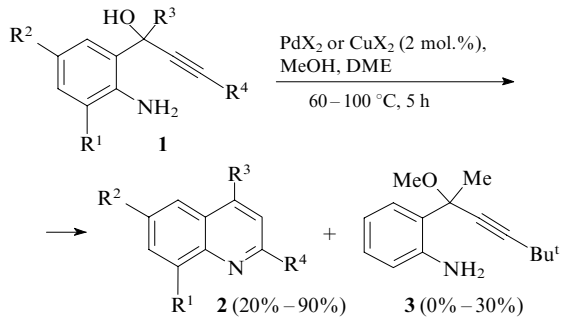
This review is devoted to methods of synthesis of quinoline, isoquinoline, coumarin, isocoumarin, chromene and isochromene derivatives from alkynes by reactions catalyzed by metal complexes (Pd, Pt, Ru, Rh, Au, Ag, Ni, Cu, *etc.*) and by Brønsted or Lewis acids. Transformations, in which the acetylene component is involved in the construction of the heterocyclic moiety of such systems, are discussed. Metal-catalyzed processes are characterized by diverse reaction mechanisms. Examples of practically important compounds — representatives of these classes of heterocycles — are given. The review covers the data published mostly in the past decade. The data are considered according to the type of the synthesized heterocyclic system.

II. Synthesis of quinoline derivatives

This section concerns with the methods of synthesis of substituted quinolines, including their di- and tetrahydro derivatives, as well as 2- and 4-quinolones.

The construction of the quinoline system is based on either intermolecular interactions of alkynes with substituted anilines or their derivatives (imines, anilides and so on) or intramolecular transformations of anilines containing alkynyl groups in the *ortho* position of the aromatic ring or at the nitrogen atom. In the presence of palladium or copper halides, *ortho*-alkynyl-substituted anilines **1** undergo annulation to form quinolines **2** (Scheme 1).[18] The reactions proceed with substrates **1** containing mainly R^1 and R^2 donor groups or a weak acceptor, for example a chlorine atom (R^2 = Cl). The reactions with compounds, which do not contain R^1 and R^2 substituents in the benzene ring, may give quinoline **2** in lower yield due to the formation of side product **3** (R^3 = Me, R^4 = Bu^t) through the methylation of the hydroxy group with methanol. Under the reaction conditions, the trimethylsilyl (TMS) substituent R^4 is eliminated to give quinolines **2** with R^4 = H. Besides, it was demonstrated that the catalyst $CuCl_2$ is as efficient as more expensive Pd catalysts with retention of the 2 mol.% catalyst loading.[18]

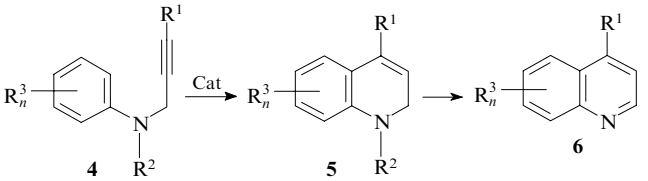
Scheme 1



X = Hal; R^1 = H, OMe; R^2 = H, Cl; R^3 = Alk, Ar; R^4 = Alk, Ph, TMS; DME is dimethoxyethane

Propargylamines **4** undergo intramolecular cyclization in the presence of Pt,[19] Au[20] or Rh[21] complexes, the Brønsted superacid CF_3SO_3H (TfOH)[22] or the Lewis acids $Cu(OTf)_2$,[23] $FeCl_3$ (see Ref. 24) to give 3,4-dihydroquinolines **5** (Scheme 2; hereinafter, unless otherwise stated, the substituent locants refer to the starting compound). In all cases, the yields of the products are > 50% (usually in the range of 70%–90%). In the presence of $FeCl_3$ (see Ref. 25) or $Hf(OTf)_2$ (see Ref. 26), the tosyl or mesyl group (R^2 = Ts or Ms) is removed from the nitrogen atom followed by the heteroaromatization to quinoline structure **6**. The presence of substituents in the benzene ring in the *meta* position relative to the N-substituent results in the formation of two isomers depending on which of the two *ortho* positions of the aromatic moiety is involved in the reaction.[19,22] In this reaction, the phosphine Au^I acetonitrile complex exhibits catalytic activity even at room temperature,[20] whereas the application of Pt or Rh complexes[19,21] or Brønsted and Lewis acids [TfOH, $Cu(OTf)_2$, $FeCl_3$, $Hf(OTf)_2$][22–26] requires higher temperatures and longer reaction times. The reactions promoted by TfOH (see Ref. 22) or $FeCl_3$ (see Ref. 24) produced quinoline derivatives **5** containing a heteroatomic substituent (SeAr, TeAr and so on) in position 4.

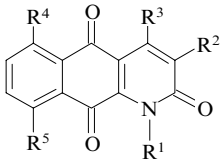
Scheme 2



R^1 = H, Alk, Ar, Het, Hal, SeAr, TeAlk, TeAr, SAr, NArTs; R^2 = H, CO_2Alk, Ms, SO_2Ar, Ar; R^3_n = 3-Me, 4-Me, 2-Pr^i, 3,5-Me_2, 2,3-benzo, 3-OMe, 4-OMe, 4-OEt, 4-Br, 4-Cl, 4-CN, 4-CH_2OTBS, *etc.*; TBS = Bu^tMe_2Si, Ts = $SO_2C_6H_4$Me-4, Ms = SO_2Me

Bala *et al.*[23] used propargylamines related to compounds **4**, which contain the 1,4-naphthoquinone moiety instead of the substituted phenyl group, to synthesize compounds structurally similar to the potent drugs dielsiquinone and marcanines (**7a**–**f**). Dielsiquinone is a natural cytotoxic agent characterized by lower cardiotoxicity compared to anthracycline (antitumour drug) used in medicine.

Structures 7



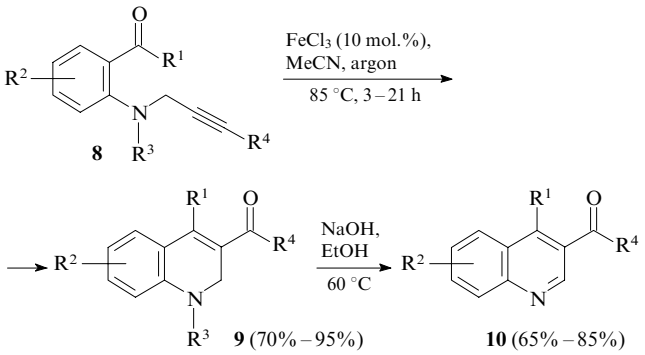
7a–**f**

Compound **7**	Name	R^1	R^2	R^3	R^4	R^5
a	Dielsiquinone	H	OMe	Me	H	H
b	Marcanine A	H	H	Me	H	H
c	Marcanine B	Me	OMe	Me	H	H
d	Marcanine C	Me	OMe	CH_2OH	H	H
e	Marcanine D	H	OMe	Me	OH	H
f	Marcanine E	Me	OMe	Me	H	OH

Marcanines A–E are natural products isolated from the stem bark of *Goniothalamus marcanii*, which exhibit biological activity against some human tumour cell lines.[23]

In the presence of $FeCl_3$ as the catalyst, aldehydes and ketones **8** undergo efficient cyclization to the corresponding dihydroquinolines **9** (Scheme 3).[27] An additional step can be utilized to remove the protecting group (R^3 = Ts, Ms) from the nitrogen atom in an alkaline medium, resulting in the formation of quinoline structures **10**.

Scheme 3



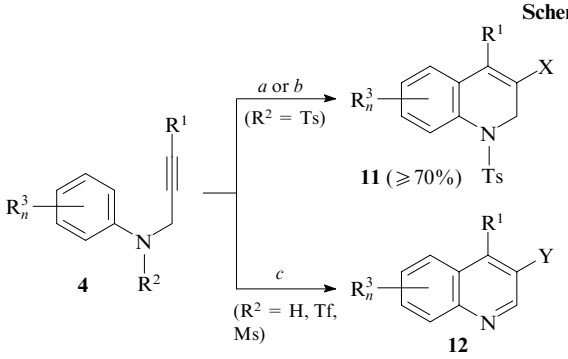
R^1 = H, Alk; R^2 = H, 3-Cl, 3-Br; R^3 = Ts, Ms; R^4 = 3-Th, Alk, Ar; Th is thienyl

The reaction of tertiary propargylamines **4** ($R^2 \neq H$) with 3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one in the presence of $Bi(OTf)_3$ (see Ref. 28) and the CuCl-catalyzed coupling with diphenyliodonium triflate[29] afford 3-substituted dihydroquinolines **11**, whereas the cyclization of related amines, including secondary amines (R^2 = H), promoted by various electrophilic reagents gives 3-substituted quinolines **12** (Scheme 4).[26] Each of the above-mentioned methods provides an original approach to modification of the structures of the reaction products, which substantially extends both the range of target quinolines and the scope of their subsequent synthetic applications.

Another procedure for transforming propargylamines **13** into benzo[*h*]quinolines **14** is based on their reactions with C-, N-, O- and S-nucleophiles (dialkyl malonates, amines, alcohols and thiols, respectively) (Scheme 5).[30, 31]

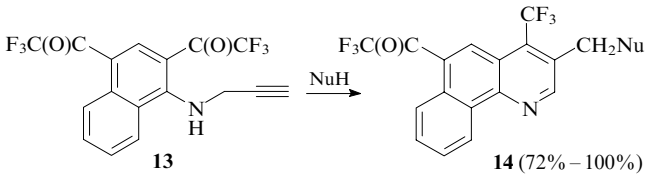
Ruthenium-based second generation Grubbs catalysts (Grubbs II catalysts) and Pd complexes catalyze the intramolecular cyclization of pyridyl-substituted propargylamines **15** to tetrahydroquinolines **16** (Scheme 6).[32] The

Scheme 4



R^1 = Ph, C_6H_4OMe-4, C_6H_4Br-2, C_6H_4Ac-4, 3-Py, Bu^n, TMS, *etc.*; R^2 = H, Ts, Tf, Ms; R^3_n = H, 4-Br, 4-NO_2, 4-OMe, 3,5-Me_2, *etc.*; X is 1-oxo-2-methyl-2,3-dihydroisoindol-3-yl, Ph; Y = I, Br, SePh, $SC_6H_4NO_2$-4; Py is pyridyl; (*a*) 3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one, $Bi(OTf)_3$; (*b*) $Ph_2I(OTf)_2$, CuCl; (*c*) I_2 or Br_2, or ICl, or PhSeBr, or 4-$ClSC_6H_4NO_2$

Scheme 5

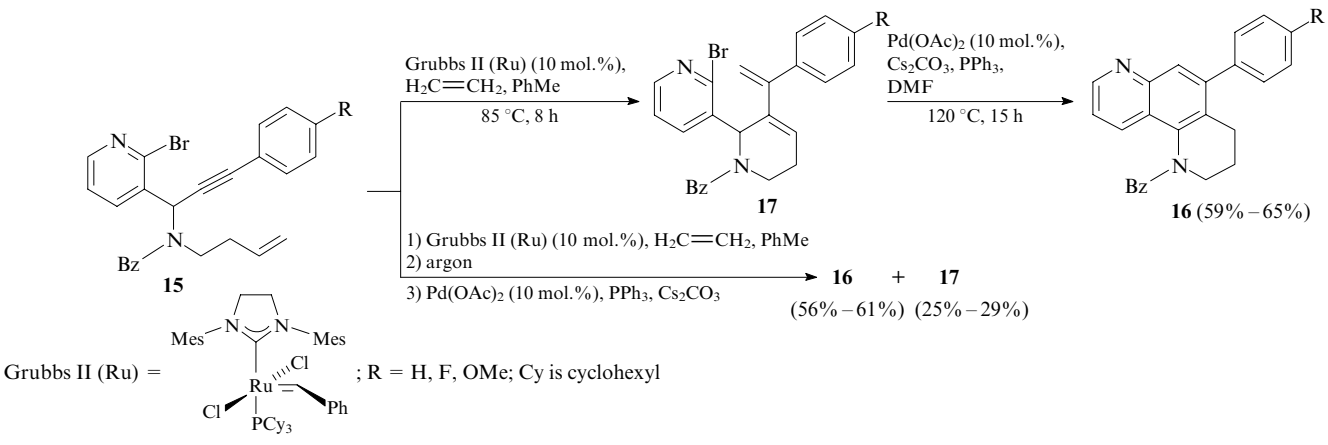


Nu = NMe_2, pyrrolidino, $NHBu^t$, NHPh, SEt, SBn, SPh, OMe, OEt, OPh, $CR^1(CO_2R^2)_2$ (R^1, R^2 = Alk)

authors proposed stepwise and one-pot methods for the synthesis of compounds **16**. The former procedure involves the formation of intermediate compound **17** followed by the intramolecular cyclization of the latter in the presence of Pd complexes to give target compounds **16**. The one-pot synthesis, in which all reactants are added successively, yields a mixture of compounds **16** and **17**.

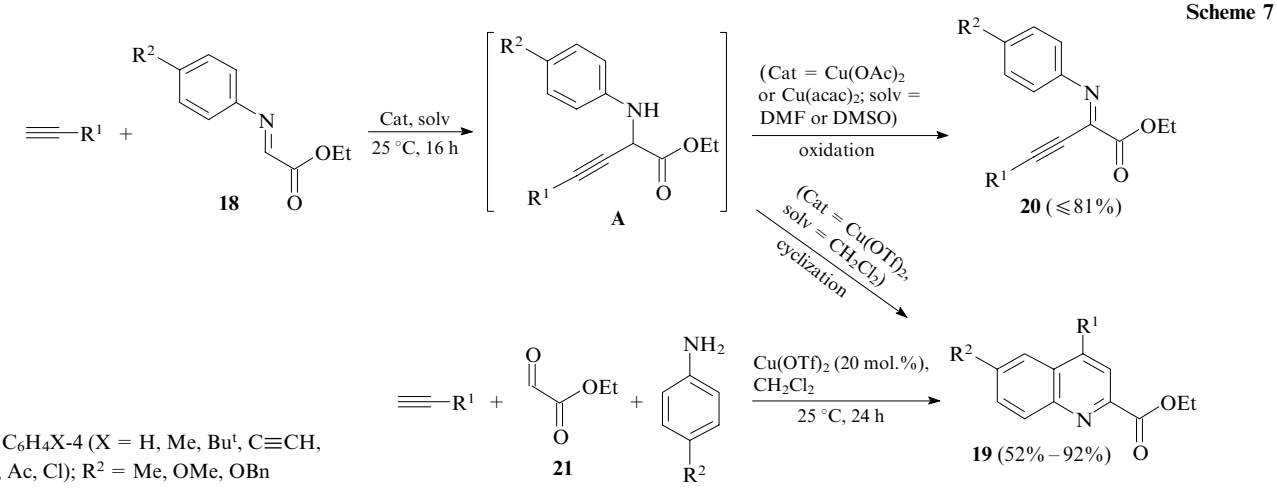
Propargylamines capable of transforming into quinoline derivatives can be synthesized *in situ* by means of different reactions. For instance, Huang *et al.*[33] applied $Cu(OTf)_2$ in dichloromethane as a catalyst in the reaction of terminal acetylenes with aromatic imines **18** (Scheme 7). Propargylamine **A**, which is produced from acetylene and imine in the

Scheme 6



Grubbs II (Ru) = ; R = H, F, OMe; Cy is cyclohexyl

Scheme 7

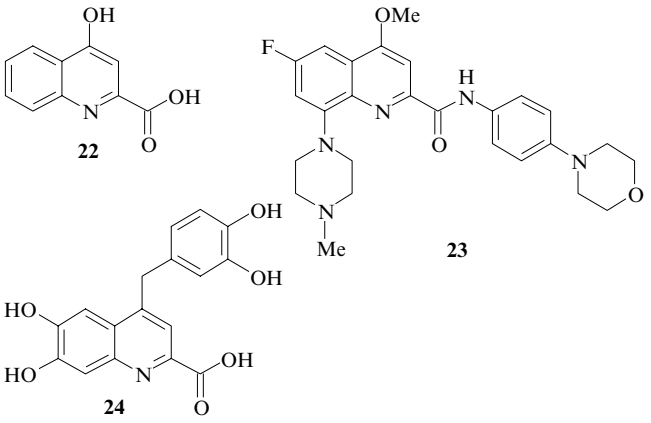


R^1 = C_6H_4X-4 (X = H, Me, Bu^t, C≡CH, OMe, Ac, Cl); R^2 = Me, OMe, OBn

first step of this reaction, undergoes intramolecular Friedel–Crafts alkenylation to give final quinoline **19**. Meanwhile, in the presence of $Cu(OAc)_2$ or $Cu(acac)_2$ (acac is acetylacetonate) as the catalyst or with DMF or DMSO instead of dichloromethane, oxidation product **20** rather than quinoline **19** is generated. Huang *et al.*[33] also proposed the three-component Cu-catalyzed reaction of terminal acetylenes with ethyl glyoxylate (**21**) and anilines giving the same quinoline-2-carboxylates **19**.

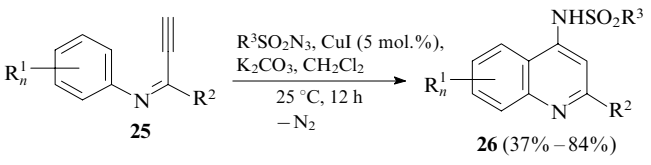
The quinoline-2-carboxylate moiety is a motif common to many biologically active compounds.[33] Thus, kynurenic acid (**22**) is used for the control of neurodegenerative disorders. Compound **23** is a potent serotonin antagonist. Compound **24** is a potent powerful insulin-like growth factor inhibitor.

Structures 22–24



Copper(I) iodide catalyzes one-step reactions of terminal ethynyl-substituted imines **25** with sulfonyl azides, which afford biologically active polysubstituted 4-sulfonylaminoquinolines **26** (Scheme 8).[34] The possible reaction mecha-

Scheme 8

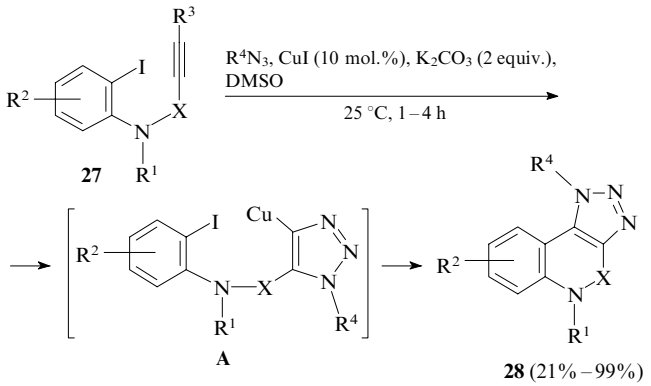


R^1_n = H, 2-Me, 4-Me, 5-Me, 4-Pr^i, 4-F, 2-Cl, 4-Br, 4-OMe, 2,3-benzo; R^2 = C_6H_4X-4 (X = H, Me, Cl, Bu^t), C_6H_4OMe-3, 2-Th; R^3 = C_6H_4Y-4 (Y = H, Me, Br, NO_2)

nism involves the formation of a triazole intermediate through the condensation of azide at the C≡C triple bond of substrate **25**, which is followed by isomerization and cyclization of this triazole accompanied by elimination of a N_2 molecule giving target quinoline **26**.[34]

Other Cu-catalyzed processes, in which the triazole moiety remains intact, were also described in the literature. Thus, in the presence of CuI, the tandem cycloaddition of *ortho*-iodoanilino-substituted alkynes **27** and azides followed by the intramolecular Ullmann cyclization of intermediate **A** affords quinoline derivatives **28** containing the fused triazole ring (Scheme 9).[35]

Scheme 9

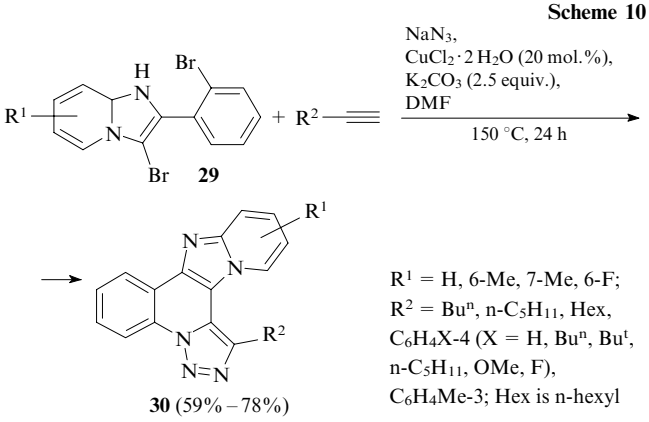


X = C=O, CH_2; R^1 = H, Me, Bn, All, Ac; R^2 = H, 3-Me, 4-Me, 4-OMe, 2-Cl, 4-Cl, 4-Br, 4-NO_2, 4-CO_2Et, 4-CN; R^3 = H, TBS; R^4 = Bu^n, All, Ph

Copper(II) chloride dihydrate promotes similar[35] tandem transformations of imidazo[1,2-*a*]pyridines **29**, aryl(alkyl)acetylenes and sodium azide that produce polycyclic structures **30** containing the quinoline moiety (Scheme 10).[36]

Not only copper salts[33,34] but also Pd,[37] Ru (see Ref. 38) and Rh (see Ref. 39) complexes can catalyze the reactions of imines with alkynes. The reactions of imidoyl chlorides **31** with terminal acetylenes afford quinoline derivatives **32** in the presence of the complex $Pd(PPh_3)_2Cl_2$,[37] as well as under UV radiation in the presence of 2 mol.% $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (bpy is bipyridine) (Scheme 11).[38] It should be noted that the latter reaction proceeds by a radical mechanism and produces 10%–20% of the minor regioisomer through the *ipso*-

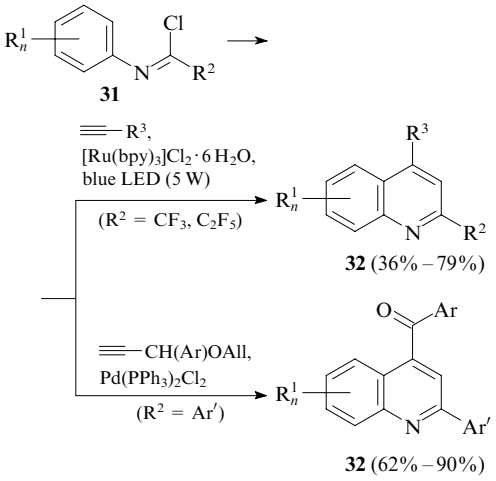
Scheme 10



30 (59%–78%)

cyclization of the vinyl radical, resulting in the formation of a spirocyclic intermediate.

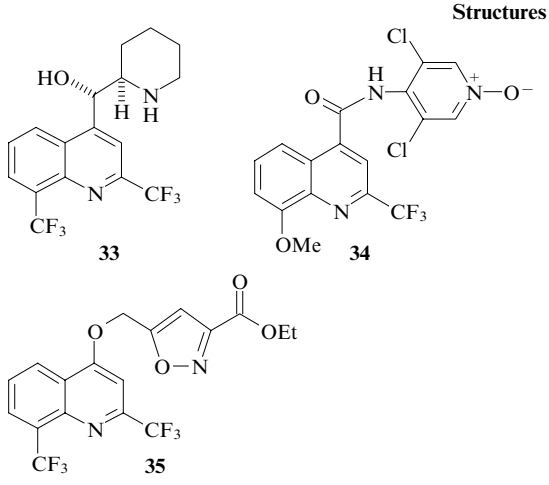
Scheme 11



R^1_n = H, 4-Me, 3-Me, 2-Me, 4-OMe, 2-Cl, 4-Cl, 4-CN, 4-CO_2Et, 2,4-Cl_2, 2,5-Me_2, 2,5-Cl_2, 2,5-$(OMe)_2$; R^2 = Ph, C_6H_4Me-4, C_6H_4Cl-4, CF_3, C_2F_5; R^3 = Ph, 3-Th, $C_6H_{5-n}X_n$ (X_n = 4-Me, 3-Me, 4-OMe, 4-CO_2Me, 4-F, 4-Cl, 4-Br, 2,4-Me_2); TMS, CH_2Bn; Ar = C_6H_4Y (Y = H, 3-Me, 4-Me, 2-OMe, 4-OMe, 4-Cl);
LED is light-emitting diode

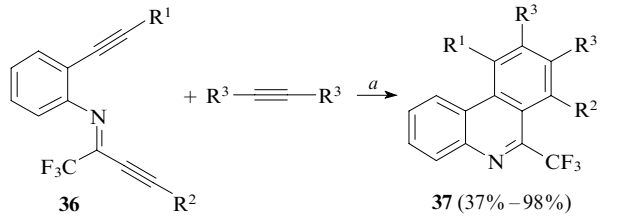
Such Ru-catalyzed reactions were applied to synthesize a library of 2-trifluoromethylquinolines **32**,[38] which are structurally similar to biologically active quinolines, in particular, to the antimalarial drug mefloquine (**33**). The compound SCH 351591 (**34**) is an efficient selective inhibitor of phosphodiesterase IV (the enzyme that catalyzes the hydrolysis of phosphodiester bonds). Compound **35** is used as an antituberculosis drug.

Structures 33–35



The rhodium complex $[Rh(PPh_3)_3Cl]$ was applied in the [2 + 2 + 2]-cycloaddition to form the benzene ring from two acetylene moieties of molecule **36** and the triple bond of alkyne in the synthesis of benzannulated 2-trifluoromethylquinolines **37** (Scheme 12).[39]

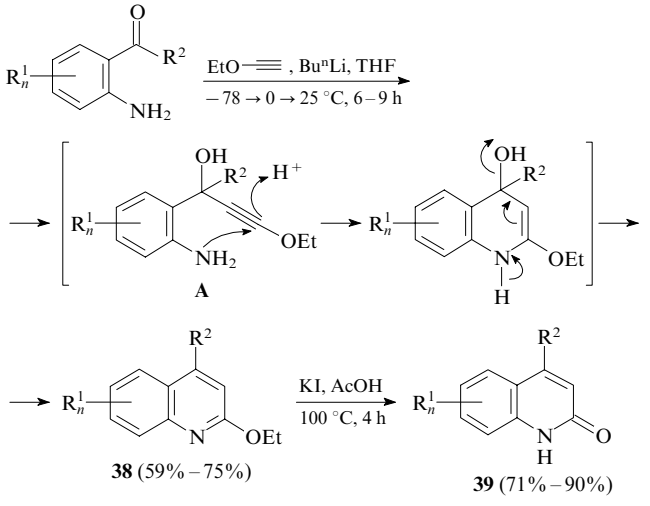
Scheme 12



R^1 = H, Bu^n, Ph; R^2 = Bu^n, Bu^t, Ph, C_6H_4X-4 (X = OMe, F, Cl, NO_2), C_6H_4Cl-2; R^3 = Et, CH_2OH, Ph, CO_2Me;
(*a*) $[Rh(PPh_3)_3Cl]$ (5 mol.%), PhMe, 90 °C, 2 h

2-Ethoxyquinolines **38** and quinolin-2-ones **39** were synthesized by the selective 6-*endo*-cycloizomerization of intermediate *o*-alkynylaniline **A** generated in the reaction of 2-aminoacetophenones with ethoxyacetylene (Scheme 13).[40]

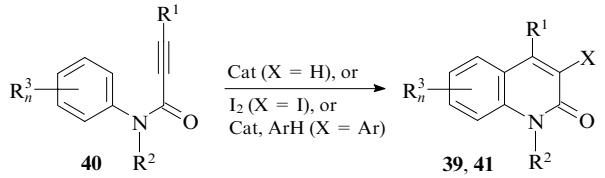
Scheme 13



R^1_n = H, 4-Cl, 4-NO_2, 3,4-$(OMe)_2$;
R^2 = H, Me, Ph, C_6H_4X-2 (X = F, Cl)

Another group of acetylene substrates, which can serve as the basis for the preparation of quinoline derivatives, includes acetylenecarboxylic acid amides. The intramolecular cyclization of amides **40** promoted by Pd complexes,[41–43] Au complexes,[44] Brønsted or Lewis acids[45–50] and acidic zeolites[45,46,50] affords substituted quinolin-2-ones **39** (X = H) in good yields (Scheme 14). Depending on the positions of the R^3 substituents, some reactions give mixtures of regioisomeric products. The reactions promoted by electrophilic reagents, for example I_2, produce 3-substituted quinolin-2-ones **41** (X = I).[51] In the presence of Pd catalysts, the aromatic C–H bonds can be activated simultaneously in compound **40** and in the additionally intro-

Scheme 14



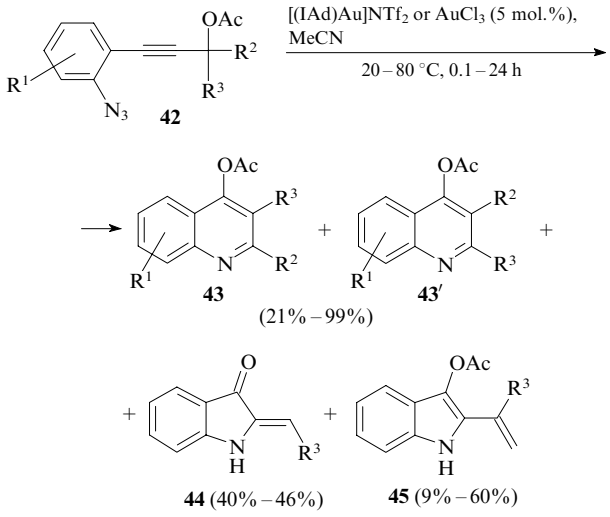
40 **39**, **41**

39: X = H; **41**: X = I, Ar;
R^1 = n-C_5H_{11}, C_6H_4Y-4 (Y = H, Me, OMe, Ac), C_6H_3Me-2-OMe-6, 2-MeO-1-naphthyl, 2-MOM-1-naphthyl (MOM is methoxymethyl); R^2 = H, Me, Bn, $CH_2C_6H_4$Z-4 (Z = Cl, CF_3); R^3_n = H, 2-Me, 3-Me, 4-Me, 3-F, 4-F, 4-Cl, 4-Br, 2-OMe, 3-OMe, 4-OMe, 4-Ac, 4-NO_2, 2,3-Me_2, 3,4-Me_2, 3,4-$(OMe)_2$, 3,5-$(OMe)_2$, 3,4-OCH_2O, 2,3-benzo, 3,4-benzo, *etc*.

duced arene molecule (PhH, PhMe), giving rise to 3-aryl-substituted quinolin-2-ones **41** (X = Ar).

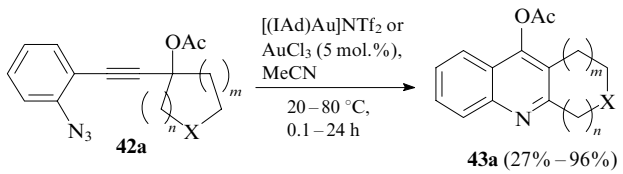
One more example of intramolecular cyclization of acetylenes has been considered.[52] This reaction promoted by Au^I and Au^{III} complexes results in the transformation of 2-alkynylaryl azides **42** into substituted quinolines **43** and **43′** (Scheme 15). The variation of the R^2 and R^3 substituents in the propargyl moiety can lead to the formation of side reaction products — indole derivatives **44** and **45**. If R^2 = H and R^3 = Ar, the reaction selectively affords quinoline **43′** and indole **44**; if R^2 = Me and R^3 = Ar, a mixture of quinolines **43**, **43′** and indole **45** is produced. The presence of a cyclic substituent in 2-alkynylaryl azides **42a** leads to

Scheme 15



42 **43** **43′** **44** (40%–46%) **45** (9%–60%)

R^1 = H, 4-Me, 6-Me, 4-OMe, 4-Cl, 4-CO_2Me, 5-CO_2Me, 5-CF_3;
R^2 = R^3 = Me; R^2 = H: R^3 = Ph, C_6H_4Cl-4, $C_6H_4NO_2$-4;
R^2 = Me: R^3 = CH_2Bn, CH_2All, CH=CH_2, $CH_2CH(OMe)_2$;
IAd is 1,3-bis(1-adamantyl)imidazole-based carbene



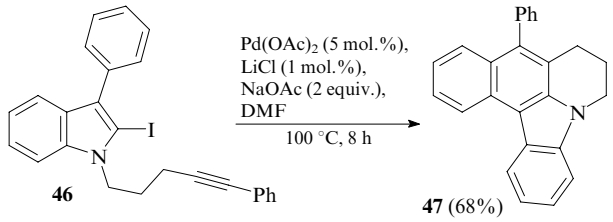
42a **43a** (27%–96%)

X = CH_2, NTs, O, C=O; *n* = 1, 2, 6; *m* = 0–2

the suppression of all side processes and the selective formation of quinolines **43a**.

The cyclization of indole **46** in the presence of palladium acetate gives rise to fused tetrahydroquinoline system **47** (Scheme 16).[53]

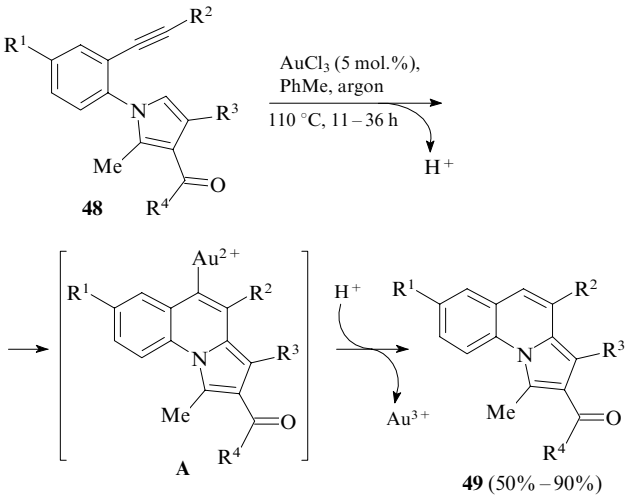
Scheme 16



46 **47** (68%)

The gold(III) chloride-catalyzed intramolecular alkenylation of the pyrrole moiety in compounds **48** affords pyrrolo[1,2-*a*]quinolines **49** (Scheme 17).[54] The resulting compounds have good fluorescence properties. The reaction mechanism involves the coordination of Au^{III} at the triple bond of alkyne **48** to form intermediate **A**, which is transformed into the final pyrroloquinoline.

Scheme 17



48 **A** **49** (50%–90%)

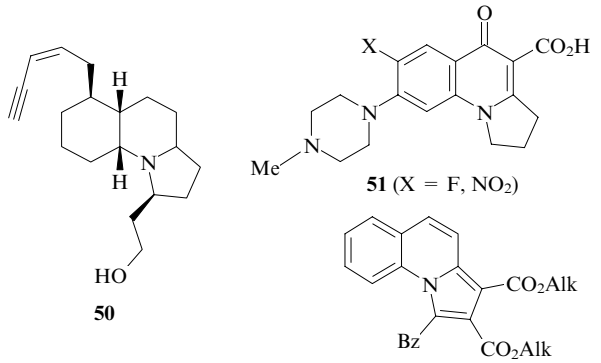
R^1 = H, Me, Cl; R^2 = Hex, Cy, C_6H_4X (X = H, 4-Me, 4-Br, 4-Cl, 4-CO_2Et, 3-NO_2); R^3 = C_6H_4Y-4 (Y = H, Cl, OMe), 2-Fu, 2-Th, 2-Naph; R^4 = Me, Ph, OEt; Fu is furyl, Naph is naphthyl

The pyrrolo[1,2-*a*]quinoline moiety is present in many naturally occurring products and pharmaceutical agents.[54] Gephyrotoxin (**50**) was isolated from the skin extracts of the frog *Dendrobates histrionics*. This compound is a muscarinic acetylcholine receptor antagonist. Pyrrolo[1,2-*a*]quinoline derivatives exhibit antitumour, antifungal and antibacterial activities (for example, compounds **51** and **52**).

Three-component reactions, in which simple and readily accessible reagents are used for the construction of the quinoline system, are of considerable interest. An example is the above-mentioned reaction of ethyl glyoxylate, terminal acetylene and aniline in the presence of copper triflate (see Scheme 7).[33]

Wang *et al.*[55] reported the $Cu(OTf)_2$-catalyzed three-component cascade transformation of diaryliodonium salts **53**, nitriles and alkynes into polysubstituted quinolines **54** (Scheme 18, the substituent locants refer to the products). The regioselective [2 + 2 + 2]-cyclization is promoted by

Structures 50 – 52



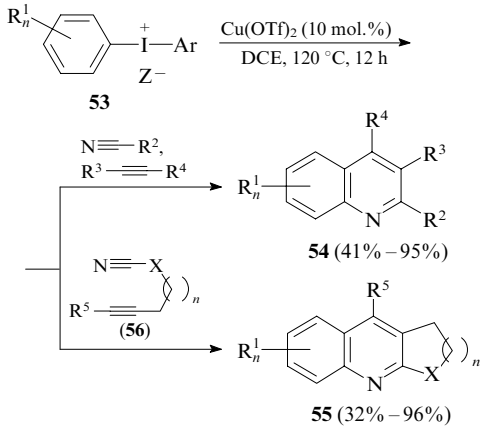
50

51 (X = F, NO_2)

52 (Alk = Me, Et)

copper complexes. In this reaction, the aryl group of diaryliodonium acts as a building block providing two carbon atoms (*ipso* and one of the *ortho* positions) to construct the quinoline core. The presence of substituents in the *meta* positions of the starting diaryliodonium **53** results in the formation of a mixture of two isomeric quinolines as the reaction products. The authors further developed this method by applying this catalytic system to synthesize quinolines **55** from diaryliodonium salts **53** and ω-cyanoalk-1-ynes **56** (see Scheme 18).[56] This synthetic strategy is suitable for the construction of tricyclic systems **55**, which are close structural analogues of biologically active natural products.

Scheme 18



53

54 (41% – 95%)

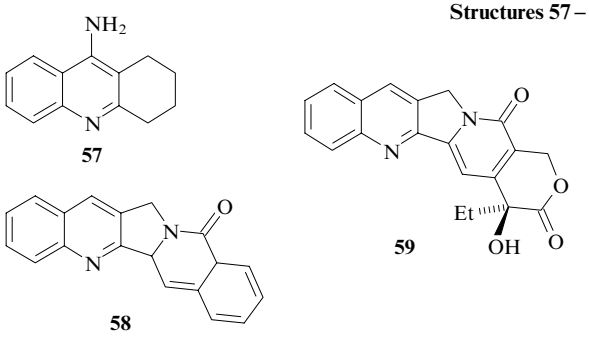
55 (32% – 96%)

Z = PF_6, OTf; X = S, CH_2; n = 1 – 4;
R^1_n = H, 5-Me, 6-Me, 7-Me, 8-Me, 5,8-Me_2, 6,8-Me_2, 6-F, 6-Cl, 6-CF_3;
R^2 = Me, Bu^n, CH=CH_2, Bn, Ph, C_6H_4Y-4 (Y = OMe, Br, CF_3), C_6H_4I-2; R^3 = H, Et, Ph, CO_2Et; R^4 = Me, Et, Ph, C_6H_4Me-4, C_6H_4F-4, *etc.*; R^5 = Br, Ph; DCE is dichloroethane

This method was applied to synthesize[56] tacrine (**57**), which is used for the treatment of Alzheimer's disease, as well as luotonin A (**58**) and camptothecin (**59**) — biologically active natural products that are able to inhibit topoisomerase I in the cancer cell leading to its death.

The condensation of aromatic aldehydes, anilines and terminal acetylenes in acidic media results in the generation of quinoline structures **60** (Scheme 19).[57 – 59] In the presence of a catalytic amount of TfOH (5 mol.%), the condensation of aniline with aldehyde gives imine. The protonation of the latter and the subsequent reaction of the intermediate cation

Structures 57 – 59



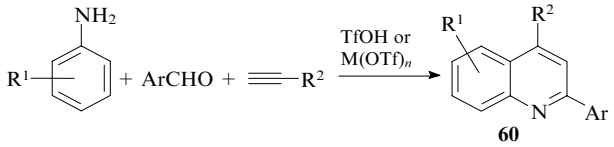
57

58

59

with alkyne followed by the intramolecular cyclization produce quinoline **60**.[57] Pericherla *et al.*[58] demonstrated that Lewis acids can act as catalysts in such three-component cascade reactions involving *p*-phenylenediamine, resulting in the formation of 6-benzylaminoquinolines **60** (R^1 = 6-NHBn). The elimination of the N-benzyl group affords 6-aminoquinoline derivatives **60**, which can serve as precursors for the synthesis of various practically valuable compounds. The use of ferrocenylacetylenes makes it possible to prepare 4-ferrocenylquinolines **60** (see Scheme 19).[59] This reaction is catalyzed by triflates of La, Y, Sc, Yb, Ce, Cu and Ag. The highest yield of the reaction products (75%) was achieved with cerium triflate $Ce(OTf)_3$.

Scheme 19

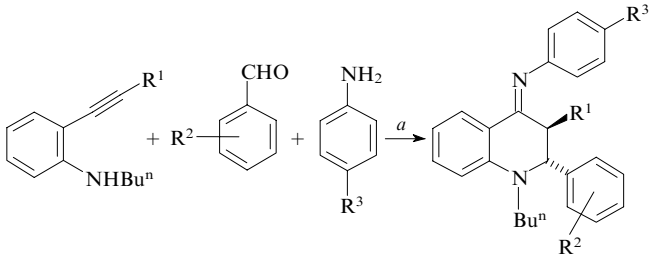


60

R^1 = H, 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 2-F, 2-Cl, 3-Cl, 3-NO_2, 4-NH_2; Ar = C_6H_4X-4 (X = H, Me, OMe, F, Cl, NO_2), C_6H_4Me-2, C_6H_4Br-3, $C_6H_2(OMe)_3$-3,4,5; R^2 = Pr^n, Ph, C_6H_4Me-4, Fc; M = Yb, La, Y, Sc, Ce, Cu, Ag; Fc is ferrocenyl

The reaction of *o*-alkynylanilines with aldehydes and amines in the presence of hexafluoroisopropanol (HFIP) and 4 Å molecular sieves (MS) results in the selective formation of 4-iminotetrahydroquinolines **61** (Scheme 20).[60]

Scheme 20



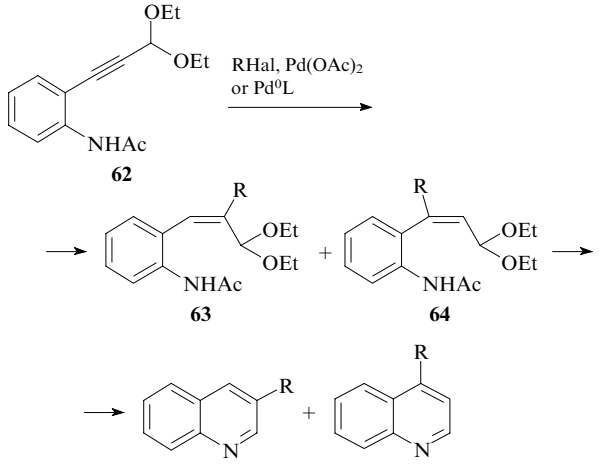
61 (32% – 80%)

R^1 = Bu^n, Ph; R^2 = H, 4-Me, 2-OMe, 3-OMe, 4-OMe, 4-F, 4-NO_2; R^3 = H, Me, OMe, F, Cl, CN, NO_2; (*a*) MS 4 Å, HFIP, 45 °C, 18 – 42 h

The $Pd(OAc)_2$-catalyzed reaction of *ortho*-alkynyl-substituted acetanilide **62** with iodoarenes or vinyl bromides was used to synthesize a mixture of 3- and 4-aryl(vinyl)-substituted quinolines (Scheme 21).[61] The initial step in

these transformations involves the hydroarylation or hydrovinylation of the triple bond of the starting anilide **62** promoted by a Pd catalyst to form regioisomeric intermediates **63** and **64**, which are transformed into quinolines containing substituents in positions 3 or 4. In continuation of this study,[61] the authors applied another catalytic system — the Pd^0 complex with (*E*,*E*,*E*)-1,6,11-tris(*p*-toluenesulfonyl)-3,8,13-triazacyclopentadecatriene (L) in the $[bmim]BF_4$ ionic liquid (bmim is 1-n-butyl-3-methylimidazolium) — to prepare quinolines.[62] An advantage of the latter method is that the Pd catalyst–ionic liquid system can be regenerated at least six times without a substantial loss of catalytic activity.

Scheme 21

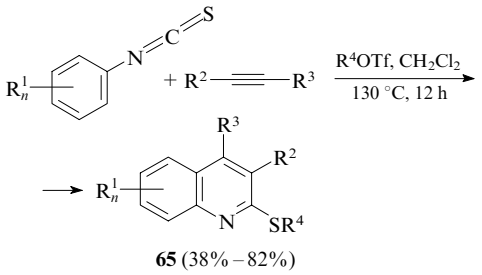


R = Ar, CH=CHPh, CH=CHTMS

Zhao *et al.*[63] described the three-component reaction involving aryl isothiocyanate, alkyne and alkyl triflate that gives rise to polysubstituted 2-alkylsuflanylquinolines **65** (Scheme 22). The S-alkylation of isocyanates with alkyl triflate takes place in the first step of this reaction.

The Brønsted acid TfOH (see Ref. 64) or Lewis acids [$InCl_3$, $InBr_3$, $In(OTf)_3$][65] promote the cyclization of 2-alkynylphenyl isothiocyanates to substituted quinoline-2-thiones **66**–**68** in the presence of arenes, aryl sulfides and benzenethiols (Scheme 23). The reaction mechanism involves the protonation of the isothiocyanate nitrogen atom and the triple bond to form a dication followed by the reaction of the latter with arene.[64] The distinguishing

Scheme 22



65 (38%–82%)

R^1_n = H, 3-Me, 4-OMe, 2,3-benzo, *etc.*; R^3 = Ph: R^2 = Me, Br, Ph, CO_2Et; R^2 = H: R^3 = Hex, C_6H_4F-4; R^2 = R^3 = Et; R^4 = Me, Et, $(CH_2)_3Cl$

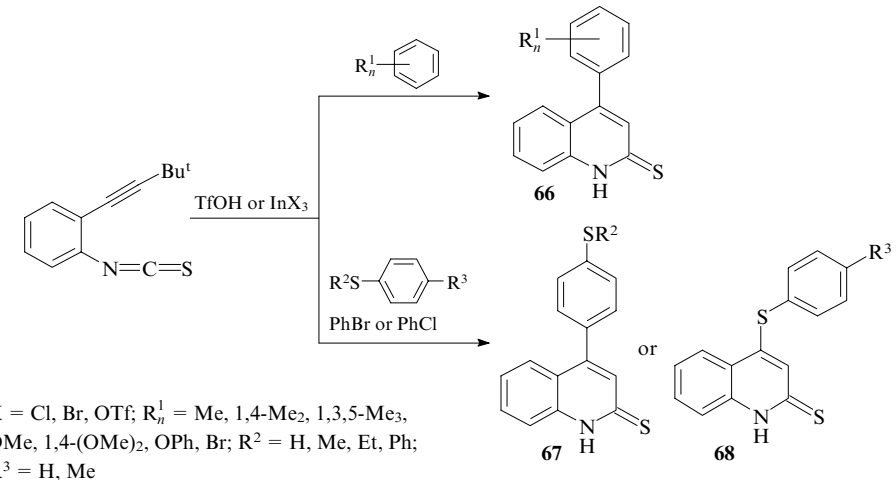
features of the reactions using In^{III} salts[65] as compared to TfOH[64] are that they proceed at rather high temperatures (up to 200 °C) and take a long time to be completed (up to 60 h). Otani *et al.*[65] showed that aryl sulfides and benzenethiols react with isothiocyanates to form quinoline-2-thiones **67** or arylsulfanylquinoline-2-thiones **68** depending on the electronic properties of the R^2 and R^3 substituents.

One other interesting method of synthesis of 2-sulfanyl-substituted quinolines is based on the reaction of aryl isothiocyanates with radical species **69** (Scheme 24).[66] Aryl radical **69** is generated *in situ* by gradually adding diazonium tetrafluoroborate **70** to a heated mixture of a base and the appropriate isothiocyanate. The ratio of isomeric quinolines **71** and **72** is determined by the nature of the R^2 substituent. Thus, the percentage of compound **72** increases with increasing electron-withdrawing properties of this substituent.

o-Ethynylphenyl isocyanides **73** undergo free-radical cyclization[67] accompanied by the competitive formation of 6-*endo*-*dig*- (**74**) and 5-*exo*-*dig*-cyclization (**75**) products (Scheme 25) and react with alcohols in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to give 2-alkoxy(aroxy)-3-substituted quinolines **76**.[68]

The six-membered heterocyclic moiety of the quinoline system can also be constructed by the intermolecular condensation of *o*-ethynylanilines (which can also be synthesized by the Sonogashira coupling of *o*-iodoanilines with alkynes) with isocyanides,[69] carbon monoxide[70,71] or carbon dioxide.[72] The C atom of carbon oxides is involved in the final quinoline structure as the C(2) atom.

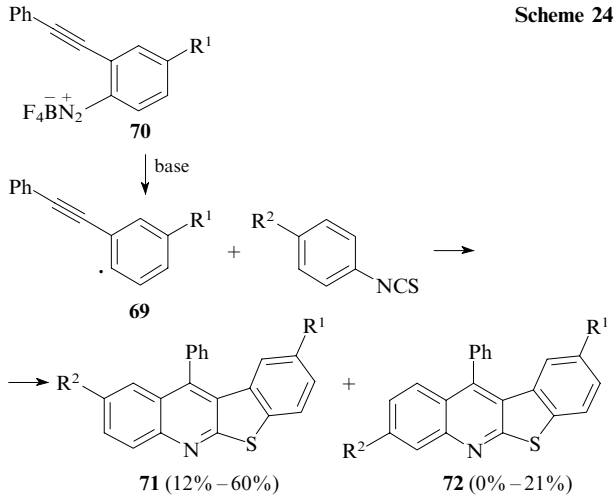
Scheme 23



X = Cl, Br, OTf; R^1_n = Me, 1,4-Me_2, 1,3,5-Me_3, OMe, 1,4-$(OMe)_2$, OPh, Br; R^2 = H, Me, Et, Ph; R^3 = H, Me

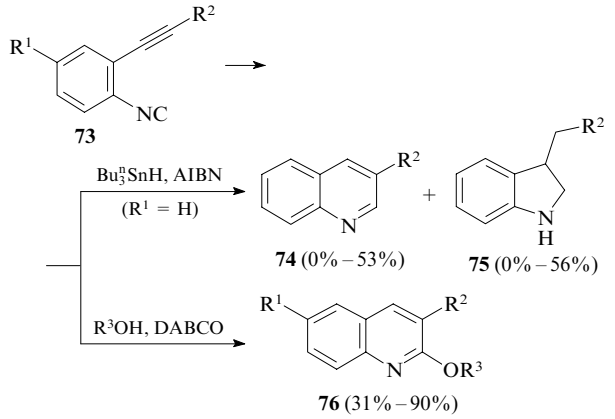
R^2	R^3	Product	Yield (%)
Me	H	**68**	31–67
Et	H	**68**	55
Ph	H	**67**	61
Me	Me	**68**	53
H	H	**68**	64–72
H	Me	**68**	75

Scheme 24



R^1 = H, CN; R^2 = H, Me, OMe, Cl, CN

Scheme 25



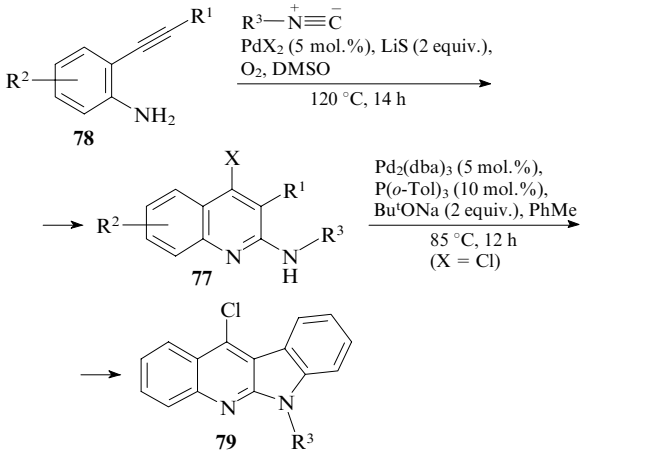
R^1 = H, Me, Cl; R^2 = H, Bu^n, Bu^t, Ph, C_6H_4Me-4, C_6H_4OMe-4, C_6H_4Cl-3, C_6H_4Ac-4, TMS, CH_2OBn; R^3 = Et, Pr^n, Pr^i, Bu^i, n-C_5H_{11}, Cy, Bn, $CH_2C{\equiv}CH$, Ph, C_6H_4Cl-2, C_6H_4Me-2, $C_6H_4Bu^t$-2, 2-Py, *etc.*; AIBN is azobis(isobutyronitrile)

Liu *et al.*[69] developed the regioselective synthesis of 2-amino-4-haloquinolines **77** in good yields. This method is based on the Pd-catalyzed intermolecular aerobic oxidative cyclization of *o*-ethynylanilines **78** with isocyanides (Scheme 26). The authors extended the scope of this reaction and synthesized indolo[2,3-*b*]quinolines **79** from compounds **77** (X = Cl, $R^1 = C_6H_4Br$-2, R^2 = H) using an additional step — the intramolecular Buchwald–Hartwig cross-coupling. Indolo[2,3-*b*]quinoline moieties are present in numerous naturally occurring drugs.[69]

o-Iodoaniline derivatives **80** react with terminal and internal alkynes and CO in the presence of a catalytic amount of palladium acetate to form a mixture of regioisomeric quinolin-2-ones (Scheme 27).[70,71] The reactions using unsymmetrical alkynes give mixtures of regioisomers and proceed with low regioselectivity.[71] Regioisomers containing a bulkier substituent in position 3 of the quinoline system are generated as the major products.[70,71]

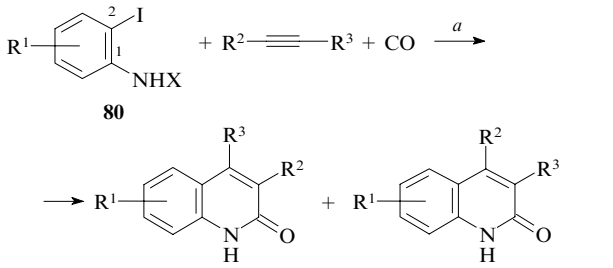
Silver complexes can also catalyze the formation of the quinolone system (Scheme 28). Thus, intermediate benzoxazin-2-ones **A** are generated from *o*-ethynylanilines **78** and carbon dioxide under atmospheric pressure in mild condi-

Scheme 26



R^1 = Ph, C_6H_4Y (Y = 4-Me, 4-OMe, 4-Et, 2-Cl, 3-Cl, 4-Cl, 4-CF_3, 4-NO_2, *etc.*), 2-Th, Hex, TMS, $SiPr^i_3$, C(OH)PhMe, CPh_2OH, *etc.*; R^2 = H, 4-Me, 4-F, 4-Cl, 5-Cl, 4-Br, 4-CF_3, 4-CO_2Me, *etc.*; R^3 = Pr^i, Bu^n, Bu^t, Hex, Bn, C_6H_4OMe-4, $C_6H_3Me_2$-2,6, CH_2CO_2Et, *etc.*; X = Cl, Br; dba is dibenzylideneacetone, *o*-Tol = C_6H_4Me-2

Scheme 27



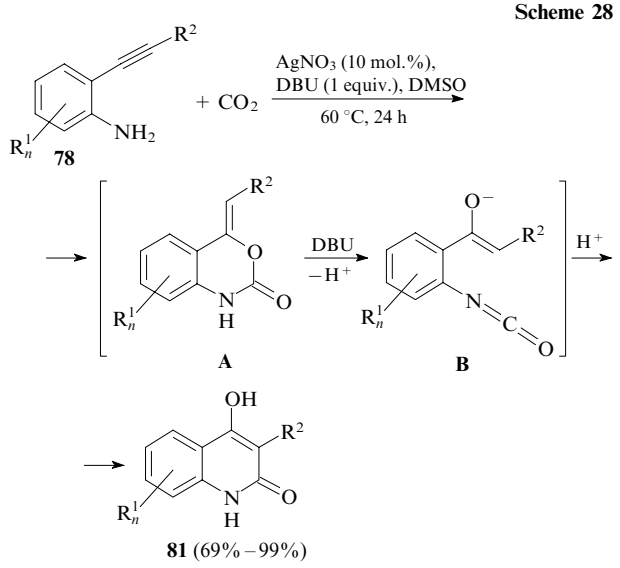
X = H, Me, Tf, Ac, CHO, Ts, C(O)NMe_2, Ms, $C(O)CF_3$, CO_2Et, CO_2Bu^t; R^1 = H, 4-OMe, 5-OMe, 4-NO_2, 4-CO_2Me; R^2 = R^3 = Pr^n, Ph, CH_2OH, CH_2OBn; R^2 = Ph: R^3 = Me, Et, Bu^t, CH_2OH, CH_2OMe; R^2 = Me: R^3 = Bu^t, TMS; R^3 = Bu^n: R^2 = C_6H_4OMe-2, pyrimidin-5-yl; R^2 = Et, R^3 = Ac; (*a*) 1) $Pd(OAc)_2$ (5 mol.%), PyH (2 equiv.), Bu^n_4NCl (1 equiv.), DMF, 100 °C, 12 h; 2) NaOH, EtOH, 20 °C, 30 min

tions in the presence of $AgNO_3$ as the catalyst.[72] In the presence of a base (1,8-diazabicycloundec-7-ene, DBU), benzoxazinones **A** undergo deprotonation. Subsequent transformations of the isocyanate moiety of anionic intermediates **B** afford 4-hydroxyquinolin-2-ones **81**.

Substituted quinolines **82** can be synthesized by the $Pd(OAc)_2$-catalyzed reaction of *o*-iodoaniline (**80a**) with alkyne diamine **83** (molar ratio 1 : 3) (Scheme 29).[73] In order to examine the scope of this reaction, amines **84** were used instead of diamine **83**, resulting in the synthesis of a series of 4-substituted (**85**) and 2,3,4-trisubstituted quinolines (**86**). Two molecules of aminoalkynes **84** are involved in the formation of structures **86**.[73]

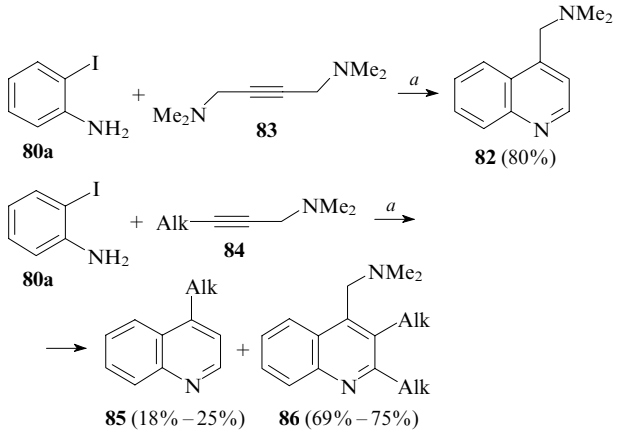
Apart from the above-considered approaches,[70–73] there are other Pd-catalyzed methods of synthesis of substituted quinolines from iodoanilines. In the presence of the $Pd(PPh_3)_2Cl_2$–CuI system and an aqueous solution of tetrabutylammonium hydroxide (TBAOH), the Sonogashira cross-coupling of *o*-iodoaniline (**80a**) with terminal alkynes **87** affords 2-substituted quinolines **88**

Scheme 28



R^1_n = H, 4-Me, 5-Me, 6-Me, 4-F, 4-Cl, 4-CF_3, 5,6-benzo; R^2 = H, Bu^n, Ph, 1-Naph, C_6H_4OMe-4, $C_6H_4NO_2$-4, $C_6H_4CF_3$-3, 2-Py, Bz

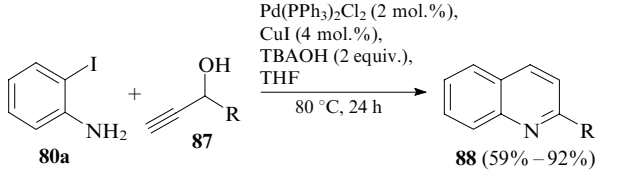
Scheme 29



Alk = Bu^n, n-C_5H_{11}, n-C_8H_{17}; (*a*) $Pd(OAc)_2$ (5 mol.%–10 mol.%), K_2CO_3 (2–5 equiv.), LiCl, DMF, 100 °C, 20 h

(Scheme 30).[74] First, the Sonogashira reaction of iodoaniline with alkyne **87** gives 1-aryl-3-(2-aminophenyl)prop-2-yn-1-ol, which is isomerized to allenol. The latter undergoes cyclodehydrogenation to quinoline **88**.

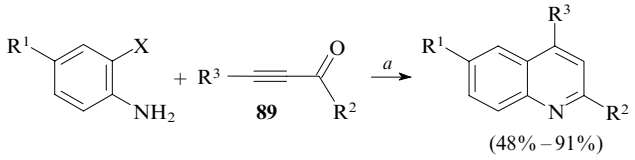
Scheme 30



R = Ph, C_6H_4X (X = 2-Me, 3-Me, 4-Me, 4-Cl, 4-F, 2-OMe, 3-OMe, 4-OMe, *etc.*), 2-Th, 2-Naph

Like palladium compounds,[70, 71, 73, 74] the nickel complex Ni(dppe)Br_2 [dppe is bis(diphenylphosphino)ethane] catalyzes the reaction of *o*-haloanilines with propynyl ketones **89** producing 2,4-substituted quinolines (Scheme 31).[75] An important prerequisite for this reaction is the presence of metallic zinc, which reduces Ni^{II} to Ni^0.

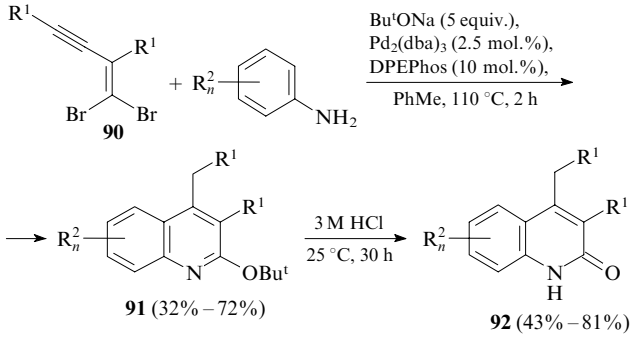
Scheme 31



X = I, Br; R^1 = H, Me, Cl, CF_3; R^2, R^3 = Alk, Ar; (*a*) Ni(dppe)Br_2 (5 mol.%), Zn (2 equiv.), MeCN, N_2, 80 °C, 12 h

Meng *et al.*[76] developed a method for the synthesis of quinolines based on the reaction of *gem*-dibromoenynes **90** with anilines (Scheme 32). This reaction produces a mixture of 2-*tert*-butoxyquinolines **91** and a small amount of their hydrolysis products — quinolin-2-ones **92**. The authors transformed compounds **91** into quinolinones **92** by treating the reaction mixture with 3M HCl for 30 min at room temperature.

Scheme 32

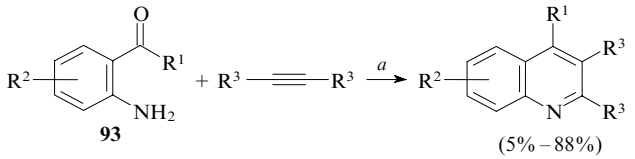


R^1 = Pr^n, Bu^n, Hex; R^2_n = H, 2-Pr^i, 4-Bn, 2-Ph, 2-OMe, 4-OMe, 4-F, 2,3-benzo, 2,5-$(OMe)_2$, 3,5-$(OMe)_2$, *etc.*; DPEPhos = $(2\text{-}Ph_2PC_6H_4)_2O$

The reaction of amines with diarylacetylenes promoted by Pd complexes affords indolo[1,2-*f*]phenanthridines, which are structurally similar to the natural alkaloids manitidine, fagaronine and coralyne possessing antitumour activity.[77]

Recently, a one-pot method was developed for the synthesis of polysubstituted quinolines from aromatic ketones **93** containing the 2-amino group and alkynes in the presence of a Pd catalyst (Scheme 33).[78] Dialkylacetylenes are not involved in this reaction.

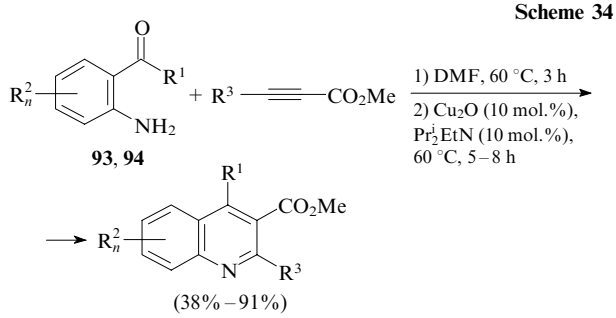
Scheme 33



R^1 = Alk, Ar, CH=CHPh; R^2 = H, 3-Me, 4-F, 5-F, 5-Cl, 5-NO_2, R^3 = CO_2Alk, Ar; (*a*) $PdBr_2$ (5 mol.%), AcOH or PivOH, PhCN, CH_2Cl_2, 130 °C, 18 h; Piv is pivaloyl

Copper(I) oxide promotes the one-pot two-step cyclization of ketones **93** and related aldehydes **94** with methyl alkynoates giving substituted quinolines (Scheme 34).[79]

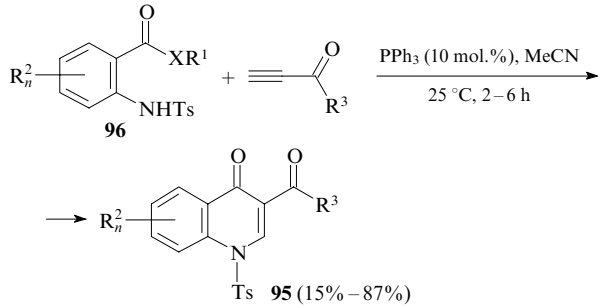
Scheme 34



R^1 = H (**94**), Alk, Ar (**93**); R^2_n = H, 5-Cl, 5-Br, 5-NO_2, 3-OMe, 4,5-OCH_2O; R^3 = CF_3, C_2F_5, Alk

Khong and Kwon[80] described a procedure for the synthesis of 3-substituted quinolin-4-ones **95** by the condensation of aminobenzoic acid derivatives **96** with terminal alkynones (Scheme 35). This approach is suitable for the synthesis of compounds **95** structurally similar to ciprofloxacin and levofloxacin — powerful quinolone-based antibiotics.

Scheme 35

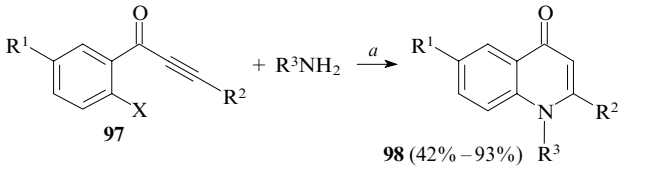


X = S, O; R^1 = Alk, Ar; R^2_n = H, 5-Me, 5-OMe, 5-F, 5-Br, 5-I, 4,5-$(OMe)_2$; R^3 = OAlk, Ar, 2-Th

The reaction of *o*-halogen-substituted aryl alkynyl ketones **97** with primary amines produces 2-substituted quinolin-4-ones **98** (Scheme 36).[81]

Alkynes can react, apart from anilines, with guanidine[82–84] and urea.[85] The reaction of guanidine with

Scheme 36

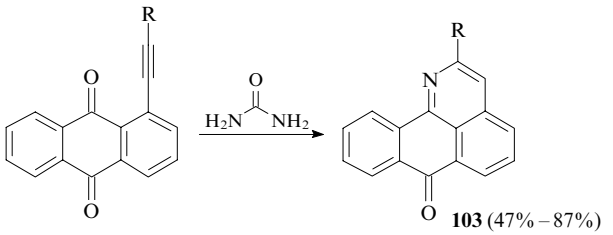


X = Br, Cl; R^1 = H, Br; R^2 = Ph, C_6H_4Y-4 (Y = Et, OMe, F, Cl), 3-Py; R^3 = Alk, Ar, 1-Naph, pyrimidin-5-yl; (*a*) $Pd(dba)_3$ (5 mol.%), PPh_3 (10 mol.%), K_2CO_3 (2 equiv.), dioxane, N_2, 99 °C, 3–36 h

1-ethynyl-9,10-anthraquinone under reflux in butanol gives a mixture of different products depending on the nature of the R substituent (Scheme 37).[82–84] Multistep transformations, which involve the addition, elimination, cyclization and dehydrocyclization, afford quinoline-containing fused structures **99a–c** and compounds **100–102** (see Scheme 37). Possible mechanisms of the formation of molecules **99–102** were proposed and discussed in detail.[82–84] The effect of electron-donating and electron-withdrawing substituents at the C≡C triple bond on the competitive addition of guanidine and the cyclization to the final products was examined.

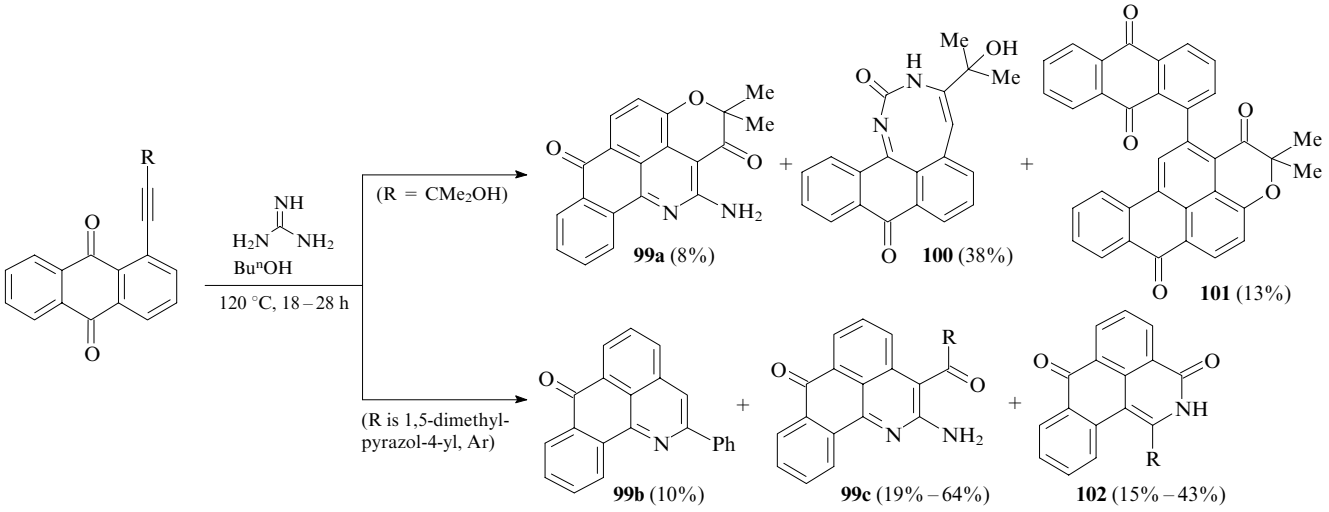
As opposed to guanidine,[82–84] the cyclization of 1-ethynyl-9,10-anthraquinones with urea proceeds selectively to give the only compound **103** (Scheme 38).[85] This reaction is performed in molten urea without solvents and cocatalysts.

Scheme 38

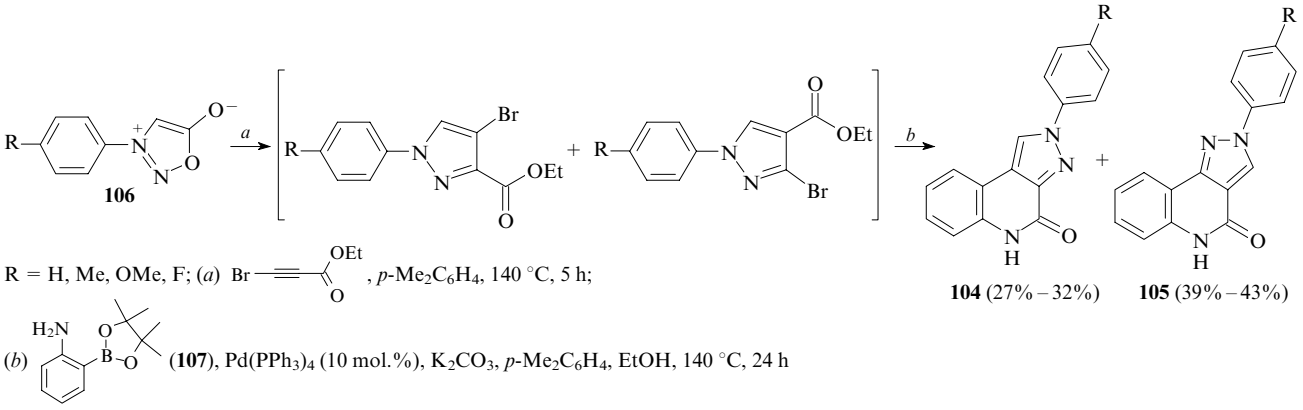


R = CMe_2OH, CH_2OPh, Alk, Ar, 2-Py

Scheme 37



Scheme 39

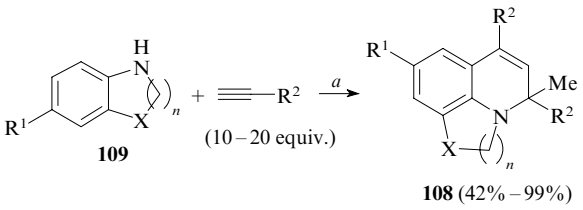


Chang *et al.*[86] proposed a one-pot synthesis of regioisomeric arylpyrazoloquinolin-2-ones **104** and **105** using the $Pd(PPh_3)_4$-promoted reaction of 3-arylsydnones **106**, ethyl 3-bromopropionate and pinacolyl 2-aminophenylboronate (**107**) (Scheme 39). The cycloaddition of sydnone **106** to 3-bromopropionate affords isomeric pyrazoles followed by the arylation of the pyrazole ring at position 3 or 4 *via* the Suzuki cross-coupling with ester **107**. The subsequent intramolecular cyclization yields pyrazolo[3,4-*c*]- (**104**) and pyrazolo[4,3-*c*]quinolinones (**105**).

Quinolinones **104** are powerful and selective bovine adenosine A_1 and A_{2A} receptor antagonists and cloned human A_1 receptor antagonists.[86] Their structural isomers **105** are also strong selective adenosine A_3 receptor antagonists. The biological activity of the pyrazoloquinoline structure towords the central nervous system and a series of peripheral systems has been extensively investigated.[86]

Yi *et al.*[87] described the application of the $Ru_3(CO)_{12} - NH_4PF_6$ catalytic system in the synthesis of dihydroquinolines **108** from five- and six-membered heterocycles **109**, which are fused to the benzene system, and terminal acetylenes (Scheme 40). The reactions with internal or sterically crowded terminal alkynes do not produce appropriate quinoline derivatives.

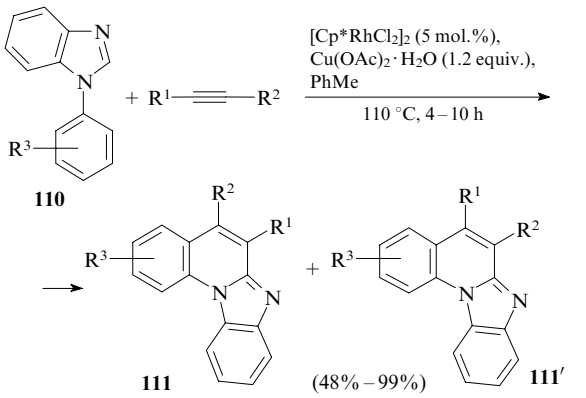
Scheme 40



N-Arylbenzimidazoles **110** can react with acetylenes in the presence of rhodium(III) complexes to form fused quinolines, the reaction with unsymmetrical internal alkynes giving a mixture of regioisomers **111** and **111′** (Scheme 41).[88]

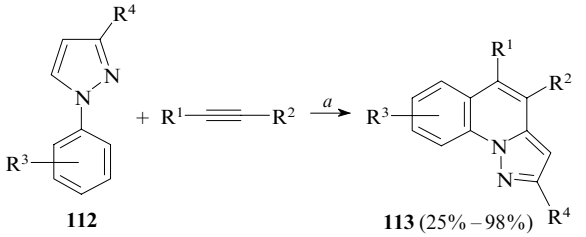
Not only *N*-arylbenzimidazoles[88] but also *N*-arylpyrazoles **112** can react with alkynes to give substituted pyrazoloquinolines **113** (Scheme 42).[89] These transformations are catalyzed by the complex $[Cp^*RhCl_2]_2$ in the presence of

Scheme 41



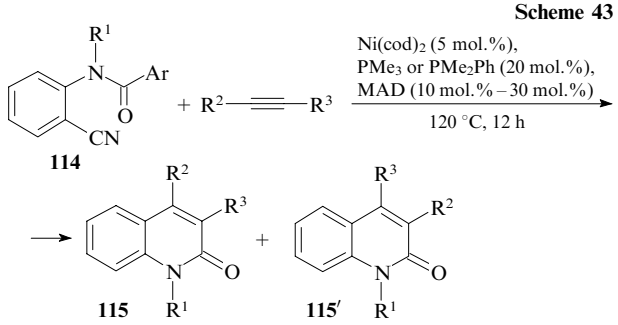
sodium carbonate. In the absence of the base, the yield of pyrazoloquinolines **113** is < 10%. The reactions with compounds containing the R^3 substituent in the *meta* position of the aryl moiety produce mixtures of isomers depending on which of the *ortho* positions of the aromatic ring is involved in the reaction.

Scheme 42



In the presence of the $Ni(cod)_2$ – MAD catalytic system [cod is cycloocta-1,5-diene, MAD is methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)], the reactions of *o*-cyanophenylbenzamides **114** with internal alkynes produce quinolin-2-ones **115** (Scheme 43).[90] Unsymmetrical

Scheme 43



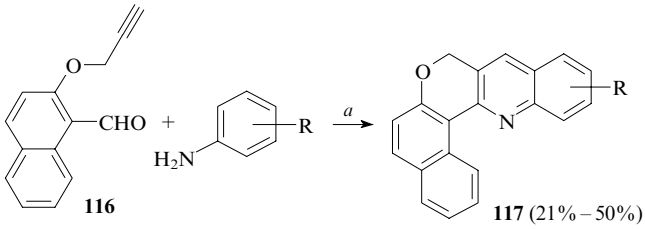
114 → **115** + **115′**

R^1 = Me, C_6H_4X-4 (X = H, OMe, CF_3), Bn;
R^2 = R^3 = Me, Pr^n, Ph; R^2 = Me: R^3 = Pr^i, Bu^t, n-C_5H_{11}, TMS;
R^2 = Pr^n: R^3 = $(CH_2)_2OMe$, Ph; R^2 = Et, R^3 = C(=CH_2)Me;
R^2 = TMS, R^3 = C≡CTMS

acetylene compounds give a mixture of products **115** and **115′**, with the isomer containing a sterically bulkier substituent (Pr^i, Pr^n, Bu^t, Ph) in position 4 of the quinolinone system predominating.

The copper(I) chloride-promoted imino Diels–Alder reaction of 2-(propargyloxy)-1-naphthaldehyde **116** with monosubstituted anilines yields chromenoquinolines **117** (Scheme 44).[91]

Scheme 44

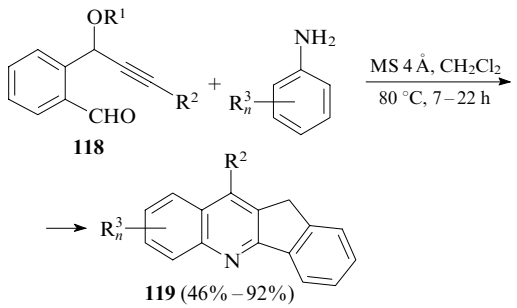


116 → **117** (21%–50%)

R = 2-NHBoc, 3-NHBoc, 4-NO_2; Boc = C(O)OBu^t;
(*a*) CuCl (30 mol.%), DMF, 100 °C, 6 h

o-Propargylbenzaldehydes **118** are subjected to condensation with anilines in the presence of 4 Å molecular sieves to form indeno[1,2-*b*]quinolines **119** (Scheme 45).[92]

Scheme 45



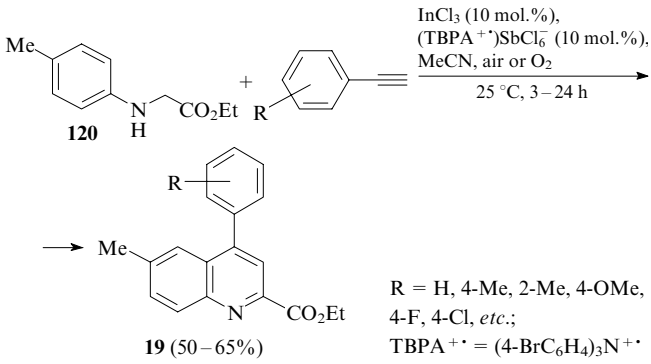
118 → **119** (46%–92%)

R^1 = Piv, Bz; R^2 = Bu^n, cyclo-C_3H_5,
C_4H_6X-4 (X = H, OMe, Cl), 2-Th; R^3_n = H, 2-Pr^i, 4-Bu^t, 2-F, 4-F, 4-Cl, 4-Br, 2-I, 4-CF_3, 4-OMe, 4-CO_2Me, 2,3-benzo

Alkynes are involved in the catalytic radical reaction with the *N*-(*p*-tolyl) derivative of glycine **120** to form quinoline structures **19** (Scheme 46).[93]

The Pd-catalyzed reactions provide a facile, efficient and most commonly used approach to the synthesis of quinoline derivatives. Despite considerable advances in the development of these methods, some problems remain to be addressed. Thus, it is desirable to regenerate an expensive catalyst, particularly for scaled-up processes. Besides, many reactions require an inert atmosphere and absolute solvents. In the above-analyzed studies, examples of regeneration of the catalyst using ionic liquids were reported.[43] In some studies, aqueous reaction solutions were used,[74] which makes the synthesis much cheaper. However, such investigations are scarce because these approaches are limited by the range of the starting compounds and, correspondingly, they can be used to synthesize only particular reaction products.

Scheme 46



120 → **19** (50–65%)

R = H, 4-Me, 2-Me, 4-OMe, 4-F, 4-Cl, *etc.*;
$TBPA^{+\bullet}$ = $(4\text{-}BrC_6H_4)_3N^{+\bullet}$

An analysis of published data on metal-catalyzed methods of synthesis of quinolines and their derivatives shows that, apart from traditional Pd- and Pt-based catalytic systems, catalysts based on Ru, Rh, Au, Ag, Ni and Cu complexes have been extensively used in recent years. Of particular note are copper complexes, which often can serve as an efficient alternative to Pd catalysts.[18] Meanwhile, the application of Brønsted or Lewis acids holds great promise for the formation of the quinoline system not only based on the intramolecular cyclization of alkynylamines,[22,24,25,27,28] amides[45–50] or isocyanates[63–65] but also *via* the intermolecular condensation of such simple compounds as aldehydes, anilines and terminal acetylenes.[57–59] Of particular interest are methods based on heterogeneous catalysis using acidic zeolites[45,46,50] or molecular sieves,[60,92] which allow for the repeated regeneration of the catalyst.

III. Synthesis of isoquinoline derivatives

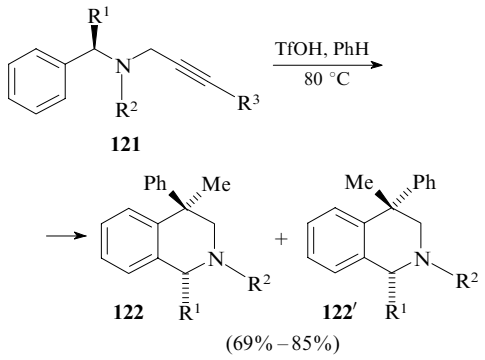
Benzylamines, arylnitriles, benzoic acid amides, imines or oximes of aromatic aldehydes and ketones are most commonly employed as the nitrogen-containing component for the construction of the isoquinoline moiety.

Propargyl-substituted benzylamines **121** undergo TfOH-promoted intramolecular cyclization accompanied by the addition of one benzene molecule to form diastereomeric tetrahydroisoquinolines **122** and **122′** (Scheme 47).[94]

Palladium complexes can catalyze the regio- and stereoselective 6-*exo*-*dig* cyclization of benzylamines **123** to polysubstituted 1,2,3,4-tetrahydroisoquinolines **124** (Scheme 48).[95]

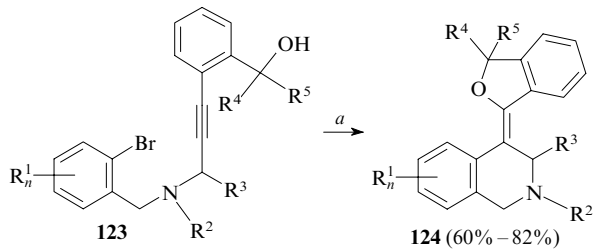
The Lewis acids $FeCl_3$ and $Yb(OTf)_3$ promote the Friedel–Crafts cyclization of amino-substituted propargyl

Scheme 47



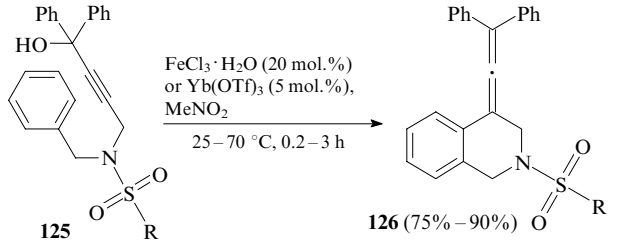
R^1, R^2 = H, Me; R^3 = H, TMS

Scheme 48



R^1_n = H, 4,5-$(OMe)_2$; R^2 = Bn, $CH_2C_6H_4Me$-4;
R^3 = H, C_6H_4X-4 (X = Me, OMe, Cl), 1-Naph, 2-Th, 3-Fu, 9-ethyl-9*H*-carbazol-3-yl, 3-fluorenyl; R^4 = R^5 = H, Et;
R^4 = H: R^5 = Et, Ph, C_6H_4Me-4; (*a*) $Pd(PPh_3)_4$ (10 mol.%), K_2CO_3 (5 equiv.), DMF, 100 °C, 0.5–3 h

Scheme 49



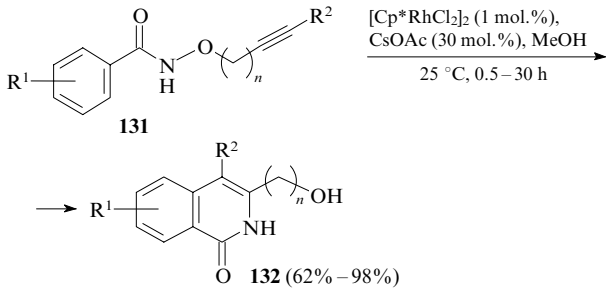
R = Me, C_6H_4X-4 (X = H, Cl, Br, NO_2)

alcohols **125** giving tetrahydroisoquinolines **126** (Scheme 49).[96]

Benzylamines can also be subjected to intermolecular reactions with acetylenes. Villuendas and Urriolabeitia[97] described the Ru-catalyzed two-component synthesis of isoquinolines **127** from benzylamines **128** and internal alkynes (Scheme 50). The reactions using unsymmetrical acetylenes produce mixtures of isomeric products **127** and **127′**, with the regioisomer containing a bulkier substituent in position 3 of the heterocyclic system predominating. In some cases, the reactions with diethylacetylene gave isoquinoline **127** (**127′**) along with side products **129**. In the presence of a strong electron-withdrawing group (R^1_n = 4-NO_2, 4-CF_3, 4-Cl) in the *para* position of the starting benzylamine, the amount of the side products increased to 20%. The reactions with arylacetylenes resulted in the insertion of two alkyne molecules to form products **130**. It should be noted that the reaction was regioselective if R^3 = Me and R^4 = Ph.

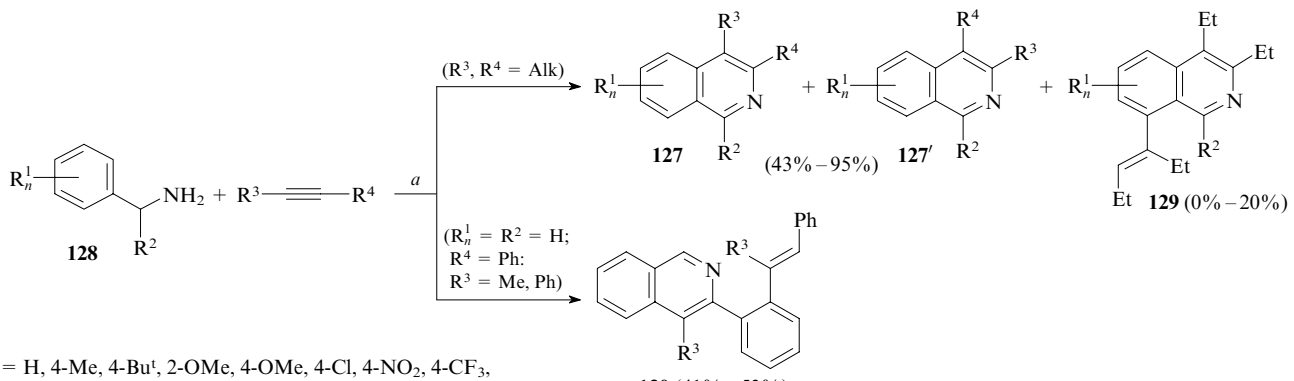
The Rh^{III}-catalyzed annulation of alkynyloxybenzamides **131** produces isoquinolones **132** (Scheme 51).[98] This reaction is distinguished from the whole series of related procedures by rather mild conditions: room temperature, low catalyst loading (1 mol.%) and short reaction time. Xu *et al.*[98] applied this procedure to prepare the natural alkaloids (±)-antofine (**133a**), (±)-tylophorine (**133b**) and rosettacin (**134**) with a broad spectrum of pharmacological activities.

Scheme 51



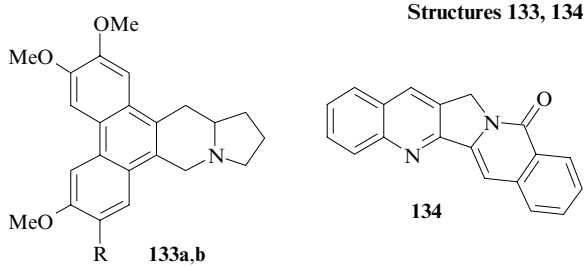
R^1 = H, 4-Me, 4-OMe, 4-Cl, 4-CF_3, 4-CN, 4-NO_2, 2-Me, 2-Br, 3-Me, 3-CO_2Me; R^2 = Me, TMS, Ph, C_6H_4OMe-4, C_6H_4Cl-4; *n* = 2–4

Scheme 50



R^1_n = H, 4-Me, 4-Bu^t, 2-OMe, 4-OMe, 4-Cl, 4-NO_2, 4-CF_3, 3,5-$(OMe)_2$, 3,4-$(OMe)_2$, 2,3-benzo, 3,4-benzo; R^2 = H, Me;
R^3 = R^4 = Et, Ph; R^3 = Me: R^4 = Pr^n, Bu^t, Ph;
(*a*) [Ru(*p*-cymene)Cl_2]$_2$ (10 mol.%), $Cu(OAc)_2$ (1 equiv.), KPF_6 (10 mol.%), MeOH, 100 °C, 6–24 h

Structures 133, 134

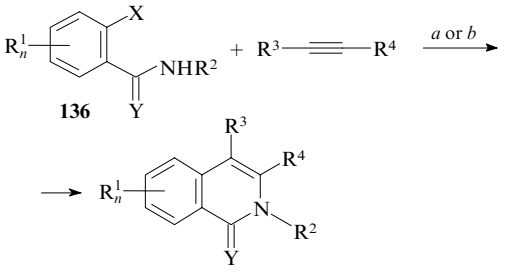


133a,b **134**

R = H (**a**), OMe (**b**)

Larock *et al.*[99] developed a procedure for the synthesis of dihydroisoquinolines **135** based on the $Pd(OAc)_2$-catalyzed cyclization of *N*-(*o*-iodobenzyl)acetamide **136** (Y = 2H, R^2 = Ac) with internal alkynes (Scheme 52). Acetylenes containing the phenyl or ethoxycarbonyl group give compounds **135** in higher yields (80%–83%) compared to methyl- and formyl-substituted alkynes (56%–62%). 2-Halobenzamides (Y = O) undergo similar cyclization to isoquinolin-1-ones **135** in the reaction with acetylenes catalyzed by nickel complexes (see Scheme 52).[100]

Scheme 52

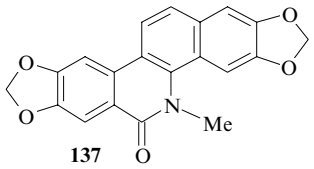


136 **135** (56%–92%)

Y = 2H, X = I, R^2 = Ac, R^1_n = H; Y = O: X = Cl, Br, I; R^1_n = H, 4-Cl, 5-OMe, 4,5-$(OMe)_2$; R^2 = H, Me, Pr^n, Bn, All, Ph, C_6H_4Me-4; R^3 = R^4 = H, Pr^n, Ph, CH_2OMe; R^3 = Ph: R^4 = H, Me, Et, CHO, Ac, CO_2Et; (*a*) $Pd(OAc)_2$ (5 mol.%), LiCl or Bu^n_4NCl (1 equiv.), base (1–2 equiv.), PPh_3 (5 mol.%), DMF, 100–120 °C, 24–48 h; (*b*) Ni(dppe)Br_2 (5 mol.%), Zn (3 equiv.), Et_3N, MeCN, N_2, 80 °C, 16 h

Liu *et al.*[100] developed a new efficient method for the synthesis of the natural alkaloid oxyavicine (**137**) containing the isoquinolone moiety. Subsequently, Korivi and Cheng[101] synthesized a series of isoquinoline alkaloids.

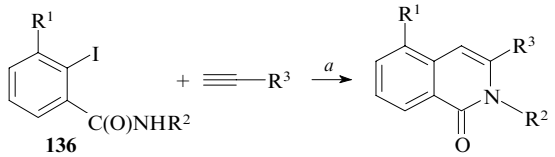
Structure 137



137

The Sonogashira reaction of 2-iodobenzamides **136** with terminal alkynes followed by the intramolecular cyclization through an attack of the nitrogen atom on the triple bond gives isoquinolin-1(2*H*)-ones **138** (Scheme 53).[102] The reaction of unsubstituted 2-iodobenzamide (R^1 = R^2 = H) in the presence of a twofold excess of copper acetate with terminal acetylenes produces isoquinolin-1(4*H*)-one.

Scheme 53



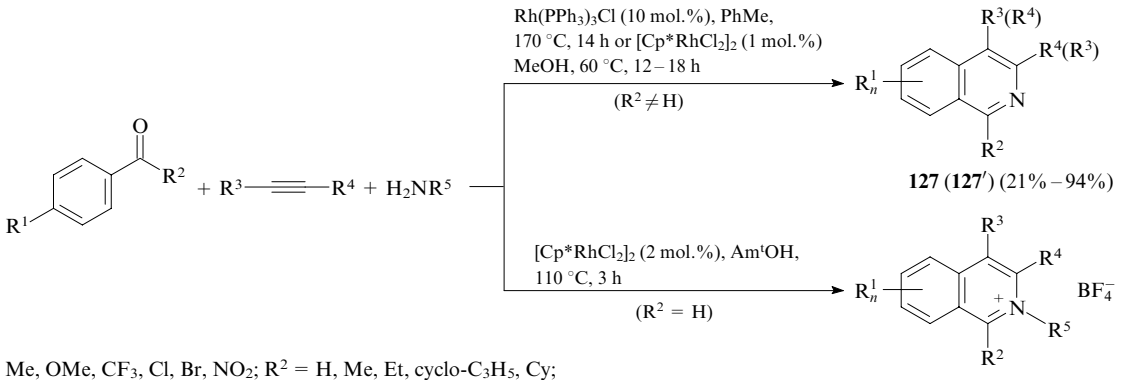
136 **138** (56%–93%)

R^1 = H, Cl, OMe; R^2 = H, C_6H_4OMe-4, $C_6H_3Me_2$-3,5; R^3 = Hex, $(CH_2)_3Cl$, (cyclo-C_6H_{10})OH-1, Ph, C_6H_4X-4 (X = Me, n-C_5H_{11}, OC_5H_{11}-n, Br); (*a*) $Cu(OAc)_2$ (20 mol.%), Cs_2CO_3 (2 equiv.), PEG-400, N_2, 80–90 °C, 3–4 h; PEG is polyethylene glycol

The three-component reaction of aromatic carbonyl compounds with alkynes and amines catalyzed by Rh complexes yields substituted isoquinolines **127** (R^2 = Alk)[103,104] or isoquinolinium salts **139** (R^2 = H)[105] (Scheme 54). The reaction with the use of unsymmetrical acetylenes affords a mixture of isomeric products **127** and **127′**, which differ in the positions of the R^3 and R^4 substituents.

The one-pot coupling of aromatic aldehydes, amines and alkynes[105] underlies a new method for the synthesis of the natural alkaloid oxychelerythrine (**140**), which exhibits antitumour properties through stimulation of glutathione

Scheme 54



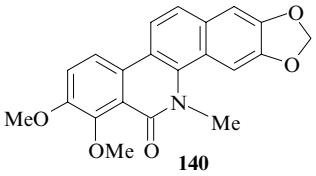
127 (**127′**) (21%–94%)

139 (58%–96%)

R^1 = H, Me, OMe, CF_3, Cl, Br, NO_2; R^2 = H, Me, Et, cyclo-C_3H_5, Cy; R^3, R^4 = Me, Pr^n, Ph, CH_2OH, CH_2OMe, *etc.*; R^5 = Me, Pr^n, Ph, C_6H_4OMe-4, Bn, OH; Am^t = CMe_2Et

transport and inhibition of BclXL (mitochondrial transmembrane proteins that regulate cell death).

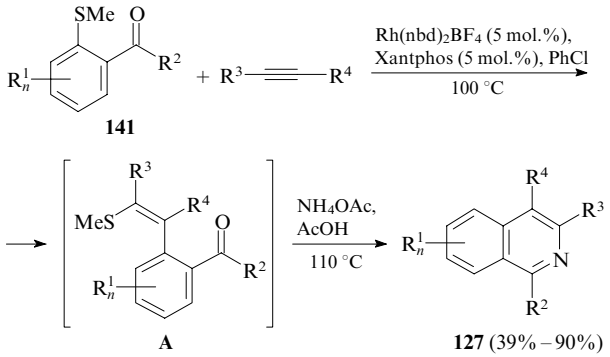
Structure 140



140

The stepwise three-component formation of the isoquinoline skeleton was described by Arambasic *et al.*[106] (Scheme 55). Thus, the coupling of sulfides **141** with alkynes catalyzed by the Rh^{I} complex affords the intermediate carbothiolation product **A**. An additional treatment of the latter with ammonium acetate in acetic acid produces polysubstituted isoquinolines **127**.

Scheme 55

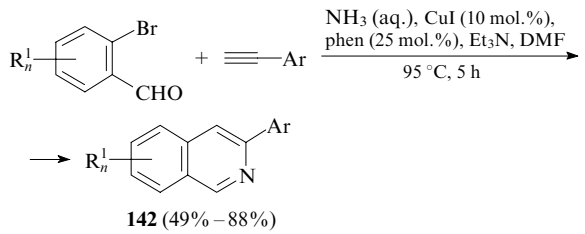


141 **A** **127** (39%–90%)

R^1_n = H, 4,5-$(OMe)_2$, 5-CF_3, 4-SMe, 4-Br; R^2 = Me, n-C_8H_{17}, cyclo-C_3H_5, Cy, CH=CHBu^t; R^3 = H: R^4 = 3-Th, $(CH_2)_3Pr^i$, Cy, Fc, Ph, C_6H_4F-4, C_6H_4OMe-4, *etc.*; R^3 = R^4 = Et, Ph;
nbd is norbornadiene, Xantphos is 4,5-bis(diphenylphosphino)-9 9-dimethylxanthene

A similar multicomponent reaction is the Sonogashira coupling of 2-bromobenzaldehydes with arylacetylenes in the presence of ammonia giving isoquinolines **142** (Scheme 56).[107] The presence of electron-withdrawing groups (R^1 = F, NO_2) in the starting aldehyde provides higher yields of target products **142** compared with those obtained using compounds with electron-donating groups (R^1 = Me, OMe).

Scheme 56

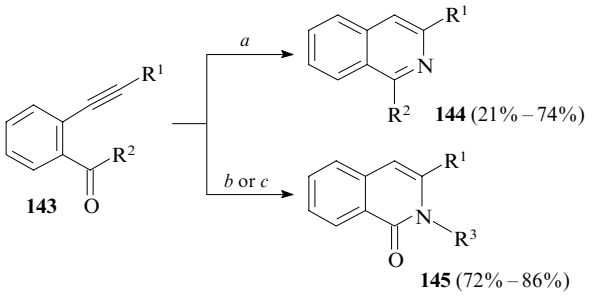


142 (49%–88%)

R^1_n = H, 4-Me, 4-F, 5-NO_2, 4,5-$(OMe)_2$, 3,4,5-$(OMe)_3$;
Ar = C_6H_4Z-4 (Z = H, OMe, Bu^t); phen is 1,10-phenanthroline

The reaction with TfOH followed by the treatment with gaseous ammonia[108] or heating under reflux in an ethanol solution of KOH with hydroxylamine[109] promotes the cyclization of carbonyl compounds **143** to isoquinolines **144** or N-substituted isoquinolin-1-ones **145**, respectively (Scheme 57, conditions *a* and *b*). The heating of aroylhydrazines **143** (R^1 = Alk, R^2 = $NHNH_2$) under reflux in an ethanolic alkali solution also gives *N*-aminoisoquinolin-1-ones **145** (R^3 = NH_2) (see Scheme 57, conditions *c*).[110]

Scheme 57

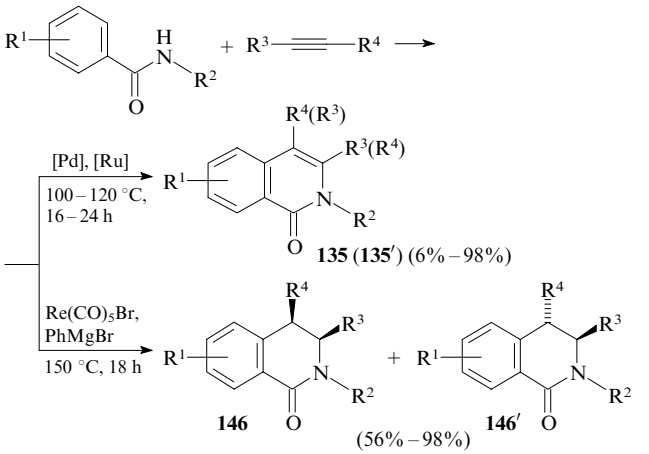


143 **144** (21%–74%) **145** (72%–86%)

(*a*) TfOH, NH_3 (gas), CH_2Cl_2; or R^1 = H, TMS, Ph, C_6H_4Me-4, $C_6H_4(C_{10}H_{21}$-n)-4; R^2 = H, Ph, OEt, NMe_2;
(*b*) KOH, NH_2OH, MeOH; for R^1 = Bu^n, 2-Th; R^2 = OMe (R^3 = OH);
(*c*) KOH, EtOH; for R^1 = Alk, R^2 = $NHNH_2$ (R^3 = NH_2)

In reactions with alkynes catalyzed by Pd (see Ref. 111) or Ru (see Ref. 112) complexes, substituted benzamides undergo intermolecular annulation to give substituted isoquinolin-1-ones **135** (Scheme 58). The reaction in the presence of the [Re]–[Mg] catalytic system[113] yields 3,4-dihydroisoquinolin-1-ones **146**, **146′**. The use of unsymmetrical acetylenes results in the formation of a mixture of isomers **135** and **135′**, with the isomer containing the bulkier phenyl substituent in position 3 of the isoquinoline system being the major product. The presence of electron-donating substituents in the benzene ring of the starting amides is favourable for an increase in the yield of the target isoquinolinones **135**.[111] The yield of the final isoquinolines decreases in the series of N-substituents R^2 = Me, Et, Bu^n, Pr^i, cyclo-C_3H_5 (71%, 35%, 35%, 23% and 6% for R^3 = Ph, R^4 = cyclo-C_3H_5, respectively), which is fully in line with the values of the steric substituent constants.[112] The reaction of n-propylcyclopropylacetylene (R^3 = Pr^n,

Scheme 58



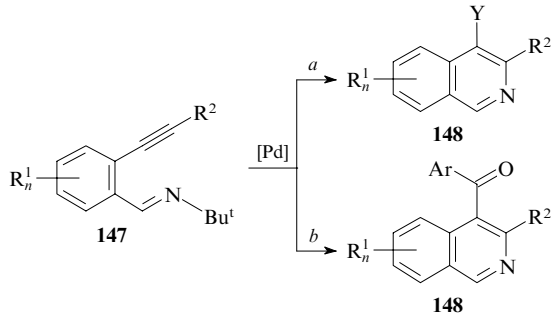
135 (**135′**) (6%–98%) **146** **146′** (56%–98%)

R^1 = H, 2-Me, 3-Me, 4-Me, 3-OMe, 4-OMe, 3-Cl, 4-Cl, 4-F, 4-NO_2, 4-CF_3, 4-CO_2Me; R^2 = Me, Et, Pr^i, cyclo-C_3H_5, Bu^n, OMe, OPr^i;
R^3, R^4 = Alk, Ar, 2-Th

R^4 = cyclo-C_3H_5) with methylbenzamide (R^1 = H, R^2 = Me) affords a mixture of 3-cyclopropyl- and 4-cyclopropylisoquinolinones **135**, **135′** in a ratio of 2.75 : 1.[112] It was shown that the reaction performed in the presence of the [Re]–[Mg] binary catalyst gives *trans*-3,4-dihydroisoquinolinones **146′** as the major products at high concentrations of the components in the reaction mixture,[113] while *cis*-3,4-dihydroisoquinolinones **146** are generated as the major products in dilute solutions.

A facile method for the synthesis of isoquinolines is based on the intermolecular reaction of 2-alkynyl-substituted arylaldimines promoted by metal complexes or electrophiles. In the presence of Pd catalysts, 2-alkynylarylaldimines **147** undergo cyclization to 4-substituted isoquinolines **148** through either cross-coupling with alkenes,[114, 115] aryl, allyl, benzyl and alkynyl halides[116, 117] or aryl halides in the presence of carbon monoxide[118, 119] or in the presence of electrophilic agents[120, 121] (Scheme 59).

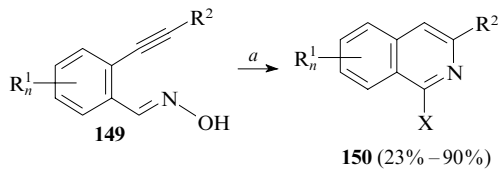
Scheme 59



Y = R^3 or E; E = I, SPh, $SC_6H_4NO_2$-4, SePh; R^1_n = H, 3,4-OCH_2O, 4,5-OCH_2O, 4,5-$(OMe)_2$, 3,4,5-$(OMe)_3$, 4-NMe_2, 5-NMe_2; R^2 = Alk, Alkenyl, Ar; R^3 = Alk, Ar, All, Bn, CO_2Alk, C(O)NAlk; (*a*) [Pd], alkene (R^3H) or halide (R^3X), 70–100 °C, 4–120 h or EHal, 25–100 °C, 0.1–72 h; (*b*) ArX, CO (1 atm), 80–100 °C, 12–48 h; X = Cl, Br, I

The reactions of oximes **149** with phenols[122] or silver trifluoromethylsulfide[123] produce isoquinoline derivatives **150** (Scheme 60). In the presence of silver(I) salts, 2-alkynylbenzaldoximes **149** initially undergo cyclization to intermediate isoquinoline *N*-oxides followed by the reaction of the latter with phenols or $AgSCF_3$ in the presence of TsCl. In the final step, the isoquinoline system **150** is formed *via* the elimination of the tosyloxy group.

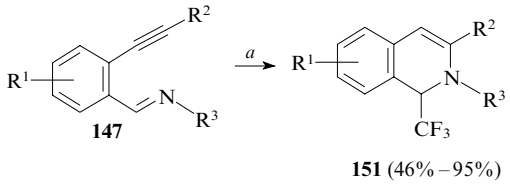
Scheme 60



R^1_n = H, 5-Me, 4-OMe, 4,5-$(OMe)_2$, 4-F, 5-F, 5-Cl; R^2 = Bu^n, cyclo-C_3H_5, C_6H_4Z-4 (Z = H, Me, OMe, F, Cl); X = OAr, SCF_3; Ar = C_6H_4Y-4 (Y = H, Me, Bu^t, OMe, CO_2Et, F, Cl), $C_6H_3Me_2$-2,6; (*a*) ArOH or $AgSCF_3$, AgOTf (10 mol.%), TsCl (1.5 equiv.), 25 °C, 1 h

The reaction of substrates **147** with CF_3TMS catalyzed by silver salts in the presence of acetic acid under mild conditions affords 1-trifluoromethyl-1,2-dihydroisoquinolines **151** (Scheme 61).[124] Under similar conditions, the three-component reaction of 2-alkynylbenzaldehyde, primary amines and CF_3TMS yields related derivatives **151**.[124]

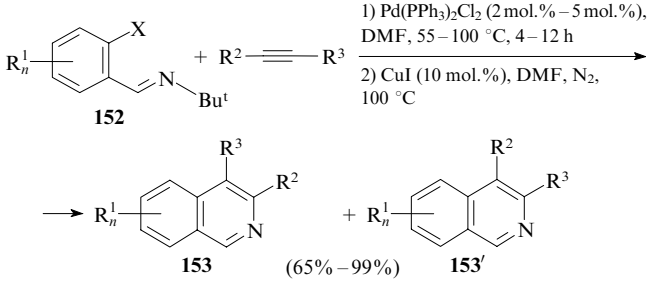
Scheme 61



R^1 = H, 5-Me, 3-OMe, 4-F, 5-Cl; R^2 = cyclo-C_3H_5, Bu^n, C_6H_4X-4 (X = H, Me, OMe, F); R^3 = Bu^t, Ph, Bn; (*a*) CF_3TMS, $AgSbF_6$ (5 mol.%), AcOH (1.1 equiv.), MeCN, 25 °C, 12–24 h

The $Pd(OAc)_2$-promoted annulation of imines **152** with alkynes produces isoquinolines **153** (Scheme 62).[125] Unsymmetrical acetylene compounds give a mixture of isomers **153** and **153′** with the isomer containing a bulkier substituent [Ph, C≡CPh, C(=CH_2)Me] in position 3 of the isoquinoline system predominating. Terminal acetylenes (R^3 = H) do not react with imines **152** under similar conditions.[125] In the presence of palladium catalysts, alkyne undergoes only condensation with compound **152** to form intermediate 2-alkynylimine, which is subjected to intramolecular cyclization in the second step after the addition of copper(I) iodide.[126]

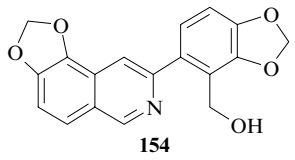
Scheme 62



X = I, Br; R^1_n = H, 4,5-OCH_2O, 4-CH=NBu^t; R^2, R^3 = H, Alk, Ar, Cy, C(=CH_2)Me, CO_2Et, CH(Me)OH

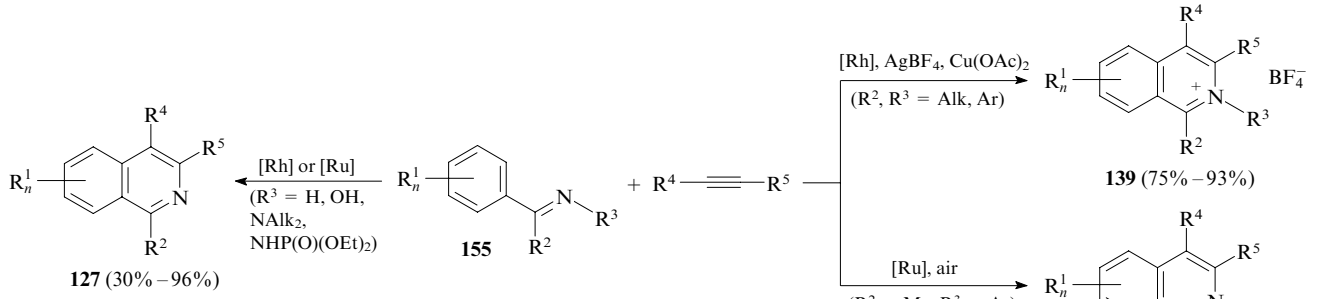
In order to demonstrate the synthetic potential of this method, Roesch and Larock[126] prepared the natural isoquinoline alkaloid decumbenine B (**154**), which had been earlier isolated from the tubers of *Corydalis decumbens*. This herb is used in traditional Chinese medicine for the treatment of cerebral infarction and rheumatoid arthritis.

Structure 154



Rhodium and ruthenium complexes catalyze the intermolecular cyclization of alkynes with ketimines[127, 128] **155** (R^2, R^3 = Alk, Ar), arylhydrazones[129, 130] [R^2 = Alk, Ar, R^3 = NMe_2, $NHP(O)(OEt)_2$], oximes[131] (R^3 = OH) or imidines[132] (R^2 = NHAlk, R^3 = H) giving isoquinoline deriv-

Scheme 63



[Rh] = $[Cp^*RhCl_2]_2$, $Cp^*Rh(MeCN)_3(SF_6)_2$;
[Ru] = $[Ru(p\text{-cymene})Cl_2]_2$, $[Ru_2(p\text{-cymene})_2Cl_3(PF_6)]$; R^1_n = H, 4-Me, 4-OMe, 4-Br, 4-I, 3,4-Me_2, 3,4-$(OMe)_2$, 3,4-*N*-butylbenzopyrrolo[*b*], *etc.*; R^2 = H, Me, Et, Bn, Ph, NHAlk, *etc.*; R^3 = H, Me, Bu^n, Bn, C_6H_4OMe-4, *N*-ethylcarbazol-3-yl, NMe_2, $NHP(O)(OEt)_2$, OH, *etc.*; R^4, R^5 = Alk, Ar

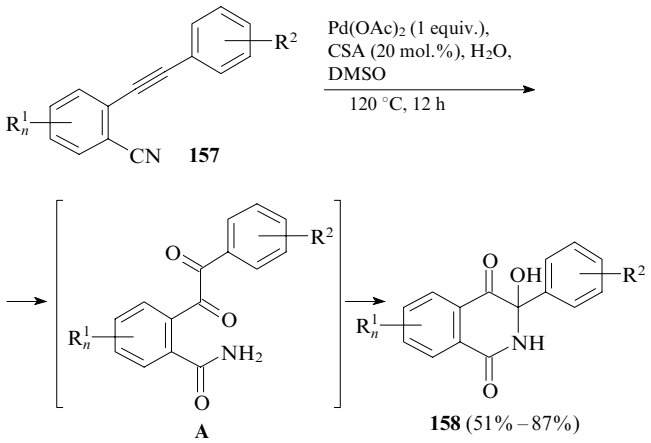
atives **127** or appropriate isoquinolinium salts **139** (Scheme 63). Li and Ackermann[128] described the synthesis of 1-methylene-1,2-dihydroisoquinolines **156** by the $[Ru(p\text{-cymene})Cl_2]_2$-promoted annulation of ketimines with acetylenes in air. The reaction of arylhydrazones with internal acetylenes catalyzed by rhodium compounds involves the activation and cleavage of the *ortho* C–H bond in the aromatic ring followed by the formation of new carbon–carbon and carbon–nitrogen bonds.[129] The distinguishing feature of this reaction is that acetic acid is added in order to protonate the $R^2 = NMe_2$ group, thus facilitating the elimination of dimethylamine. In similar transformations,[130] the *N*-diethoxyphosphoryl moiety was used as a leaving group in the staring arylhydrazones **155**.

In the presence of the $Pd(OAc)_2-H_2O-$camphorsulfonic acid (CSA) catalytic system, *o*-alkynylbenzonitriles **157** undergo oxidative cyclization to isoquinolinediones **158** (Scheme 64).[133] Under the reaction conditions, the triple bond is oxidized to the α-diketo moiety, while the nitrile group is hydrated to the amide group, resulting in the formation of intermediate **A**, which undergoes the intramolecular cyclization to compound **158**.

The oxidative cyclization of aromatic nitriles with internal alkynes in the presence of the complex $[Ru(p\text{-cymene})_2Cl_2]$ yields substituted isoquinolin-1-ones.[134] Acetic acid promotes hydrolysis of nitrile to benzamide and is involved in the regeneration of $Cu(OAc)_2$. The reaction of *o*-halobenzonitriles with diphenylacetylene in the presence of methyl triflate (MeOTf) produces fused indeno[1,2-*c*]dihydroisoquinoline.[135]

The $Pd(OAc)_2$-catalyzed intermolecular annulation of indole **159** with *tert*-butylamine affords fused dihydroisoquinolines **160** (Scheme 65).[53] The first step involves the

Scheme 64

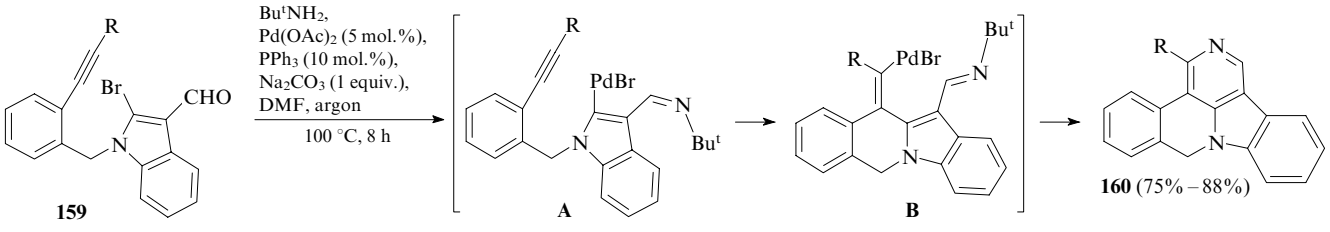


R^1_n = H, 5-OMe, 4,5-$(OMe)_2$, 4,5-OCH_2O; R^2 = H, 4-Me, 4-OMe, 2-OMe, 4-Cl, 4-NO_2

condensation of amine with compound **160** at the aldehyde group to form imine followed by the oxidative addition of Pd^0 to the halogen atom to form intermediate **A**. The intramolecular cyclization at the triple bond through the *exo-dig* addition produces vinylpalladium species **B**, which is finally transformed into pentacyclic system **160**.

A special group of reactions comprises condensation reactions of nitrogen-containing heterocyclic compounds with terminal and internal alkynes giving fused isoquinolines[136–141] or their salts[142,143] (Scheme 66). Arylbenzimidazoles,[136,137,142] arylpyrazoles,[138,139] arylpyridines,[142,143] 3-arylisoquinolones[140] and quinazolinones,[141] as well as

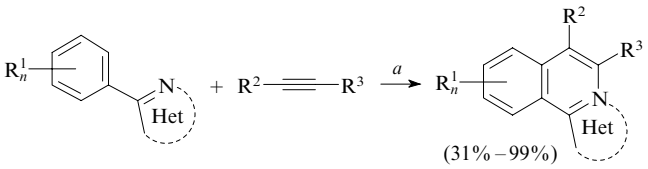
Scheme 65



R = Bu^n, Ph

various oxazoles and thiazoles,[142] are involved in such reactions catalyzed by Pd, Rh and Ru complexes.

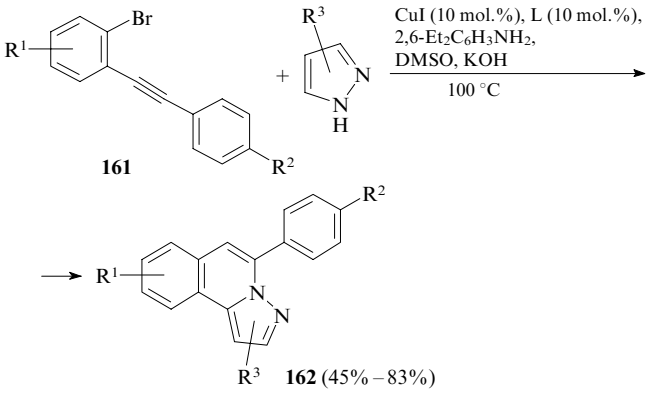
Scheme 66



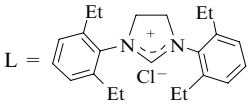
R^1 = H, 2-Me, 3-Me, 4-Me, 3,5-Me_2, 4-Bu^t, 4-OMe, 4-Ac, 4-F, 4-Cl, 4-Br, 4-NMe_2, 2,5-$(OMe)_2$, 2,3-benzo, *etc.*; R^2 = H, Br, Alk, Ar, CO_2Alk; R^3 = 2-Th, $(CH_2)_3$OBz, Alk, Ar; Het is pyrazole, imidazole, pyridine, pyrimidine, 1,2-oxazole and other, including benzannulated, heterocycles; (*a*) $Pd(OAc)_2$, K_2CO_3, or [Rh], or [Ru], 85–130 °C, 12–24 h

The annulation of *o*-alkynylbromobenzenes **161** with pyrazoles catalyzed by copper(I) compounds produces pyrazolo[5,1-*a*]isoquinolines **162** (Scheme 67).[144] The best result was achieved when the starting compounds contained an electron-withdrawing group (R^2 = Cl) in the second aromatic ring. Similar reactions of terminal or alkyl-substituted acetylenes produce isoquinolines **162** only in trace amounts.

Scheme 67



R^1 = H, 4-Cl, 5-Me; R^2 = H, Me, Bu^t, OMe, Cl; R^3 = H, Alk, Ar;



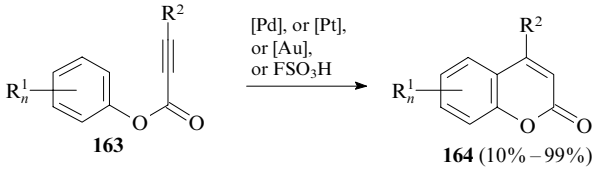
An analysis of published data demonstrates that the isoquinoline skeleton can be constructed by means of reactions of alkynes with substituted benzylamines, benzoic acid amides, aryl ketone imines or nitrogen-containing heterocycles catalyzed by Pd, Rh and Ru complexes. The range of the synthesized functional isoquinoline derivatives can be substantially extended using Brønsted or Lewis acids, as well as various electrophilic reagents.

IV. Synthesis of coumarins

The present section is devoted to methods of synthesis of coumarins from acetylene compounds based on reactions catalyzed by complexes of different metals and those promoted by electrophilic reagents. The coumarin system can be constructed by means of intramolecular transformations of aryl acetylenecarboxylates and by intermolecular reactions of phenols with acetylenecarboxylic acids (or their esters) or with alkynes through the carbonylation in the presence of carbon monoxide.

The cyclization of aryl propynoates **163** catalyzed by Pd,[41] Pt,[19,145] Au complexes,[20,44,146–148] as well as by FSO_3H (see Ref. 149) or $AlCl_3$, $AlBr_3$ (see Ref. 149) produces coumarins **164** (Scheme 68).

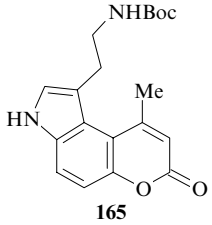
Scheme 68



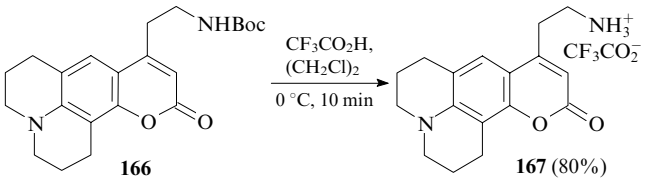
R^1_n = H, 2-Me, 3,5-Me_2, 4-Bu^t, 4-Ph, 4-Br, 3-NEt_2, 4-OMe, 3,4,5-$(OMe)_3$, 3,4-benzo, *etc.*; R^2 = H, Me, Et, Bu^t, TMS, $(CH_2)_3$OTBS, CO_2Me, Ph, C_6H_4Me-4, $C_6H_3(OMe)_2$-3,5, 2-methoxy-1-naphthyl, *etc.*

The $PtCl_4$-catalyzed reactions of esters **163** were applied to synthesize various pyrrolocoumarins and octahydroquinolysinocoumarins, *e.g.*, compounds **165** and **166** (in 93% and 91% yields, respectively).[145] The latter compound was synthesized in order to be subsequently transformed into ammonium derivative **167** (Scheme 69), which is applied as a fluorescent false neurotransmitter in studies of the brain activity. In the cited study,[145] it was also demonstrated that the gold(I)-based catalytic system — $Au(PPh_3)Cl$ (5 mol.%) – $AgSbF_6$ (5 mol.%) (25 °C, 10 min) — is efficient in the synthesis of compounds **165** and **166**.

Structure 165

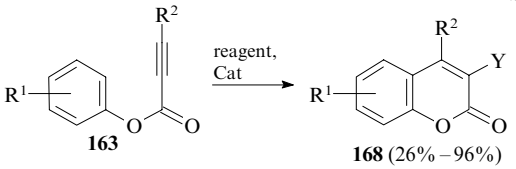


Scheme 69

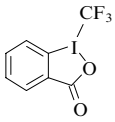


The intramolecular cyclization of aryl esters **163** shown in Scheme 68 provides a quite general approach to the synthesis of substituted coumarins. This method is suitable for the preparation of new derivatives using the additional insertion of substituents at the triple bond followed by cyclization of the resulting intermediates (Scheme 70). For instance, silver salts catalyze the radical cyclization of esters **163** in the presence of phosphine oxides or phosphonates giving 3-phosphorylated coumarins **168** [Y = $P(O)(OEt)_2$ and $P(O)Ph_2$] (see Scheme 70).[150] Copper salts promote the direct trifluoromethylation of the triple bond in molecules **163** and subsequent cyclization to 3-trifluoromethyl-

Scheme 70



R^1 = H, 3-Me, 4-Me, 2-Bu^t, 4-Bu^t, 4-F, 4-Cl, 4-Br, 4-I, 4-OMe, 4-OPh, *etc.*; R^2 = H, Me, Bu^n, n-C_5H_{11}, Ph, C_6H_4Me-4, C_6H_4OMe-4, C_6H_4Me-2, C_6H_4Cl-4, $C_6H_4CF_3$-3, *etc.*

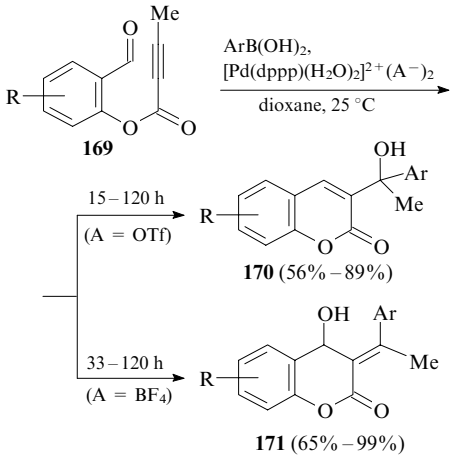
Reagent	Catalyst	Y	Yield of **168** (%)	Ref.
$HP(O)R^3_2$ (R^3 = OMe, OEt OBu^i, Ph)	Ag_2CO_3, $Mg(NO_3)_2 \cdot 6H_2O$	$P(O)R^3_2$	47–90	150
	$Cu(OAc)_2$, K_2CO_3	CF_3	26–70	151
R^3XXR^3 (X = Se: R^3 = Bu^n, Ph, C_6H_4Me-2, C_6H_4Me-4, C_6H_4Cl-4, $C_6H_4CF_3$-3; X = Te, R^3 = Ph)	[Fe]	XR^3	41–96	152
$R^3SO_2NHNH_2$ (R^3 = Ph, C_6H_4Me-4, C_6H_4F-4, C_6H_4Cl-4, C_6H_4Br-4, $C_6H_4CF_3$-2, 2-Naph)	Bu^n_4NI	SO_2R^3	60–94	153

coumarins **168** (Y = CF_3).[151] A combination of iron(III) chloride and organic diselenide or ditelluride was utilized for the cyclization of esters **163** to 3-selenyl- or 3-telluryl-2*H*-coumarins **168** (Y = SeAlk, SeAr, TeAr).[152] Wei *et al.*[153] proposed a combined procedure for the sulfonation of esters **163** with sulfonyl hydrazides followed by their cyclization to 3-sulfonylcoumarins **168** (Y = SO_2Ar) in the presence of tetra-n-butylammonium iodide.

Such tandem reactions of aryl butynoates **169** with arylboronic acids produced coumarins **170** and dihydrocoumarins **171** (Scheme 71).[154] The reactions were performed using the same cationic palladium complex $[Pd(dppp)(H_2O)_2]^{2+}$ but different counterions (A^-). Thus, compounds **170** are selectively formed in the case of TfO^-, whereas BF_4^- provides the exclusive formation of compounds **171**. Han and Lu[154] suggested that in the presence of TfO^-, the reaction initially also generates dihydrocoumarins **171**, which are isomerized to coumarins **170** in the presence of catalytic amounts of TfOH that is formed through the decomposition of the catalyst.

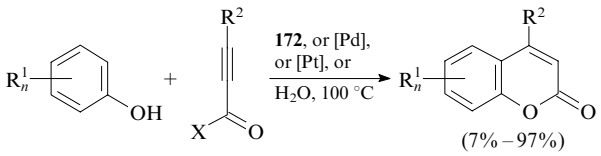
Coumarins can also be synthesized by the intermolecular reaction of phenols with acetylenic aldehydes,[155–157] acids[158,159] and their esters.[41,158,160–166] Bode's team[155–157] developed a general strategy for the construction of pyran rings based on N-heterocyclic carbene-catalyzed reactions of conjugated acetylenic aldehydes with enols (Scheme 72). In this process, triazolium salt **172** serves as a source of the aminocarbene species that reacts with arylpropynal to form the acyltriazolium salt, and the adduct that is formed by the latter salt with the enol component

Scheme 71

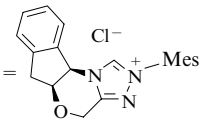


R = H, 4-Me, 4-Br, 4-Cl, 6-OMe, *etc.*; Ar = Ph, C_6H_4X-4 (X = Me, Ph, F, OMe), C_6H_4Me-3, 2-Naph; dppp = $Ph_2P(CH_2)_3PPh_2$

Scheme 72



R^1_n = H, 3-Me, 4-Me, 3,4-Me_2, 3,5-Me_2, 3-OMe, 4-OMe, 3,5-$(OMe)_2$, 4-Br, 3,4-benzo, 3,4-OCH_2O, 3-OH, 3-OH-5-OMe, *etc.*; R^2 = H, Alk, Ar, $(CH_2)_2OCO_2Et$, $(CH_2)_2CN$, CO_2Et; X = H, OH, OAlk;

172 = 

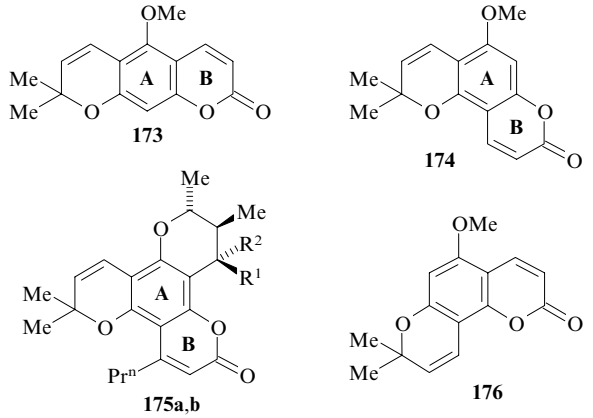
undergoes the Claisen rearrangement to the target products.[155]

The synthesis of coumarins catalyzed by Pd compounds (see Scheme 72) starting from esters and phenols containing electron-donating substituents was developed in the late 1990s–early 2000s by the research teams headed by Trost[160–162] and Fujiwara.[41,163–165] This method was used to construct rings **B** from the appropriate alkynes and phenols as a step in the synthesis of analogues of biologically active natural coumarin derivatives: xanthoxyletin (**173**) and alloxanthoxyletin (**174**),[161] as well as calanolides A and B (**175a**,**b**).[162]

Phenols containing one or two additional hydroxy or methoxy groups are activated as π-nucleophiles to an extent that they react with propionic acid (X = OH) to form coumarins even upon boiling in water in the absence of catalysts (see Scheme 72).[159] This approach was employed to synthesize a series of pyranocoumarins, including the antibacterial drugs alloxanthoxyletin (**174**) and 5-methoxyseselin (**176**).[159]

The research group headed by Larock[70,167,168] found that palladium acetate catalyzes the annulation of *o*-iodophenols and alkynes that is accompanied by carbonylation and gives the coumarin system (Scheme 73). The reactions of unsymmetrical acetylenes produce mixtures of regioisomers, the ratio and yield of which depend mainly on the bulkiness of the R^2 and R^3 substituents in the starting

Structures 173–176

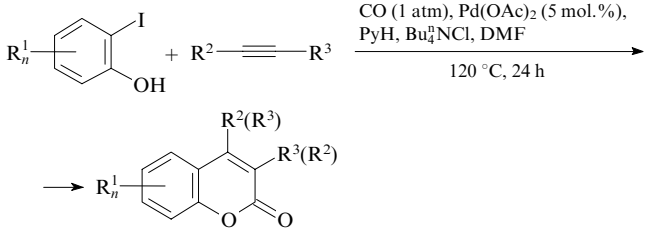


173 **174** **175a,b** **176**

R^1 = H, R^2 = OH (**a**); R^1 = OH, R^2 = H (**b**)

alkyne. An increase in the volume of these substituents (Pr^i, Bu^t) causes a decrease in the yield of the target coumarins and results in the predominant formation of the regioisomer containing a bulkier substituent in position 3 of the coumarin ring.[168] Terminal alkynes produce coumarins in lower yields as compared to internal alkynes.[70] These reactions give 3-substituted isomers as the major reaction products. The exclusive formation of 3-substituted isomers is observed in the reactions of phenyl- and silyl-substituted acetylenes (R^3 = H: R^2 = Ph, TMS, $SiEt_3$, $SiPr^i_3$), while alkylacetylenes (R^3 = H: R^2 = Bu^n, n-C_8H_{17}) give mixtures of regioisomers, with 3-substituted coumarin predominating.

Scheme 73

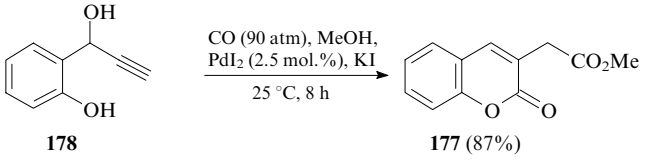


R^1_n = H, 4-OMe, 5-OMe, 4-Ac, 4-CO_2Et, 5-CO_2Me, 3,4-benzo, 5,6-naphthoquino; R^2, R^3 = Alk, Ar, $SiAlk_3$, CH_2OBn, CO_2Et, CH_2OMe, Bz, Ac; R^2 = H: R^3 = Alk, Ar, $SiAlk_3$

A series of anthrapyranones, which are of great importance as antitumour and antibacterial drugs, was synthesized by the carbonylation (CO pressure ~20 atm) from 1-hydroxy-2-iodo-substituted anthraquinones and terminal alkynes (see Scheme 73).[169]

Gabriele *et al.*[170] reported the PdI_2-catalyzed addition of two CO molecules to the triple bond in the synthesis of 3-substituted coumarins from phenols containing hydroxypropargyl substituents in the *ortho* position (*e.g.*, coumarin **177** from phenol **178**; Scheme 74).

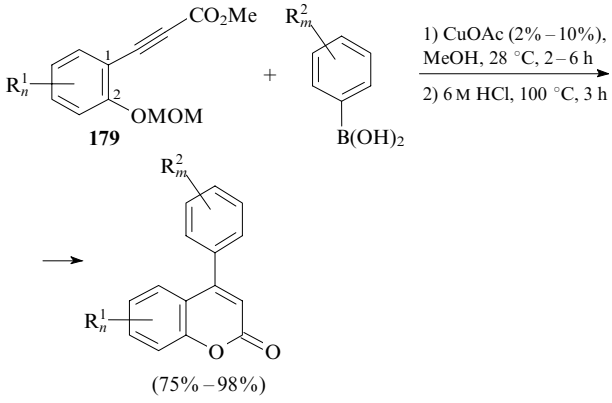
Scheme 74



178 **177** (87%)

In addition to the above-described types of reactions intended to construct the coumarin ring, a number of examples of the synthesis of these heterocycles are available in the literature. Thus, copper(I) acetate promotes the transformation of esters **179** containing the MOM-protected phenolic hydroxy group and arylboronic acids to 4-arylcoumarins (Scheme 75).[171] The reaction involves two steps. In the first step, the triple bond of boronic acid undergoes *syn*-hydroarylation. Then the MOM protecting group is removed by treatment with hydrochloric acid under reflux, resulting in cyclization to coumarin. A series of coumarins analogous to natural compounds (in the product, R^1, R^2 = OH, OMe) was synthesized based on MOM-protected derivatives **179**.

Scheme 75



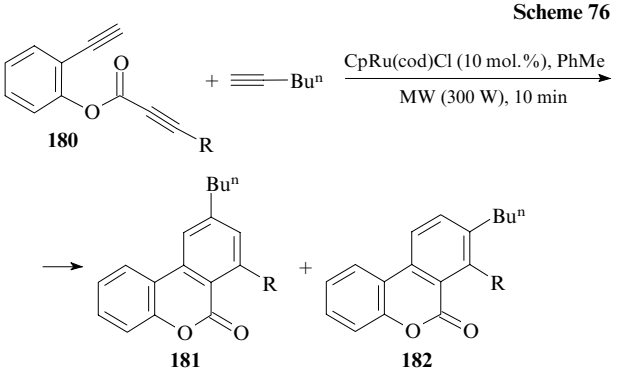
179

(75% – 98%)

R^1_n = H, 4-OMOM, 4,6-$(OMe)_2$, 4-OMe-5-OMOM;
R^2_m = H, 2-Me, 3-Me, 4-Me, 4-Cl, 4-I, 4-OMe, 4-OH, 3-NO_2, 3,4-benzo

The microwave (MW)-mediated CpRu(cod)Cl-catalyzed reaction can be applied to construct the benzene ring from three acetylene moieties (two from ester **180** and one from hex-1-yne) in benzocoumarins **181** and **182** (Scheme 76).[172] Regioisomer **181** is produced as the major product.

Scheme 76



180 **181** **182**

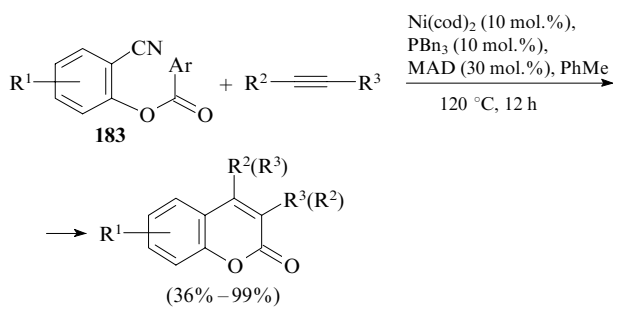
(**181** + **182**: 31% – 81%; **181** : **182** от 95 : 5 до 76 : 24)

R = H, Me, TMS; Cp = η^5-C_5H_5

In the presence of the $Ni(cod)_2$ – MAD catalytic system, *o*-cyanoaryl arenecarboxylates **183** react with internal alkynes to form coumarins (Scheme 77).[173] The cocatalyst MAD proved to be more efficient than other Lewis acids [$AlMe_3$, BPh_3, $B(C_6F_5)_3$]. Unsymmetrical alkynes give a mixture of isomers, in which coumarin containing a bulkier substituent (Pr^i, TMS, Ph) in position 4 predominates. Nakai *et al.*[173] suggested that this catalytic system causes

the insertion of alkyne at the $C_{arom}-CN$ bond followed by the elimination of the ArCN molecule and cyclization to coumarin.

Scheme 77



Ar = Ph, C_6H_4X-4 (X = Me, OMe, NMe_2, CF_3), $C_6H_2Me_3$-2,4,6; R^1 = H, 2-Me, 3-OMe, 4-OMe, 3-F, 3-CF_3; R^2 = R^3 = Pr^n, Ph; R^2 = Me: R^3 = Pr^i, n-C_5H_{11}, TMS; R^2 = Pr^n: R^3 = $(CH_2)_2OMe$, Ph

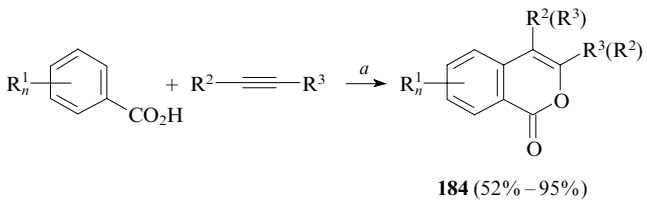
In terms of the mechanism of the above-considered reactions giving coumarins, Pt^{II}, Pt^{IV}, Au^{I} and Au^{III} complexes often act as Lewis acids. They are coordinated at the triple bond of alkynes thus providing electrophilic activation of the latter, which promotes subsequent intra- or intermolecular reactions with phenols.

V. Synthesis of isocoumarins

ortho-Alkynyl-substituted benzoic acids or their esters are precursors of isocoumarins in intramolecular transformations. Intermolecular reactions giving isocoumarins can be accomplished using alkynes along with benzoic acids, their esters and substituted phthalic anhydrides.

The Rh^{III} complex-catalyzed reaction of benzoic acids with internal alkynes affords isocoumarins **184** (Scheme 78).[174–176] Ruthenium complexes can also catalyze the aerobic oxidative cyclization of aromatic acids with alkynes (see Scheme 78).[177] With unsymmetrical alkynes, a mixture of isomeric isocoumarins **184** is produced, with the isomer containing a bulkier substituent in position 3 of the heterocyclic system predominating. As a follow up of this study,[174] Shimizu *et al.*[175] synthesized 8-amino-substituted isocoumarins **184** (R^1 = 2-NHAr) from 2-aminobenzoic acids and alkynes in the presence of a dimeric Rh complex. In the solid state, these isocoumarins exhibit fluorescence properties.

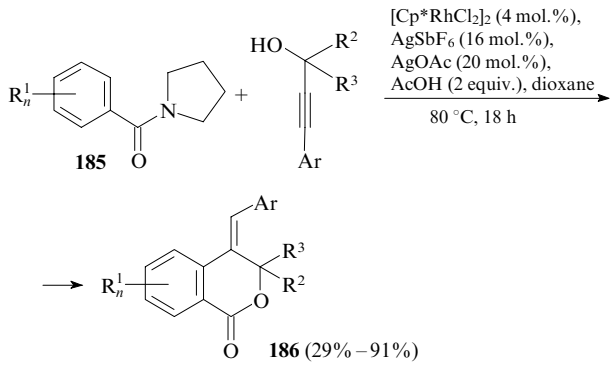
Scheme 78



R^1_n = H, 3-Me, 4-Me, 3-OMe, 4-OMe, 3,4-$(OMe)_2$, 3,4,5-$(OMe)_3$, 4-Cl, 2,3-benzo, 2-NHAr, 4-Ac, 3,4-OCH_2O; R^2 = R^3 = Me, Et, Pr^n, n-C_7H_{15}, Ph, C_6H_4Me-4, C_6H_4Cl-4, 2-Th; R^2 = Ph: R^3 = Me, Bu^n; (*a*) [Rh] or [Ru], 100–140 °C, 2–12 h

The rhodium complex-catalyzed reaction of 1-benzoylpyrrolidines **185** with propargyl alcohols yields dihydroisocoumarins **186** (Scheme 79).[178] The use of enantiomerically pure propargyl alcohols enables the synthesis of appropriate optically active lactones **186**.

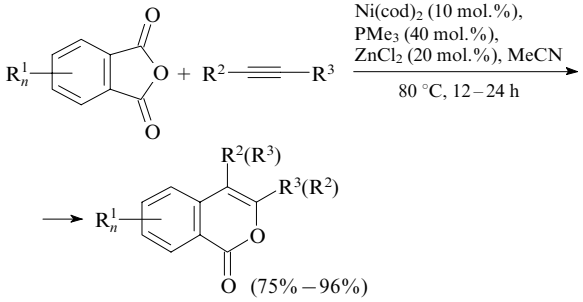
Scheme 79



R^1_n = H, 4-Me, 3,4-Me_2, 4-Ph, 4-OMe, 4-Cl, 4-Br, 3-F, 3-Cl, 3,4-OCH_2O, 3,4-benzo; R^2 = R^3 = H, Me; R^3 = H: R^2 = Me, Et, Ph; Ar = Ph, C_6H_4X-4 (X = Me, Bu^t, OMe, CF_3, Cl, Br, CN, CO_2Me), C_6H_4Y-3 (Y = Me, OMe, F), $C_6H_3Me_2$-2,5

The coupling of phthalic anhydrides with alkynes giving isocoumarins can be accomplished using the nickel complex $Ni(cod)_2$ in the presence of $ZnCl_2$ as the cocatalyst (Scheme 80),[179] the reactions with unsymmetrical alkynes giving rise to a mixture of regioisomeric products.

Scheme 80

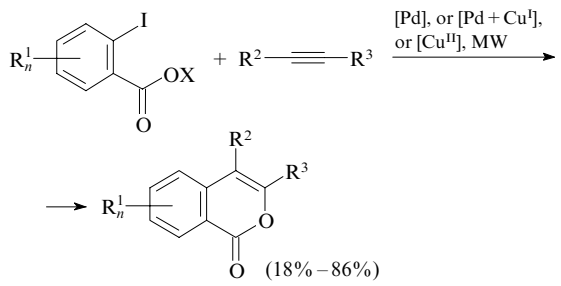


R^1_n = H, 3-Me, 4,5-benzo; R^2 = Pr^n: R^3 = Pr^n, CH_2OMe; R^2 = Me: R^3 = Pr^i, n-C_5H_{11}, TMS; R^2 = Ph: R^3 = Ph, TMS

The isocoumarin skeleton can also be constructed by the intermolecular reaction of *o*-halobenzoic acids[180–183] or their esters[184] with alkynes (Scheme 81). The $Pd(OAc)_2$-promoted annulation of methyl *o*-iodobenzoates with internal acetylenes proceeds through the formation of vinylpalladium intermediates, which give final isocoumarins after a series of transformations.[184] Copper(II) chloride catalyzes similar intermolecular cyclization.[181] Terminal alkynes react with *o*-iodobenzoic acids to form substituted isocoumarins in the presence of the 10% $Pd/C-Et_3N-CuI-PPh_3$ catalyst system[180] or under microwave irradiation conditions[182] (see Scheme 81). This process involves the Sonogashira reaction giving intermediate 2-alkynylbenzoic acids followed by their 6-*endo*-*dig* cyclization to isocoumarins.[180,182] Subramanian *et al.*[180] noted that ethanol should be used as the solvent for the regioselective synthesis of isocoumarins. In DMF, dioxane, isopropyl or *tert*-butyl alcohol, the reaction produces a mixture of isocoumarin and 3-substituted phthalide. For the microwave-assisted reaction,[182] DMF is a suitable solvent. In this case, the

treatment time decreases to 10 min. Wang *et al.*[182] demonstrated that the thermal treatment leads to a 48-fold increase in the reaction times (*i.e.*, to 8 h) at the same catalyst loading (10 mol.% CuI, 20 mol.% PPh_3, 1.5 equiv. K_2CO_3). 2-Iodo-3-nitrobenzoic acid is involved in the Castro–Stephens reaction with copper acetylides to form isocoumarins.[183]

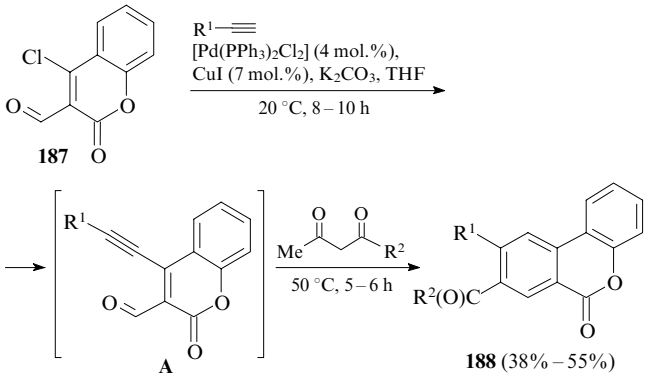
Scheme 81



R^1_n = H, 3-Me, 5-Me, 3-OMe, 4,5-$(OMe)_2$, 5-Cl, 3-NO_2, 5-NO_2, *etc.*; X = H, Me, Et, Pr^i, Bu^t, *etc.*; R^2, R^3 = Alk, Ar, $SiAlk_3$; R^2 = H: R^3 = CMe_2OH, CHMeOH, $(CH_2)_2OH$, $(CH_2)_3OH$, $CH_2CHMeOH$, TMS, Ph; $R^2 = R^3 = CO_2Me$; R^2 = Cu, R^3 = Ar

Using a similar methodology, Iaroshenko *et al.*[185] developed a procedure for the modification of 4-chloro-3-formylcoumarins **187** based on the palladium complex-catalyzed reaction of these compounds with terminal acetylenes giving fused isocoumarin systems **188** (Scheme 82). This process involves the Sonogashira reaction giving intermediate **A** followed by its intermolecular condensation with the 1,3-dicarbonyl derivative yielding target compounds **188**.

Scheme 82

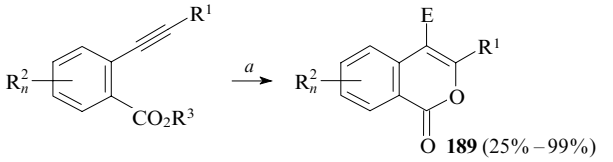


R^1 = Alk, Ar; R^2 = Me, OMe, OEt, OPr^i, OBu^t, OAll

Below, we consider methods of synthesis of isocoumarins based on the annulation of *o*-alkynyl-substituted benzoic acids and enediynes.

The intramolecular 6-*endo-dig* cyclization of *o*-alkynyl-substituted benzoic acids and their esters affords isocoumarins **189** (Scheme 83).[183,186–191] This reaction is not selective and often gives, apart from isocoumarin **189**, side products.[186,187,190,191] Thus, the presence of bulky groups (R^1 = Bu^t, Ph, TMS) at the triple bond interferes with the $Pd(MeCN)_2Cl_2$-catalyzed 6-*endo-dig* cyclization and results in the additional formation of phthalides through the 5-*exo-dig* ring closure.[186] Transformations promoted by copper(II) halides and $Cy_2NH \cdot HX$ yield, in addition to halo-substituted isocoumarins **189**, nonhalogenated products. The solid-phase synthesis of isocoumarin derivatives from acetylenes attached to a polymer support *via* an ester linkage additionally produces the appropriate phthalide depending on the nature of the electrophilic reagent and the R^1 substituent at the triple bond.[190] Under iodine-mediated reaction conditions, polymethoxy-substituted esters in acetonitrile give the Kucherov reaction product in the presence of water.[191] In some works, substituted isocoumarins were selectively synthesized *via* cyclization, which is microwave-assisted and mediated by *p*-toluenesulfonic acid (PTSA),[188] promoted by strong electrophiles[189] or by mercury(II) salts in the presence of sulfuric acid.[183] The microwave irradiation makes it possible to substantially reduce the reaction time and extend the range of reacting substrates.[188]

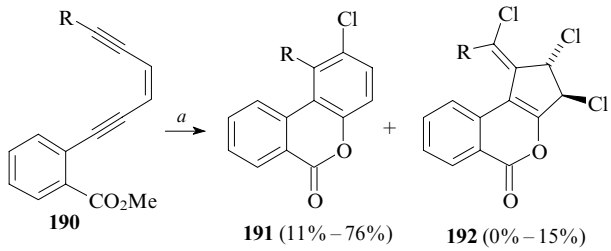
Scheme 83



E = H, I, Br, Cl, $SC_6H_4NO_2$-4, SePh; R^1 = Alk, Ar, $SiAlk_3$, $(CH_2)_nOH$ (n = 1, 3, 4), 3-Th, $(CH_2)_3CO_2H$, $(CH_2)_4CN$; R^2_n = H, 3-Me, 4-Me, 6-Me, 3-OMe, 5-OMe, 3,4-benzo, 5,6-OCH_2O, 5-F, 5-Cl, 4-CO_2Me, 3-NO_2, 5-NO_2, *etc.*; R^3 = H, Alk or 4-$CH_2C_6H_4OCH_2C_6H_4$-PS (PS is polystyrene); (*a*) [Pd], or $CuX_2 + Cy_2NH \cdot HX$ (X = Cl, Br), or electrophiles, or PTSA, MW, or $HgSO_4$, H_2SO_4; electrophiles: ICl, I_2, 4-$O_2NC_6H_4SCl$, PhSeCl, HI, $CuCl_2$, $CuBr_2$, CF_3CO_2H

The $PdCl_2$-catalyzed cyclization of enediynes **190** affords fused isocoumarins **191** and **192** (Scheme 84).[192] As in the above-described examples,[180,186] the presence of a bulky group (R = Bu^i, Bu^t), the phenyl group (R = Ph) or aromatic moieties containing electron-donating substituents (R = C_6H_4OMe-4, C_6H_4Me-2, C_6H_4Me-4) at the end of the enediyne moiety is favourable for the formation of 5-*exo-dig*-cyclization products **192**. Meanwhile, the presence of aromatic moieties containing electron-withdrawing groups (R = $C_6H_4CF_3$-4, $C_6H_4CF_3$-2) or the pyridine ring (R = 2-Py) completely suppresses the formation of structures **192**, resulting in the exclusive formation of isocoumarins **191**.

Scheme 84



R = Alk, CH_2OH, $(CH_2)_4OH$, 2-Py, 2-Th, Ar; (*a*) $PdCl_2$ (5 mol.%), $CuCl_2$ (3 equiv.), MeCN, 85 °C, 1 h

Enediynes **190** (R = H) were subjected to 6-*endo-dig* cyclization promoted by gold(I) and gold(III) chlorides to form substituted isocoumarins containing the *o*-ethynylphenyl moiety in position 3.[193] The enediyne precursor

undergoes complete condensation in the presence of the complex $Ph_3PAu^INTf_2$.

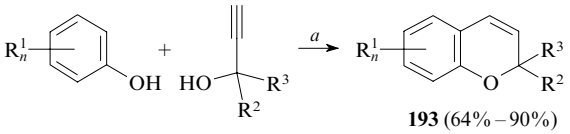
It was noted that in acidic media, enediynes can be transformed into lactones, which are used to prepare stable acylated derivatives.[194]

An analysis of the published data shows that the intramolecular cyclization of *o*-alkynylbenzoic acid derivatives promoted by Brønsted acids or other electrophilic reagents provides a general approach to the construction of the isocoumarin skeleton. This approach is suitable for the synthesis of isocoumarins containing substituents required for further transformations, *e.g.*, iodine, sulfanyl and so on. Complexes of Pd, Au, Rh, Ru, Ni and Cu also act as catalysts for intra- and intermolecular annulation of acetylene compounds giving isocoumarin derivatives. Noteworthy are transformations promoted by Rh and Ru complexes, which can be employed for the direct activation of C–H bonds in aromatic compounds.[174–178]

VI. Synthesis of chromenes and isochromenes

The common approach to the construction of the chromene system is based on intramolecular reactions of *o*-alkynylphenols or phenol ethers containing propargyl substituents. Meanwhile, the synthesis of chromenes from propargyl alcohols can be accomplished using intermolecular transformations as well. Boron trifluoride diethyl etherate $BF_3 \cdot Et_2O$ is a highly efficient catalyst, which promotes intermolecular reactions of a wide range of phenols and propargyl alcohols giving 2*H*-chromene **193** (Scheme 85).[195] Madabhushi *et al.*[195] suggested that the intermolecular dehydration of alcohol and phenol results in the formation of propargyl ether, which undergoes intramolecular cyclization to chromene **193**.

Scheme 85



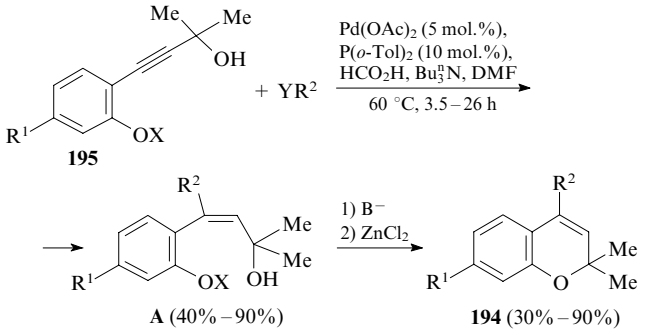
193 (64%–90%)

R^1_n = H, 2-Me, 3-Me, 4-Me, 3,5-Me$_2$, 2,5-Me$_2$, 4-OMe, 4-Br, 4-F, 4-NO$_2$, 4-CF$_3$, 2,3-benzo; R^2, R^3 = Me, Ph, CF$_3$; R^2–R^3 = (CH$_2$)$_5$; (*a*) $BF_3 \cdot Et_2O$ (15%), CH_2Cl_2, 25 °C, 6–48 h

The two-step synthesis of 2*H*-chromenes **194** was performed starting from arylpropargyl alcohols **195** containing the protected hydroxy group in the *ortho* position of the aromatic ring (Scheme 86).[196] The first step involves the Pd-catalyzed hydroarylation or hydroalkenylation of the triple bond of substrates **195** through the reaction with iodoarenes or cycloalkenyl triflates. The resulting adducts **A** are hydrolyzed in a basic medium to 1,5-diols, which are transformed into target chromenes **194** in the presence of $ZnCl_2$.

Arylpropargyl ethers **196** undergo intramolecular cyclization to substituted 2*H*-chromenes **197** in the presence of $PtCl_4$,[19,197] acetonitrile phosphine complexes of gold(I),[20,198] rhodium(II) trifluoroacetate,[21] the Brønsted superacid TfOH (see Ref. 91) or various Lewis acids[24,195] (Scheme 87). Gold complexes[20,198] or bismuth triflate[28] efficiently promote the annulation of ethers **196** containing both electron-donating and electron-withdrawing groups R^1 in the O-phenyl moiety giving target products in good

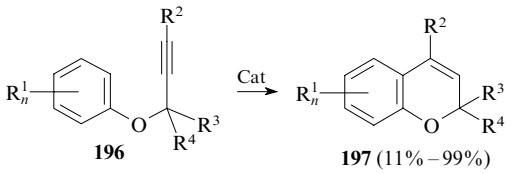
Scheme 86



R^1 = H, Me, CN, Bz; X = Ac, Bz; Y = I, R^2 = Ar; Y = OTf, R^2 is cycloalkenyl; B is base

yields. Besides, it was shown[198] that the gold(I) complexes that were examined are more versatile catalysts compared with silver(I) compounds, *e.g.* AgOTf. The latter also catalyzes such reactions but only with substrates **196** containing electron-donating substituents R^1. In reactions which can produce regioisomers (if R^1 = 3-Me), Au^I complexes exhibit high regioselectivity, resulting in the exclusive formation of 7-substituted chromenes, whereas Ag^I compounds give mixtures of 5- and 7-substituted isomers.

Scheme 87

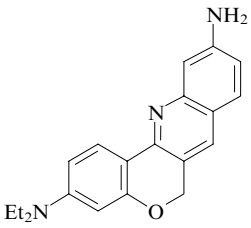


R^1_n = H, 2-Me, 3-Me, 4-Me, 3,5-Me$_2$, 2-OMe, 3-OMe, 4-OMe, 3,4-(OMe)$_2$, 2-F, 3-F, 4-F, 2-Br, 3-Br, 4-Br, 2-CN, 4-CN, 2-NO$_2$, 2-OMe-4-Ac, 2-NR′R″, 3-NR′R″, 4-NR′R″ (R′, R″ = H, Boc, Fmoc, Bu^n, C(O)Pr^n, *etc.*), 4-Bz, 4-CO$_2$Me, *etc.*; R^2 = H, Alk, CO$_2$Me, Ar, Hal, SPh, SePh, TePh, NTsPh; R^3, R^4 = H, Alk; FMOC is 9-fluorenylmethoxycarbonyl; Cat = [PtCl$_4$], [Pr$^i_2$(2-bph)PAu^{I}NCMe]$^+$A$^-$, [Rh$_2${OC(O)CF$_3$}$_4$], TfOH, CuCl, Bi(OTf)$_3$; 2-bph is biphenyl-2-yl, A$^-$ = SbF$^-_6$, Cl$^-$

Brønsted or Lewis acids can be used to promote the synthesis of functionalized chromenes. Seleno and telluro derivatives of arylpropargyl ethers **196** (R^2 = SePh, TePh) are transformed into 2*H*-chromenes **197** using TfOH-catalyzed reactions at room temperature in 5–60 min (see Scheme 87).[91] Eom *et al.*[24] demonstrated with several examples that sulfur (R^2 = SPh) and amino derivatives (R^2 = NTsPh) **196** give chromenes **197** under the combined action of two Lewis acids: $FeCl_3$ (5 mol.%) and AgOTf (15 mol.%). Chromenes **197** (R^2 = Hal) can be reduced to appropriate chromanes with the H_2–Pd/C–MeOH system accompanied by the replacement of the halogen atom.[21]

Copper(I) chloride catalyzes the reaction of propargyl ethers **196** (R^3 = R^4 = H) with diphenyliodonium triflate giving 3-phenyl-2*H*-chromenes.[29] The CuCl-catalyzed reactions of 4-(diethylamino)-2-propargyloxybenzaldehyde with anilines were used to prepare fused chromenoquinolines.[199] An example is the synthesis of chromenoquinoline **198**, which is an efficient pH sensor for fluorescent detection in living cells.

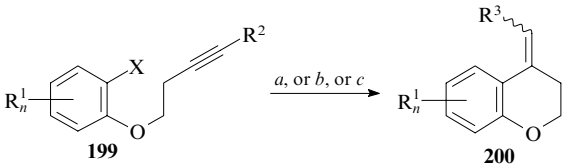
Structure 198



198

Rhodium(II) trifluoroacetate promotes intramolecular transformations of ω-chloro- and ω-bromoalkynyl ethers **199** (X = H: R^2 = Cl, Br) into 4-(halomethylidene)chromanes **200** (Scheme 88, conditions *a*),[21] with *Z*-isomers of chromanes predominating (⩾97%). The stereoselective synthesis of substituted *Z*- (conditions *b*) and *E*-chromanes **200** (conditions *c*) by the Pd-catalyzed cyclization of *o*-iodoarylalkynes **199** (X = I, R^2 = H or CH_2OH) was reported by Barberan *et al.*[200] In this process, iodoalkynes undergo intramolecular carbopalladation followed by carbonylation (conditions *b*) or hydride ion capture (conditions *c*). In conditions *b*, ester (R^3 = CO_2Me) that is formed in the first step is reduced to alcohol with lithium aluminium hydride.

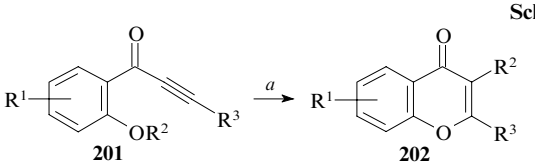
Scheme 88



(*a*) $Ph_2(OC(O)CF_3)_4$ (3 mol.% – 10 mol.%), PhMe, 80 °C, 18 h; for X = H: R^1_n = H, 2-Me, 4-OMe, 3,5-$(OMe)_2$, 2,3-benzo, 2-OMe-4-CH=CHMe; R^2 = R^3 = Cl, Br;
(*b*) $Pd(PPh_3)_4$, AgOAc, Et_3N, CO (1 atm), MeOH – DMF – H_2O, 100 °C, 10 h; for X = I: R^1_n = R^2 = H, R^3 = CH_2OH;
(*c*) 1) $Pd(OAc)_2$, PPh_3, $NaHCO_2$, Bu^n_4NCl, DMF, 80 °C, 18 h; 2) $LiAlH_4$; for X = I: R^1_n = H, R^2 = R^3 = CH_2OH

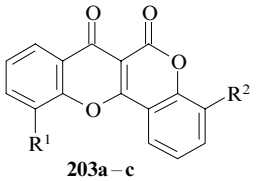
o-Hydroxyaryl ethynyl ketones **201** (R^2 = H, R^3 = Alk or Ar) are transformed into chromen-4-ones **202** in the TfOH – CH_2Cl_2 system (Scheme 89).[201] Ketones **201** containing an acylated (R^2 = Bz, CO_2All) hydroxy group in the *ortho* position of the aromatic ring are rearranged to chromenones **202** in the presence of PBu^n_3 (30 mol.%) (see Scheme 89).[202] In this reaction, PBu^n_3, as a base, adds to the C(3) atom of the triple bond of compounds **201**, thus facilitating the keto – enol tautomerism of the substrates. This step is followed by the transfer of the acyl group to the C(2) atom and the cyclization to chromenone **202**. It should be noted that, in the case of R^2 = CO_2Ph or $CO_2C_6H_4OMe$-4, the yields of products **202** were < 30%.

Scheme 89



R^2 = H: R^1 = H, 4-OMe, 5-OMe; R^3 = Bu^n, Bu^t, Cy, Ph, C_6H_4OMe-4, $C_6H_3(OMe)_2$-3,4, $C_6H_2(OMe)_3$-3,4,5 (yields of **202**: 40% – 91%);
R^1 = H, 3-THP; R^2 = Bz, CO_2Alk (Alk = Me, Et, Pr^i, Bu^t, CH_2CCl_3), CO_2All, CO_2Bn; R^3 = Ph, C_6H_4OMe-4, C_6H_4F-4 (83% – 99%);
THP is tetrahydropyranyl; (*a*) TfOH (1 equiv.), $(CH_2Cl)_2$, 40 – 80 °C, 1 – 48 h or PBu^n_3 (30 mol.%), PhMe, 30 °C, 5 – 15 min

Structures 203

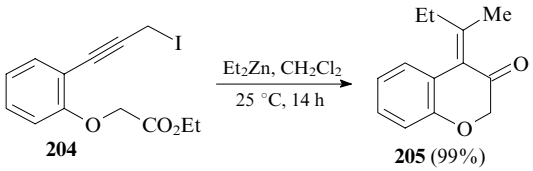


R^1 = R^2 = H (**a**);
R^1 = H, R^2 = OMe (**b**);
R^1 = OMe, R^2 = H (**c**)

203a – c

Diethylzinc was used in the reaction with polyfunctional derivatives **204** to synthesize chromen-3-one **205** (Scheme 90).[203] The EtZn group replaces the iodine atom in compound **204**. Then the organozinc intermediate undergoes the acetylene – allene rearrangement and a series of subsequent transformations to finally form chromenone **205**.

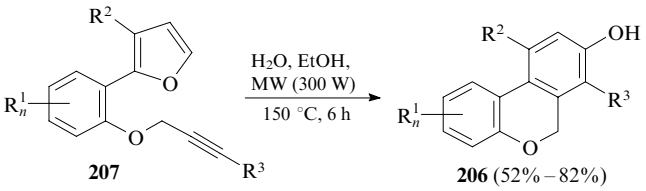
Scheme 90



205 (99%)

He *et al.*[204] developed a procedure for the synthesis of benzo[*c*]chromenes **206** based on the intramolecular Diels – Alder reaction involving the furan and acetylene moieties of substrates **207** followed by the transformation of the oxabicyclic moiety of the intermediate adduct into the benzene ring (Scheme 91). Since this reaction is performed in the absence of catalysts in aqueous ethanol under microwave-assisted conditions, it can be assigned to green chemistry methods. Chromenes **206** can be further oxidized to appropriate coumarins under mild conditions with hydrogen peroxide (EtOH, MW, 80 °C, 30 min).[204]

Scheme 91



206 (52% – 82%)

R^1_n = H, 4-Me, 4-Cl, 4-Br, 5-OMe, 4-NO_2, 3,4-benzo; R^2, R^3 = H, Me

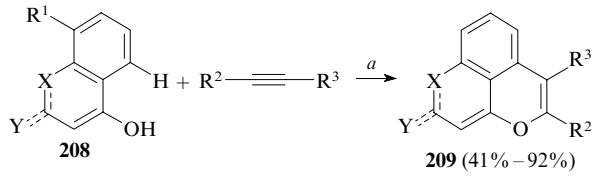
Recently, Niu and Hoye[205] have developed a three-step cascade procedure for the synthesis of various benzo[*c*]chromenes based on 1,3,8-triyne systems through the following steps: 1) the Diels – Alder reaction accompanied by the generation of a highly reactive aryne intermediate; 2) the intramolecular ene reaction of the aryne intermediate; 3) the bimolecular ene reaction.

The ruthenium(II) complex [CpRu(cod)Cl] served as the catalyst for the [2 + 2 + 2]-cycloaddition in order to construct an aromatic system from two acetylene moieties of the molecules and the triple bond of hex-1-yne in the synthesis of 2-methylidenebenzochromenes[172] by analogy with the synthesis of coumarin structures **181** and **182** (see Scheme 76).

Tanaka *et al.*[206] described an interesting example of the Rh^I-catalyzed formation of the chromene ring in the synthesis of enantiomeric helicene-like molecules based on the combined intra- and intermolecular [2 + 2 + 2]-cycloaddition involving propargyl ethers.[206]

Rhodium(III)[207] and ruthenium(II)[208] complexes catalyze intermolecular reactions of naphthols **208** (X = CH; Y = H) or hydroxy-substituted heterocycles **208** (X = O, NMe; Y = O) with alkynes giving chromene systems **209** (Scheme 92). It should be mentioned that the latter systems are formed through alkyne insertion into the C(8)–H bond of naphthol.[207] 4-Hydroxy-substituted coumarins and quinolinones **208** undergo similar transformations.[207] It should be noted that these processes are characterized by high regioselectivity.[208] The selective formation of tricyclic compounds **209** containing aryl substituents R^2 in position 2 of the chromene moiety is observed in reactions of unsymmetrical acetylenes containing aryl and alkyl groups. 4-Hydroxy-substituted coumarins and quinolinones **208** containing an addition aryl group in position 3 are involved in the same reactions catalyzed by the complexes $[Ru(p\text{-cymene})Cl_2]_2$ or $[CpRhCl_2]_2$.[209]

Scheme 92

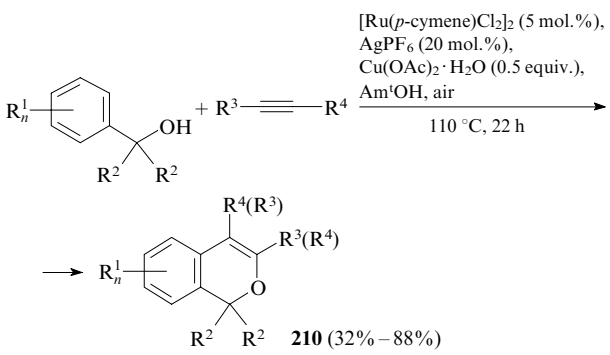


X = CH, Y = H; Y = O: X = O, NMe; R^1 = H, OMe, $NHC(O)CF_3$; R^2, R^3 = Alk, Ar; (*a*) [Rh] (0.5 mol.%) or [Ru] (2 mol.%–5 mol.%)

The $[CpRhCl_2]_2$–$Cu(OAc)_2$ system (at a high catalyst loading, up to 10 mol.%) was employed[210] to transform acetylenes and acetophenones containing electron-withdrawing substituents (CN, CO_2Et, NO_2) in the α-position first into naphthols **208**, which were then transformed, without isolation, under the reaction conditions to chromenes **209** (see Scheme 92), by analogy with the approach reported in another study.[207] The reactions of compounds containing a substituent in the *meta* position of the aromatic moiety of acetophenone produce mixtures of regioisomers **209** containing substituents in positions 4 and 6. Unsymmetrical phenylacetylenes (R^2 = Ph: R^3 = Me, Et, CH_2OMe) regioselectively form exclusively the above-mentioned isomers **209** containing the phenyl substituent in position 2 of the chromene. Tan *et al.*[210] attributed this selectivity to the effect of the phenyl group on stability of intermediate rhodium complexes.

The oxidative cyclization of benzyl alcohols with acetylenes promoted by a ruthenium catalyst affords isochromenes **210** (Scheme 93).[211] The use of unsymmetrical alkynes results in the formation of a mixture regioisomers **210**, in which the major product contains a bulkier substituent (R^3 = Ph) in position 3 of the isochromene system.

Scheme 93



R^1_n = H, 2-Me, 3-Me, 4-Me, 4-Bu^n, 3-F, 4-F, 4-Cl, 4-Br, 4-CF_3, 4-CO_2Et, 4-NO_2, 3,4-OCH_2O; R^2 = Me; R^2–R^2 = $(CH_2)_5$; R^3 = R^4 = Et, Pr^n, Bu^n, C_6H_4X-4 (X = H, Me, OMe, F, Cl, Br, CO_2Et, CF_3), C_6H_4F-3, C_6H_4Cl-3; R^3 = Ph: R^4 = Et, cyclo-C_3H_5, Bu^n, Hex

Therefore, the available procedures for the synthesis of derivatives of the chromene series are based on transformations of alkynes promoted both by metal complexes (Pd, Pt, Rh, Ru and so on) and electrophilic reagents (Brønsted and Lewis acids). The latter are highly efficient in intramolecular reactions of acetylenes.

* * *

An analysis of the published data on the methods of synthesis of (iso)quinoline, (iso)coumarin and (iso)chromene derivatives shows that reactions with acetylene compounds provide one of the most efficient and promising approaches to such heterocycles. The methods of synthesis using alkynes are characterized by the possibility of varying the starting substrates for the construction of the target heterocyclic system containing required substituents in specified positions. Besides, one can vary the catalysts (compounds of Pd, Pt, Ru, Rh, Au, Ag, Ni, Cu and so on) and activators (Brønsted and Lewis acids) of these transformations and the reactions conditions (temperature, time and solvent).

There are several new lines of investigations in this area of organic synthesis. One of them is the increasing use of rhodium and ruthenium catalysts in these processes. In the past five years, the number of publications on the synthesis of substituted (iso)quinolines, (iso)coumarins and (iso)chromenes from alkynes, particularly, using Rh and Ru complexes as catalysts, has risen sharply. Compounds of these metals gradually replace conventional catalyst systems based on Pd and Pt in activation processes of C–X single bonds (X = H, Hal, SAlk). Compared to Brønsted and Lewis acids, ruthenium and rhodium compounds are more tolerant to substituents, both labile (carboxy, ester, ether, *etc.* groups) and deactivated (amino groups and related nitrogen-containing groups), under acidic conditions. It can be expected that Rh and Ru catalysts will be used for increasingly diverse applications in the chemistry of acetylene derivatives.

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