Cyclization Reactions for the Synthesis of Phthalans and Isoindolines

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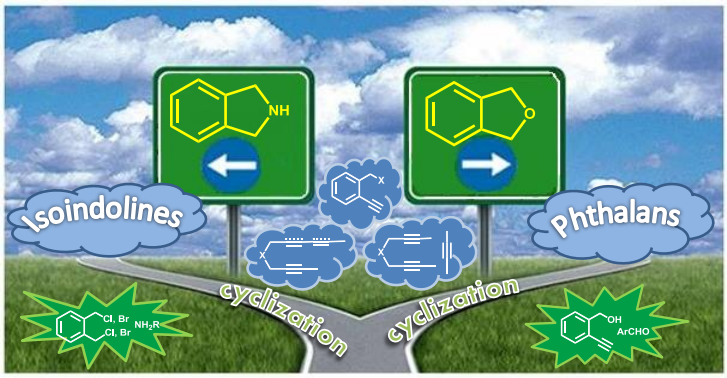

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Abstract Oxygen and Nitrogen-heterocyclic compounds are present in a vast number of natural substrates and biologically active molecules. In particular, phthalan and isoindoline subunits are found in many classes of products such as antibiotics, antioxidants, antimicotics, pigments and fluorophores. Therefore several procedure dedicated to the construction of these heterocycles have been developed. In this review a detailed analysis of literature data regarding the synthesis of these nuclei via cyclization reactions is reported.

Key words phthalan, isoindoline, cyclization, transition metal catalysis, Sonogashira reaction

1 Introduction

The chemistry of oxygen and nitrogen-containing heterocycles has attracted much attention in recent times due to its increasing importance in the fields of pharmaceutical compounds and industrial chemicals. In particular, phthalan (1,3-dihydoisobenzofuran) and isoindoline (Figure 1) subunits are present in many classes of products. For instance, phthalan moiety has been found in pestacin (Figure 2 A), isolated in 2003 by Grant *et al.* from *Pestalotiopsis microspora*, and revealed good antimycotic and antioxidant properties.[1] Many synthetic phthalans showed remarkable pharmacological activities: citalopram (Figure 2 B) developed in 1989, is a serotonine reuptake inhibitor used in the treatment of depressive syndromes and anxiety disorders.[2]

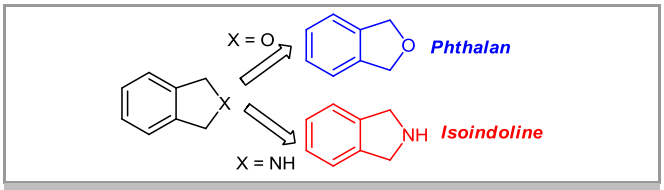


Figure 1 Phthalan and isoindolines structures.

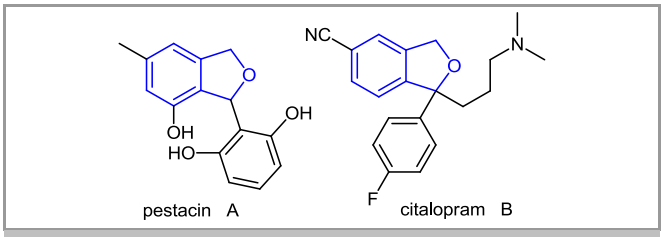


Figure 2 Chemical structure of bioactive phthalans: pestacin (A), citalopram (B).

Analogously, several isoindoline derivatives act as efficient enzymatic inhibitors,[3] display antipsychotic activity,[4] and show citotoxicity against human colon and cervical cancer cells[5] (Figure 3). Besides, isoindoline diyilidene-based compounds are the nuclei of pigments which cover the range from greenish yellow to orange, red and brown.[6]

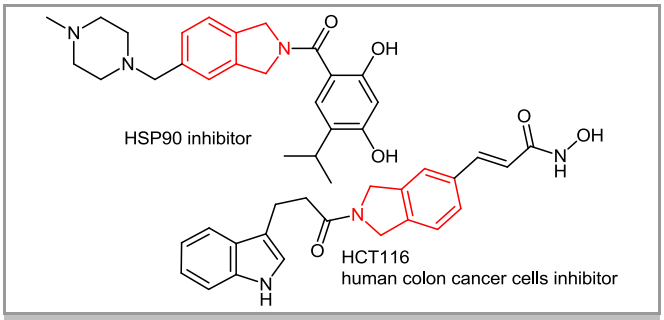
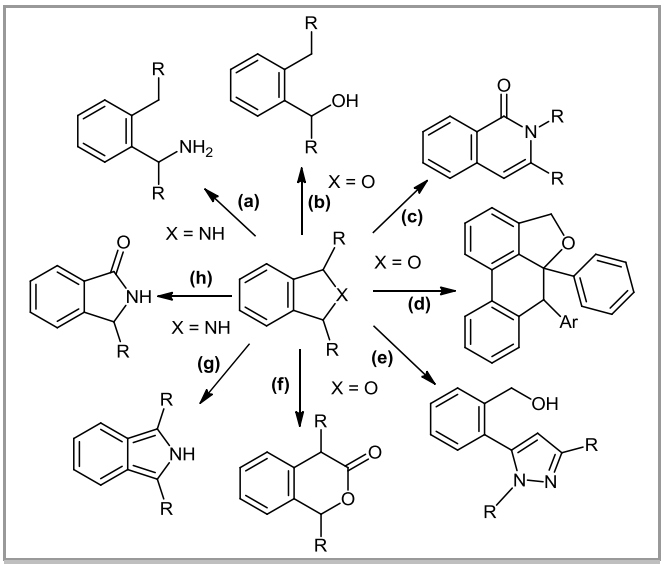


Figure 3 Examples of isoindolines-based biologically active compounds.

From the point of view of chemical reactivity, both phthalans and isoindolines are powerful building blocks for the syntheses of numerous classes of compounds: benzylic alcohols[7] and amines[8] (Scheme 1, a, b), isoquinolin-1(2H)-ones (Scheme 1, c),[9] phenanthro[10,1-*bc*]furans (Scheme 1, d),[10] pyrazoles (Scheme 1, e),[11] isochroman-3-ones (Scheme 1,f),[7] isoindoles (Scheme 1, g),[12] and isoindolinones (Scheme 1, h).[13]



Scheme 1 Chemical reactivity of phthalans and isoindolines.

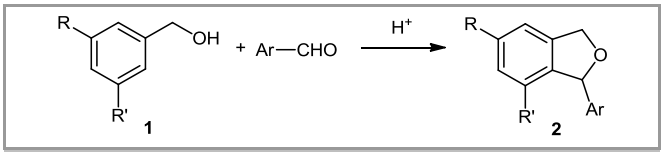
Several procedures dedicated to the construction of such heterocycles have been developed. Many of them are based on the cyclization of suitable substrates. This review is focused on the principal cyclization-based routes to the formation of phthalans and isoindolines nuclei. In particular the literature regarding each heterocycle has been organised in two chapters which have been divided into sections concerning a specific synthetic method.

2 Phthalans

Several procedures for phthalans synthesis based on cyclization strategies have been described in the literature, including a very large number of substrates, reactants and conditions. However, they can be grouped in the following sections, discussed below: a) oxa-Pictet-Spengler reaction; b) Garratt-Braverman cyclization; c) Diels-Alder and related reactions; d) [2+2+2] cyclotrimerization of alkynes; e) cycloetherification of *ortho*-substituted aromatics; f) cyclocarbonylative Sonogashira reaction.

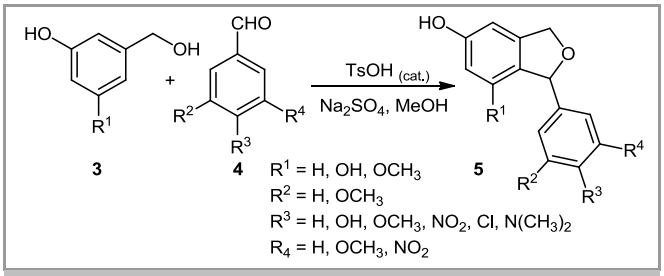
2.1 Oxa-Pictet-Spengler reaction

Widely used for obtaining isochroman systems,[14] the oxa-Pictet-Spengler reaction has also found application in the synthesis of several polysubstituted phthalans (Scheme 2).



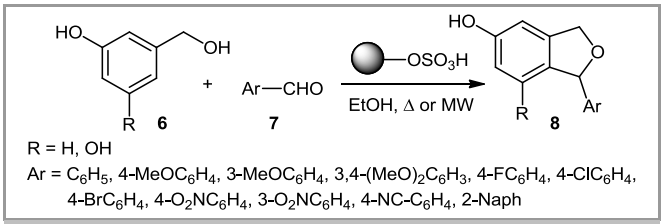
Scheme 2 Phthalans synthetic strategy by oxa-Pictet-Spengler reaction.

The first work was reported by Marra et al., which described the preparation of hydroxyphthalans **5** by acid-catalyzed condensation of benzyl alcohols **3** with 3,4,5-trisubstituted benzaldehydes **4** in methanol as solvent (Scheme 3).[15]



Scheme 3 Synthesis of hydroxyphthalans through oxa-Pictet-Spengler reaction.

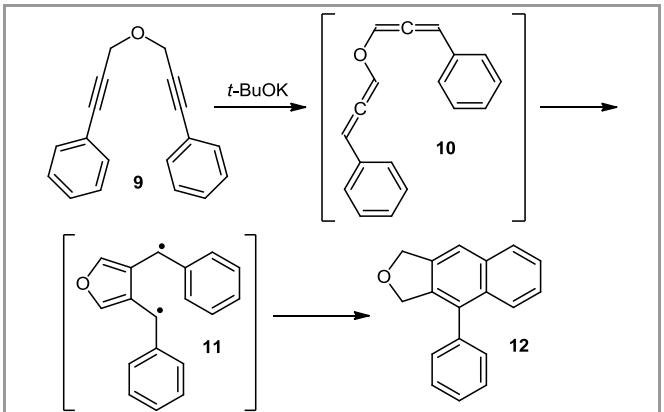
More recently, Khosropour and coll. developed a new protocol, consisting in the use of nanosilica sulfuric acid (NSSA), obtained by adding chlorosulfonic acid to nano-SiO_2 at room temperature, as reusable heterogeneous catalyst.[16] It was successfully used for the synthesis of hydroxyphthalans **8** under both conventional heating and microwave irradiation (Scheme 4).



Scheme 4 Khosropour's synthesis of hydroxyphthalans via oxa-Pictet–Spengler reaction catalyzed by nanosilica sulfuric acid.

2.2 Garratt-Braverman cyclization

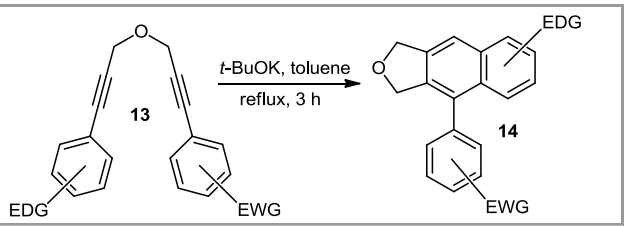
A valid synthetic approach to benzofused phthalans is the Garratt-Braverman (GB) reaction, consisting in a base-promoted cyclization of *bis*(3-aryl-2-propargyl)ethers (Scheme 5). At first reported by Iwai and Ide,[17] the mechanism was deeply investigated by Garratt et al., which hypothesized the formation of *bis*-allene **10**, followed by rearrangement to the product **12** passing through the diradical intermediate **11** (Scheme 5).[18]



Scheme 5 Garratt-Braverman (GB) approach to benzofused phthalans.

A wide study on GB route to substituted benzofused phthalans was carried out by Basak's group: in particular, for unsymmetrical *bis*-propargyl ethers they found a good selectivity in the cyclization

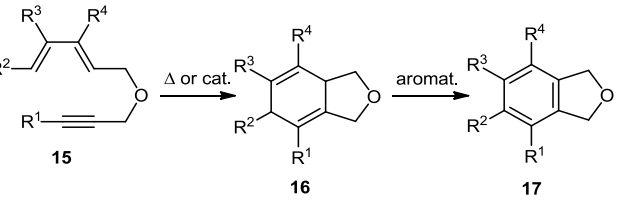
step only using aryl rings of different electronic properties, i.e. one donating and the other withdrawing (Scheme 6).[19]



Scheme 6 Selective Garratt-Braverman (GB) cyclization of unsymmetrical *bis*-propargyl ethers .

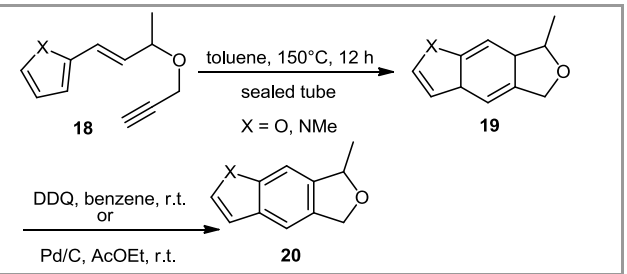
2.3 Diels-Alder and related reactions

Intramolecular Diels-Alder (IMDA) is a convenient methodology for the synthesis of many polycyclic organic compounds, including phthalans. A very common approach is the [4 + 2] cycloaddition of 2,4-dien-1-yl propargyl ethers **15** or their analogues under thermal or metal-catalyzed conditions, which provides phthalans **17** as final products after an aromatization step of resulting dihydrophthalan cycloadducts **16** (Scheme 7).



Scheme 7 Intramolecular Diels-Alder (IMDA) of 2,4-dien-1-yl propargyl ethers under thermal or metal-catalyzed conditions.

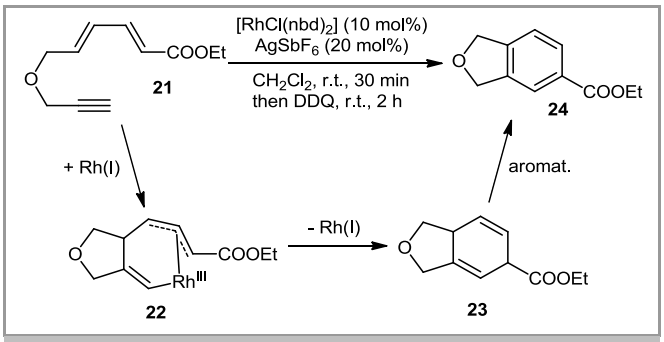
Several examples of thermal intramolecular Diels-Alder of these systems are described in the literature. Shealy et al. reported the reaction of retinyl 2-propynyl and 2-butynyl ethers, performed in refluxing ethanol and toluene respectively; cycloadducts were treated at room temperature with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry benzene yielding the corresponding phthalans.[20] Moreover, Fernandez de la Pradilla and coll. examined the IMDA of 2-sulfinyl butadienes tethered to unactivated alkynes, including propargyl ether groups.[21] Thermal IMDA on slightly different compounds was studied by Kanematsu et al.: they investigated the preparation of pyrrole- or furan-fused phthalans **20** through Diels-Alder reaction of propargyl ethers **18**, performed in toluene at 150°C in sealed tubes for 12 h, followed by aromatization of dihydrophthalans **19** with DDQ in benzene or with Pd/C in AcOEt at room temperature (Scheme 8).[22]



Scheme 8 Preparation of pyrrole- and furan-fused phthalans by thermal IMDA.

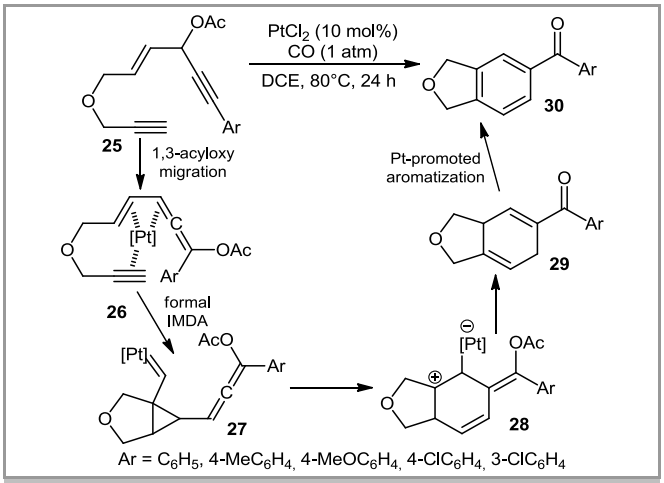
Recently, many protocols for metal-catalyzed IMDA of 2,4-dien-1-yl propargyl (and similar) ethers were also developed. The proposed mechanisms for these formal [4 + 2] cycloadditions are generally multi-step with a central role of metal species, including oxidative addition–reductive elimination sequence and/or ionic intermediate formation.

Dudley *et al.* reported a breakthrough methodology for Rh-promoted Diels-Alder-type reaction of tethered alkyne-dienoate substrates, including ether **21**: the reaction was performed at room temperature using a cationic rhodium(I) norbornadiene catalyst (10 mol%) together with silver hexafluoroantimonate (20 mol%) as additive, followed by treatment with DDQ.[23] The authors hypothesized an initial coordination of Rh(I) to the π-system, followed by cyclization to rhodium(III) intermediate **22** and reductive elimination to regenerate Rh(I) and release **23**, which is later oxidized to corresponding phthalan **24** (Scheme 9).



Scheme 9 Rh-promoted formal IMDA of tethered alkyne-dienoate substrates

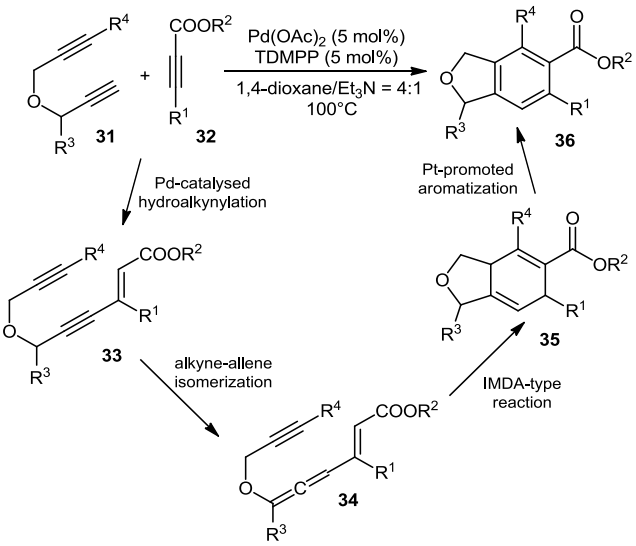
Liang and coll. described instead a Pt-catalyzed cycloaddition of 4-acetoxy-2-en-5-yn-1-yl propargyl ethers **25**.[24] Under Pt catalysis, the propargylic acetate group underwent a 1,3-acyloxy migration affording the corresponding allene intermediate **26**, followed by IMDA-type and aromatization reactions to give **30**. The proposed mechanism for formal cycloaddition proceeded with the formation of metal carbene complex **27**, which through ionic intermediate **28** gave phthalan **29** (Scheme 10).



Scheme 10 Pt-catalyzed formal IMDA of 4-acetoxy-2-en-5-yn-1-yl propargyl ethers

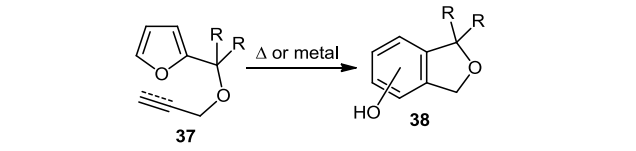
Moreover, Zhang developed a facile synthesis of polysubstituted phthalans by means of a Pd-catalyzed tandem process,[25] consisting of: a) addition of terminal alkyne groups of dipropargyl ethers **31**

to electron-poor alkynes **32** affording the 4-en-2-yn-1-yl propargyl ethers **33**; b) propargyl-allenyl isomerization to the corresponding allene derivative **34**; c) palladium-mediated formal IMDA, followed by aromatization process of cycloadducts **35** to give final products **36** (Scheme 11).



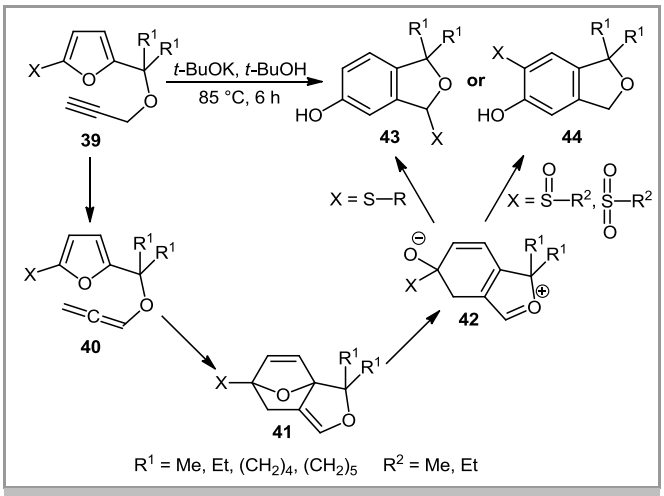
Scheme 11 Pd-catalyzed tandem hydroalkynylation, isomerization, Diels-Alder cycloaddition and aromatization developed by Zhang's group.

The IMDA route to phthalans is also possible, both under thermic and metal-catalyzed conditions, with a different class of molecules: 2-propargyloxymethyl and 2-allyloxymethyl furans (Scheme 12).



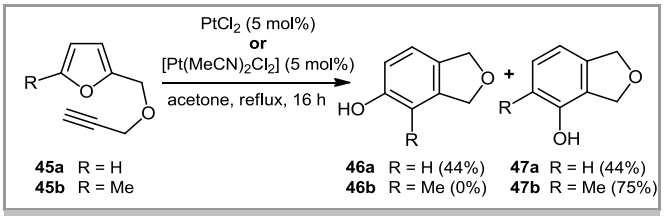
Scheme 12 Synthetic approach to phthalans by IMDA of 2-propargyloxymethyl and 2-allyloxymethyl furans under thermal or metal-catalyzed conditions.

This alternative approach was first developed by Wu *et al.*, which described the thermal cyclization of 5-sulfur-substituted furans **39**, performed at 85°C with catalytic amounts of *t*-BuOK in *t*-BuOH.[26] Surprisingly, this protocol produced 3-thio-substituted phthalans **43** if furans **39** are functionalised with a thioether group, while with a sulfoxide or sulfone group they gave 6-thio-substituted phthalans **44**. A possible mechanism is that [4 + 2] cycloaddition took place on the furfuryl allenyl ethers **40** affording the bridged cycloadduct **41**, followed by its cleavage to give the zwitterionic intermediate **42**; in the case of alkylthio group, an uncommon 1,4-rearrangement took place to yield **43**, whereas an analogous 1,2-shift generated phthalans **44** for alkyl-sulfoxide or -sulfone groups (Scheme 13). The same approach was further investigated by Torosyan[27] and, more recently, extended to 2-allyloxymethyl furans by Demircan's group.[28]



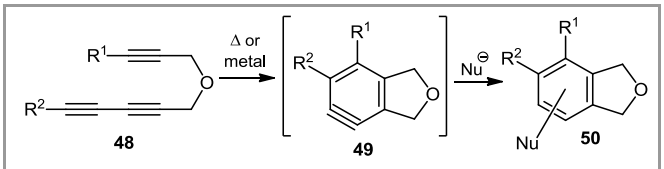
Scheme 13 Thermal IMDA of 5-sulfur-substituted furans.

Echavarren and coll. developed a platinum-catalyzed protocol for formal IMDA of furfuryl propargyl ethers: in refluxing acetone with $PtCl_2$ or $[PtCl_2(MeCN)_2]$ as catalyst (5 mol%) for 16 h, formal cycloaddition of furan **45a** gave an equimolar mixture of 5-hydroxyphthalan **46a** and 4-hydroxyphthalan **47a**, while with 5-methyl-substituted furan **45b** only product **47b** was obtained (Scheme 14).[29] In particular, the reaction seems to proceed with the formation of a cyclopropyl platinum(II) carbene intermediate. A similar mechanism (i.e. via metal carbenoid rearrangement) was also hypothesized by Hashmi *et al.* for the synthesis of several 1,3-dihydroisobenzofurans by Au-promoted formal Diels-Alder of many poly-substituted 2-propargyloxymethyl furans.[30]



Scheme 14 Hydroxyphthalans synthesis by Platinum(II)-catalyzed formal IMDA of 2-propargyloxymethyl furans.

In addition to the above discussed IMDA protocols, a more recent synthetic approach to phthalans based on [4 + 2] cycloadditions is the hexadehydro Diels-Alder (HDDA) of triynes **48**. The reaction generally proceeds with the formation (under thermal or metal-mediated conditions) of benzyne intermediate **49**, which then undergoes a nucleophilic addition step to give functionalised phthalans **50** (Scheme 15).



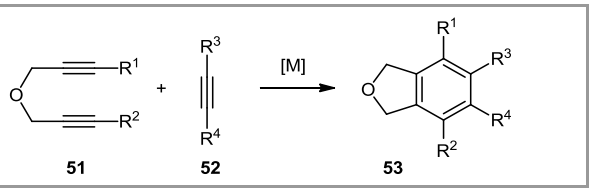
Scheme 15 Synthetic approach to functionalised phthalans by hexadehydro Diels-Alder (HDDA) reaction of triynes.

For this purpose, a very large number of nucleophiles were deeply investigated: $AgBF_4$, $AgCF_3$ and $AgSCF_3$ were used for the synthesis of fluorinated, trifluoromethylated and trifluoromethylthiolated phthalans, respectively;[31] silver trifluoroacetate found application

in the preparation of poly-substituted hydroxyphthalans, obtained from the corresponding trifluoroacetoxy derivatives after a simple chromatographic purification step;[32] Li_2CuCl_4 was very efficient for dichlorination of HDDA-generated benzynes, giving 4,5-dichloro-1,3-dihydroisobenzofurans in good yields;[33] halo-hydrocarbons such as CH_2Cl_2, $CHCl_3$, CH_2Br_2 and CH_2I_2 were used to convert many *bis*-2,4-diynyl ethers into chloro- bromo- and iodo-functionalized phthalans, in the presence of a ruthenium alkylidene complex as catalyst;[34] various phenols, instead, gave at the *ortho*-position a phenol-ene process with HDDA-generated benzynes, generating aryl-substituted phthalans;[35] linear and cyclic alkyl sulfides were applied for obtaining – through *S*-aryl sulfur ylide intermediates – many 5-alkylthio-substituted phthalans;[36] *N*-heterocyclic carbene (NHC) boranes were used in the selective hydroboration of HDDA-generated benzynes (i.e. without reacting with triyne precursor), so providing borane-functionalized phthalans;[37] very recently, also several nitriles were found able to react, in the presence of $AgSbF_6$ as catalyst, with benzyne intermediates, inducing a Ritter-type step to give amide- or imide-substituted 1,3-dihydroisobenzofurans.[38]

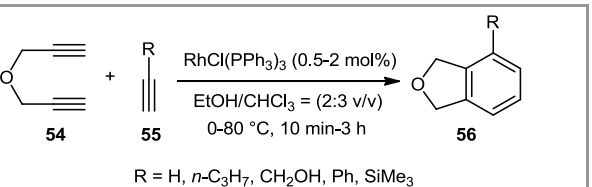
2.4 [2+2+2] Cyclotrimerization of alkynes

Metal-catalyzed [2+2+2] cyclotrimerization of alkynes is a powerful methodology for the preparation of several benzofused moieties, including phthalans. In fact, the reaction of dipropargyl ethers **51** with functionalised alkynes **52** in the presence of a transition metal catalyst provides poly-substituted phthalans **53** (Scheme 16).



Scheme 16 Synthesis of phthalans by metal-catalyzed [2+2+2] cyclotrimerization of alkynes.

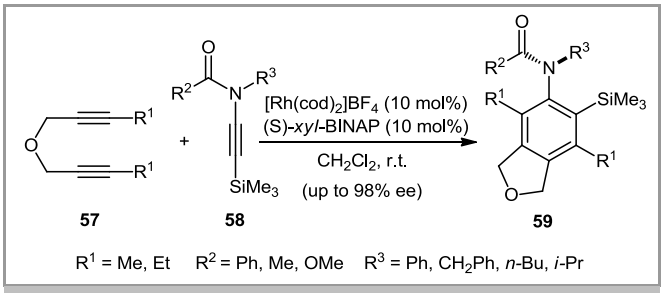
The first example of [2+2+2] cycloaddition approach to phthalans was developed by Grigg's group, which described the reaction of diynes, including *bis*-propargyl ether **54**, with monoacetylenes **55** promoted by Wilkinson's catalyst $RhCl(PPh_3)_3$ (0.5-2 mol%) under mild conditions (Scheme 17).[39]



Scheme 17 First example of Rh-catalyzed [2+2+2] cycloaddition approach to phthalans.

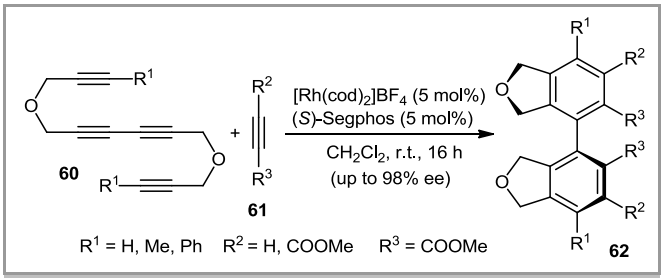
In few years, Rh-promoted [2+2+2] cyclotrimerization of alkynes became one of the most common synthetic routes to functionalised 1,3-dihydroisobenzofurans. A wide range of substrates have been investigated, including diynes and alkynes with high degree of steric hindrance,[40] perfluoroalkylacetylenes,[41] glycoside units bearing *bis*-propargyl ethers,[42] 1-alkynylphosphine sulphides,[43] propargyl glycine aminoacids,[44] as well as synthetic equivalents of alkynes like enol ethers/acetates[45] or (*Z*)-(2-bromovinyl)trifluoroborate,[46] and even solid-supported diynes.[47] In addition, several rhodium(I) complexes were found to be very efficient as catalysts, obtained by treatment of a rhodium(I) precursor with proper ligands: 4,5-bis(2-oxazolinyl)xanthene (Xabox),[48] *N*-phosphino *t*-butylsulfinamides (PNSO),[49] *tris*(*meta*-sulfonatophenyl)phosphine trisodium salt (tppts)[50] and a 2,2′-bipyridine cationic derivative[51] (both water-soluble), and more recently also *N*-heterocyclic carbenes supported on silica.[52]

A very exciting application of Rh-catalyzed [2+2+2] cycloadditions is the enantioselective synthesis of axially chiral compounds bearing phthalan moieties, performed in the presence of enantiopure chiral ligands. The first example was reported in 2006 by Tanaka and coll., in which developed a protocol for enantioselective intermolecular [2+2+2] cycloaddition of diynes **57** with trimethylsilylynamides **58** for the preparation with high enantioselectivity (up to 98% ee) of axially chiral anilides **59**, using $[Rh(cod)_2]BF_4$ and (*S*)-*xyl*-BINAP (10 mol%) as catalytic system, in CH_2Cl_2 at room temperature (Scheme 18).[53]



Scheme 18 Tanaka's synthesis of axially chiral anilides via enantioselective Rh-catalyzed [2+2+2] cycloaddition of alkynes.

The same group then developed a enantioselective synthesis of the C_2 symmetric tetra-*ortho*-substituted axially chiral biaryls **62**, performed with $[Rh(cod)_2]BF_4$ (5 mol%) as metal precursor and (*S*)-Segphos (5 mol%) as chiral ligand (Scheme 19).[54] Similar protocols have been described in the following years, concerning the synthesis of many chiral compounds bearing phthalan moieties: biaryl diphosphines,[55] diphosphonates and dicarboxylates,[56] *N*,*O*-biaryls,[57] *P*-stereogenic alkynylphosphine oxides,[58] as well as axially chiral *N*,*N*-dialkylbenzamides,[59] 1-arylisoquinolines[60] and hydroxy carboxylic acid derivatives.[61]

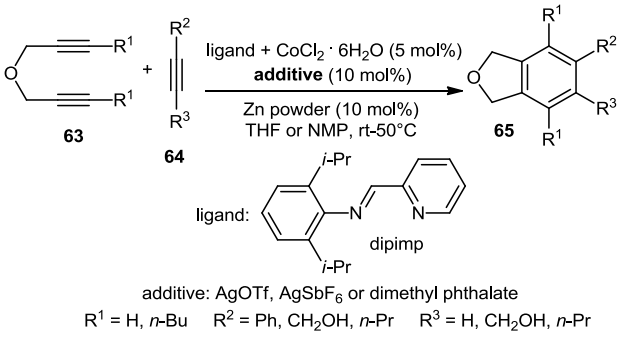


Scheme 19 Synthesis of tetra-*ortho*-substituted axially chiral biaryls via enantioselective Rh-catalyzed [2+2+2] cycloaddition of alkynes.

Although rhodium-based complexes are the most applied catalysts for phthalans synthesis via [2+2+2] cyclotrimerization of alkynes, other transition metals were also intensively studied.

In 2002, Sugihara et al. reported the first synthetic route to 1,3-dihydroisobenzofurans by Co-catalyzed [2+2+2] cyclotrimerization reactions, performed with methylidynetricobalt nonacarbonyl (2 mol%) in refluxing toluene.[62] Many cobalt-based catalytic systems

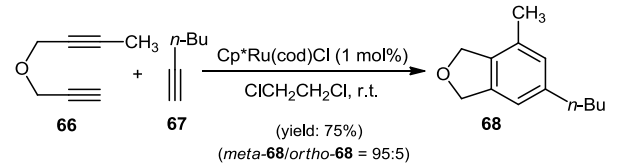
were then explored, ranging from the most common $[Co_2(CO)_8]$[63] and $[CpCo(CO)_2]$[64] to phosphine complexes like $[CoBr(PPh_3)_3]$,[65] $[CoI_2(PPh_3)_2]$[66] and $[CoCl(PPh_3)_3]$.[67] Hapke and coll. described a systematic study by ligand variation on the [CpCo^I(bisphosphite)] and [CpCo^I(olefin)(phosphite)] complexes reactivity in the [2+2+2] cycloaddition route to phthalans,[68] while Gandon et al. developed a set of air-stable cobalt cyclopentadienyl complexes incorporating a fumarate and a CO ligands.[69] Okamoto's group studied intensively a catalytic system for [2+2+2] cyclotrymerization of alkynes based on $CoCl_2 \cdot 6H_2O$/Zn in the presence of 2-(arylimino)methylpyridine (dipimp) as ligand: in particular, they found that the addition of a silver(I) salt (AgOTf or $AgSbF_6$)[70] or the dimethyl phthalate[71] as additive significantly increased its catalytic activity (Scheme 20).



Scheme 20 Okamoto's route to phthalans via [2+2+2] cycloaddition of alkynes.

Very recently, few examples of asymmetric Co(I)-catalyzed [2+2+2] cyclotrimerization of alkynes to axially chiral compounds bearing dihydrofuran-fused phthalans have been reported.[72]

Phthalans preparation by Ru-promoted [2+2+2] cyclotrimerization has long been investigated by Yamamoto and coll., always exploiting Cp*Ru(cod)Cl complex (with Cp* = pentamethylcyclopentadienyl) as catalytic system. In 2000, the cycloaddition of unsymmetrical 1,6-diynes, including ether **66**, with mono-substituted alkynes like 1-hexyne **67** was reported: the reaction, performed with low catalyst loading (1 mol%) at room temperature and in 1,2-dichloroethane as solvent, gave the corresponding cycloadduct **68** in good yields (75%) and high *meta*-regioselectivity (Scheme 21).[73] The authors then extended the same protocol to intramolecular [2+2+2] alkyne cycloadditions[74] and to more functionalized substrates, such as *bis*-propargyl ethers bearing ribosyl units,[75] diynes or alkynes with boronate groups[76] and iododiynes.[77] However, more recently the synthesis of phthalan-based compounds has been extended to other ruthenium-based catalysts.[78]

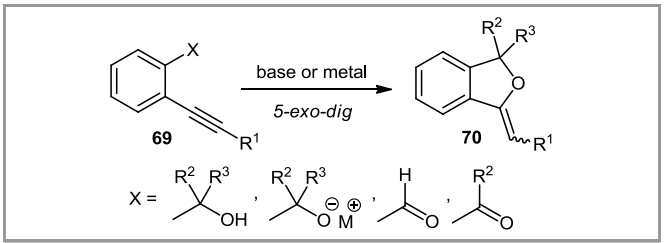


Scheme 21 First example of phthalans synthesis by Ruthenium-catalyzed [2+2+2] cyclotrimerization of alkynes.

Iridium compounds have also been studied as catalysts for [2+2+2] cycloadditions of α,ω-diynes with monoalkynes to give benzofused derivatives, including phthalans. Takeuchi and coll. have found that $[Ir(cod)Cl]_2$ combined with the 1,2-*bis*(diphenylphosphino)ethane (dppe) ligand was an efficient catalyst for these reactions,[79] while Michelet and Ratovelomanana-Vidal proposed the use of complex $[\{Ir(H)[rac\text{-binap}]\}_2(\mu\text{-}I)_3]I$, able to tolerate a broad range of groups (alcohol, alkyl, ether and halogen) on the alkynyl substrate.[80] More recently, a $SnCl_2$-induced cyclotrimerization of alkynes catalyzed by phosphine-free $[Ir(cod)Cl]_2$ was developed.[81] Moreover, a couple of protocol for the synthesis of phthalan-based axially chiral systems through enantioselective Ir-catalyzed [2+2+2] cyclotrimerization of alkynes were investigated by Shibata's group.[82] Few examples for phthalans synthesis via [2+2+2] cycloaddition of alkynes catalyzed by other transition metals like nickel,[83] iron,[84] palladium[85] and titanium[86] were also reported.

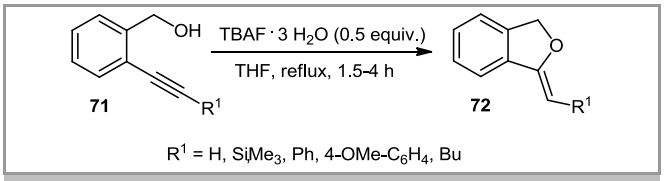
2.5 Cycloetherification of *ortho*-substituted aromatics

The most common synthetic approach to phthalans is based on the cycloetherification of benzyl alcohols (or also their derivatives, such as benzaldehydes and benzyl alkoxides generated *in situ*) having an appropriate *ortho*-substituent. Although several *ortho*-groups have been deeply investigated including epoxides,[87] oxetanes,[88] 1,2,3-triazole rings,[89] quaternary ammonium salts,[90] benzyl halides or alcohols[91] and alkenes,[92] particularly interesting is the 5-*exo-dig* cyclization of *ortho*-alkynyl *O*-benzyl-functionalized aromatics **69** to give 1-alkylidene-1,3-dihydroisobenzofurans **70** (Scheme 22), not obtainable with all the above-described methodologies. However, the reaction is generally promoted by a stoichiometric amount of base or catalytic amounts of a metal catalyst.



Scheme 22 Synthesis of alkylidenephthalans by 5-*exo-dig* cycloetherification of benzyl alcohols (or their derivatives) bearing an *ortho*-alkynyl group.

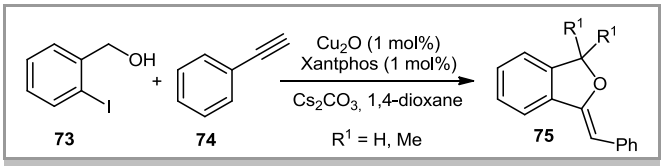
Padwa et al. reported 5-*exo-dig* cyclization of 2-(arylethynyl)benzyl alcohols with two different basic conditions (*i.e.* KOH in refluxing MeOH or NaH in refluxing THF),[93] while Liu's group proposed a *t*-BuOK-promoted protocol for the cycloetherification of very similar substrates.[94] Larock and coll. described the iodocyclization of 2-(1-alkynyl)benzylic alcohols, performed with I_2 and $NaHCO_3$ as base: although 6-*endo-dig* cyclization is generally preferred, with tertiary alcohols only (*Z*)-alkylidenephthalans were obtained, by exploiting the *gem*-dialkyl effect.[95] Hiroya and Sakamoto described a TBAF-promoted cyclization of 2-ethynylbenzyl alcohols **71** (Scheme 23): working in refluxing THF, alkylidenephthalans **72** were obtained with good yields in few hours; only with steric-hindered substrates small amounts of the corresponding 6-*endo-dig* cycloadducts were also obtained.[96]



Scheme 23 Synthesis of alkylidenephthalans by TBAF-promoted 5-*exo-dig* cycloetherification of 2-ethynylbenzyl alcohols.

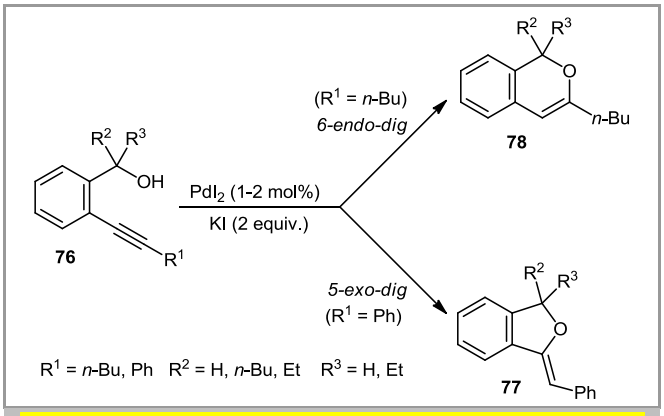
Herndon proposed instead a potassium fluoride-mediated cyclization of *O*-silylated benzyl alcohols with a carbonyl-substituted alkyne group in the *ortho*-position.[97] As an alternative, *ortho*-alkynylbenzaldehydes have been studied as substrates for 1,3-dihydroisobenzofurans preparation by base-promoted 5-*exo-dig* cycloetherifications.[98] However, metal-catalyzed 5-*exo-dig* cyclization of *o*-alkynyl benzyl alcohols (or derivatives) represents a more common methodology: alkaline earth,[99] lanthanides,[100] actinides[101] and transition metals (such as mercury,[102] zinc,[103] gold,[104] platinum[105] and rhodium[106]) compounds, in fact, have been widely investigated as catalysts for phthalan synthesis via cycloetherification. Nevertheless, the most investigated systems are based on copper or palladium.

In 2010, Lee *et al.* developed the first protocol for Cu(I)-catalyzed preparation of alkylidenephthalans through 5-*exo-dig* cyclization: treatment of 2-iodobenzyl alcohols **73** with phenylacetylene **74**, using Cu_2O and 4,5-*bis*(diphenylphosphino)-9,9-dimethylxanthene (xantphos), gave (*Z*)-alkylidenephthalans **75** in good yields (Scheme 24).[107]



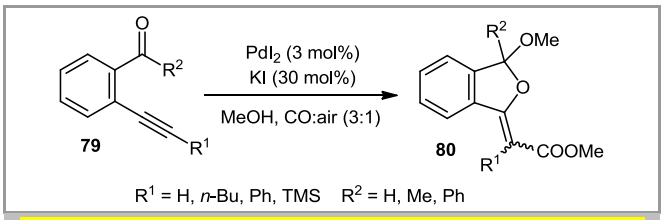
Scheme 24 Lee's synthetic route to phthalans, performed with Cu_2O and xantphos as catalytic system.

In the same year, Perumal's group described a $Cu(OTf)_2$-promoted synthesis of alkylidenephthalans,[108] while more recently Brent Gunnoe and coll. investigated the use of copper(I) complexes bearing *N*-heterocyclic carbene (NHC) ligands for intramolecular hydroalkoxylation of alkynols.[109]



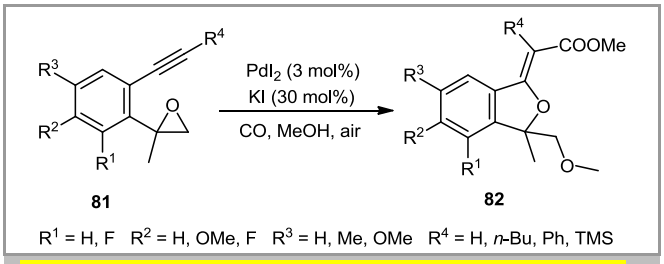
Scheme 25 Gabriele's protocol for Pd-catalyzed cyclization of 2-alkynylbenzyl alcohols into (Z)-alkylidenephthalans and 1*H*-isochromenes.

Palladium-catalyzed 5-*exo-dig* cyclization of ortho-alkynyl *O*-benzyl-functionalized aromatics have been intensely studied by Gabriele and coworkers. In 2003, they reported the cycloisomerization of 2-alkynylbenzyl alcohols **76** into (*Z*)-alkylidenephthalans **77** and 1*H*-isochromenes **78** using PdI_2 (1–2 mol%) in the presence of KI as additive:[110] in particular, benzyl alcohols with alkyl-substituted triple bond gave preferentially 6-endo-dig reaction, while substrates with an aryl-substituted triple bond afforded phthalans as main product (Scheme 25). In 2004 they extended this PdI_2/KI system to the oxidative carbonylation of *o*-alkynyl-substituted benzaldehydes and phenyl ketones **79** to give 1-(alkoxycarbonyl)methylene-phthalans **80** in good yields (Scheme 26).[111]



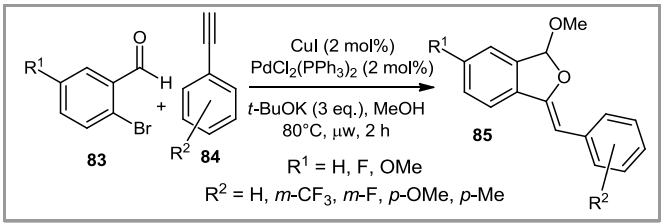
Scheme 26 Synthesis of 1-(alkoxycarbonyl)methylene-phthalans via oxidative carbonylation of *ortho*-alkynyl-substituted benzaldehydes and phenyl ketones.

More recently, they developed a similar protocol for (*Z*)-alkylidenephthalans synthesis from *ortho*-alkynyl aryloxiranes **81** through nucleophilic ring opening–heterocyclization–oxidative carbonylation process (Scheme 27).[112]



Scheme 27 Synthesis of (Z)-alkylidenephthalans from *o*-alkynyl aryloxiranes.

Although Kwon et al. developed a tandem Michael-Heck reaction of 2-iodobenzyl alcohols with electron-poor alkynes,[113] most of the Pd-promoted routes to alkylidenephthalans involved a sequential Sonogashira coupling followed by 5-*exo-dig* cyclization. Abbiati et al. developed a microwave-assisted protocol for the synthesis of (*Z*)-1-alkylidene-3-methoxy-1,3-dihydroisobenzofurans **85** by reaction of functionalised 2-bromobenzaldehydes **83** and arylacetylenes **84** with $PdCl_2(PPh_3)_2$ as catalyst, CuI as additive, *t*-BuOK as base and CH_3OH as reactant and solvent (Scheme 28).[114] In 2006, Gundersen described one-pot Sonogashira coupling/5-*exo-dig* cyclization reaction between 2-ethynylbenzyl alcohol with 6-iodopurines,[115] while a tandem Sonogashira/hydroalkoxylation protocol of functionalized 2-bromo- or 2-chlorobenzyl alcohols with several arylalkynes was reported by Buxaderas et al. in 2014.[116]



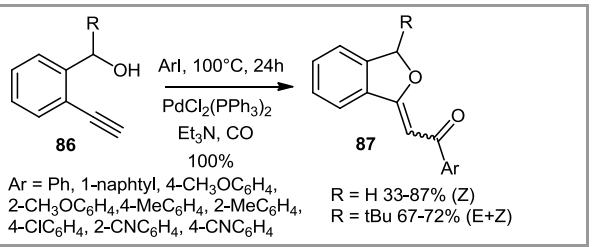
Scheme 28 Phthalans synthesis by Pd-promoted tandem Sonogashira coupling/5-*exo-dig* cycloetherification.

Recently, palladium nanoparticles dispersed in glycerol phase were applied in the synthesis of many heterocycles, including phthalans by reaction of ortho-iodobenzyl alcohols with phenylacetylene.[117]

2.6 Tandem carbonylative Sonogashira-cyclization reactions

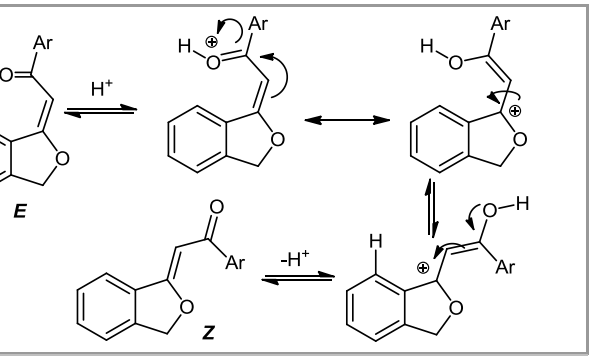
Recently Aronica et al.[118] have described the synthesis of alkylidenephthalans via a palladium-catalyzed tandem

carbonylative Sonogashira-cyclization reaction (Scheme 29). The cross coupling between *ortho*-ethynylbenzyl alcohols **86** and iodo arenes took place with complete conversion of the reagents and afforded the corresponding isobenzofurans **87** as a mixture of the two possible stereoisomers E/Z, Z being the major isomer. Notably, the relative amount of the stereoisomers changed after separation by column chromatography and the quantity of Z compound generally increased.



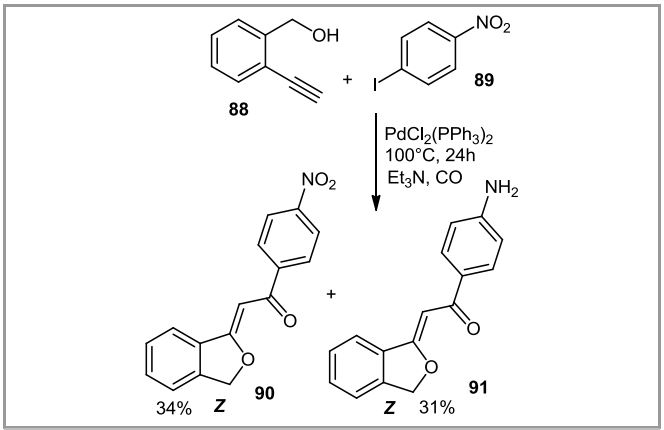
Scheme 29 Synthesis of alkylidenephthalans via cyclocarbonylative Sonogashira reactions

An experiment was performed in order to evaluate whether the observed interconversion of the two isomers was ascribable to the presence of acid during the purification step. The authors observed that a sample of pure E-isomer was converted into a Z/E mixture (92/8) when it was treated with SiO_2 in $CDCl_3$. This result was explained with the mechanism depicted in Scheme 30.



Scheme 30 Interconversion between (*E*) and (*Z*) stereoisomers.

The scope of the cyclization reaction was investigated by reacting aryl iodide bearing electron-donating (Me, OMe) or electron-withdrawing substituents (Cl, CN) in the *ortho* and *para* positions. In almost all cases alkylidenephthalans were obtained quantitatively except for the reactions performed with o- and p-cianoaryl iodides, where significant amount of carbonylative Sonogashira by-products were also found. Finally, a curious behaviour for the reaction of 2-ethynylbenzyl alcohol **88** with 1-iodo-4-nitrobenzene **89** was described by the authors: in addition to the expected phthalans **90**, almost equal amounts of the corresponding amino derivative **91** were obtained. Its formation was explained with a reduction of $-NO_2$ into $-NH_2$ due to the presence of Pd-hydride species in the reaction conditions (Scheme 31).



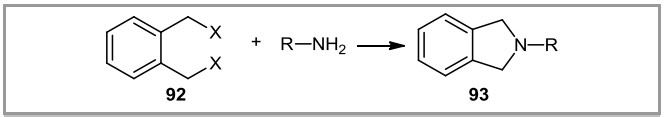
Scheme 31 Tandem carbonylative Sonogashira-cyclization reactions between (2-ethynylphenyl)methanol and 1-iodo-4-nitrobenzene.

3 Isoindolines

Several methods for the preparation of isoindolines scaffolds are reported in the literature. In particular many procedures based on cyclization strategies have been described. They can be divided into the following sections: a) amination of dihalides; b) intramolecular hydroamination; c) Diels-Alder and related reactions; d) [2+2+2] cyclotrimerization of alkynes; e) cyclocarbonylative Sonogashira reaction.

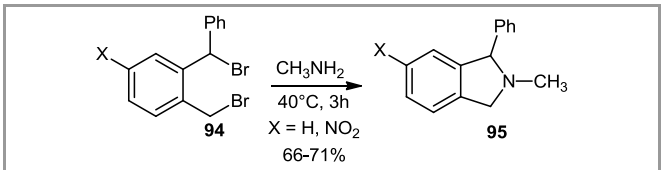
3.1 Amination of dihalides

A traditional strategy for the construction of isoindoline motifs is based on the amination of suitable dihalides (Scheme 32).



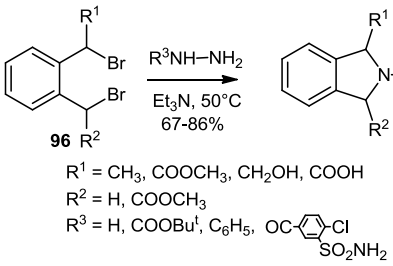
Scheme 32 Amination of dihalides-based strategy.

Indeed, one of the first example of isoindoline synthesis was reported in 1971 by Fraser and Renaud who generated the heterocyclic nucleus **95** through the reaction of methylamine with 1-(bromomethyl)-2-[bromo(phenyl)methyl]benzenes **94** (Scheme 33).[119]



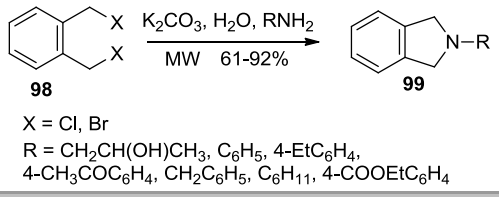
Scheme 33 First example of isoindolines synthesis via amination of dihalides

A few years later, the same method was employed by Cignarella and co-workers for the preparation of N-NH-functionalised isoindolines **97** (Scheme 34), useful precursors of indapamide, an effective diuretic agent used in the therapy of hypertension.[120]



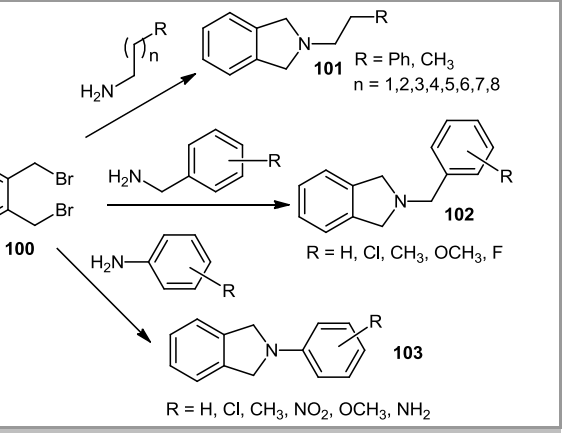
Scheme 34 Cignarella's synthesis of N-NH-suntionalised isoindolines.

More recently, Varma et al. developed a microwave-assisted heterocyclization approach which was applied to the synthesis of the isoindoline nucleus.[121] The reaction of primary amines with α,α-bishalo-*ortho*-xylenes **98** in sealed vessel under aqueous MW irradiation turned out to be extremely useful for the synthesis of N-substituted isoindolines **99** with good to excellent yields (Scheme 35). Moreover, the work-up of the reaction was greatly simplified because the products precipitated from the reaction medium at the end of the reaction and no column chromatography purification was necessary to isolate the products.



Scheme 35 Microwaves promoted amination of α,α-bishalo-o-xylenes.

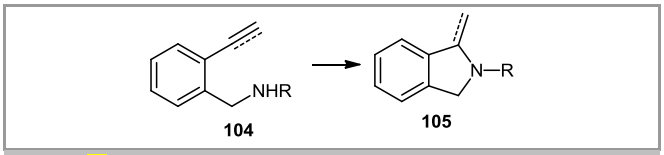
The work of Varma and Ju was then scaled up from 1 mmol to 1 mole by Bernard and co-workers, who performed the reactions in a microwave apparatus with open vessels at atmospheric pressure.[122] The reactions were completed after 30 minutes and the isoindolines derivatives were obtained with similar yields.
Finally, in 2009, Subbarayappa et al. reported the synthesis of N-substituted isoindolines from α,α-dibromo-*o*-xylene and various primary amines in basic medium and at room temperature.[123] In particular, the reactions performed using 1,4-dioxane as solvent and NaOH as base afforded the heterocycle derivatives **101-103** in excellent yields (Scheme 36). Anilines, benzyl and alkyl amines could be successfully used and the reaction can be applied to functionalised substrates containing both electron-donating and electron-withdrawing groups.



Scheme 36 Amination of α,α-dibromo-o-xylene with different primary amines.

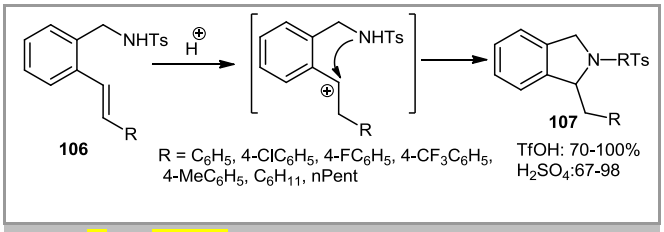
3.2 Intramolecular Hydroamination

A convenient method for the synthesis of 1-substituted isoindolines is based on the hydroamination of 2-vinyl or 2-ethynyl benzilamines (Scheme 37), generally promoted by acid or basic reagents.



Scheme 37 General hydroamination method.

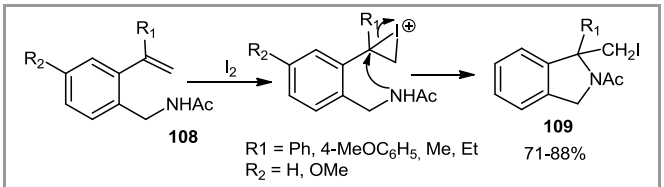
An acid-catalyzed intramolecular hydroamination approach to isoindolines was described by Henderson and co-workers in 2012.[124] The reaction of 2-alkenylphenylsulphonamides with small amounts of triflic acid afforded the desired heterocycles with excellent yields (Scheme 38).



Scheme 38 Acid-catalyzed intramolecular hydroamination.

The reaction was supposed to take place through the formation of a benzylic cationic intermediate that was then trapped by the amine nitrogen. A drawback of this methodology was that it required triflic acid, a highly corrosive and expensive reagent. For these reasons the authors tested sulphuric acid and observed that all the precursors **106** underwent successful cyclization generating the isoindolines products **107** with only slightly inferior yields respect to the reactions performed with TfOH.

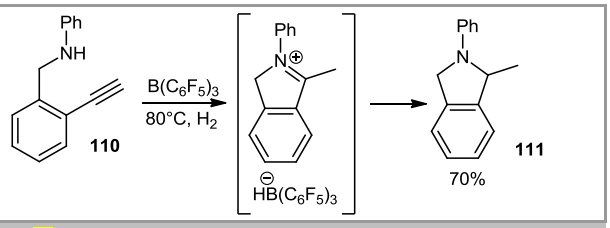
A facile synthesis of 1,1-disubstituted isoindolines derivatives was achieved by Kobayashi et al. via intramolecular cyclization of 2-(acetylaminomethyl)styrenes **108** (Scheme 39).[125] Treatment of these compounds with iodine in the presence of sodium hydrogenocarbonate in acetonitrile resulted in a regioselective conversion to 1-iodomethylisoindolines in good yields. In this case, I_2 acted as Lewis acid and added to the double bond. Isoindoline nucleus is formed through the nucleophylic attack of the amine moiety. Products **109** can be further transformed by reduction with *n*-Bu_3SnH or conversion into the corresponding 1-sulfenylmethyl derivatives by means of treatment with sodium thiolates.



Scheme 39 Intramolecular iodoamination of 2-vinylbenzylamine derivatives.

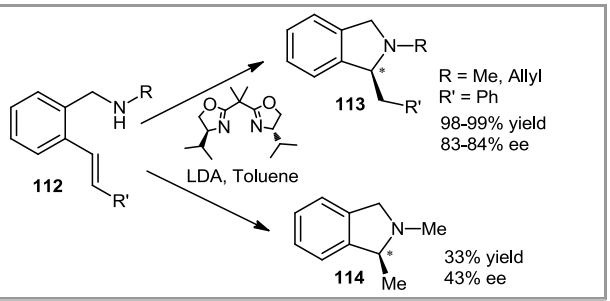
Another example of intramolecular hydroamination promoted by a Lewis acid, was described by Stephan's group in 2015.[126] Treatment of N-(2-ethynylbenzyl)aniline **110** with 10% *tris* (perfluorophenyl)borane ($B(C_6F_5)_3$) in toluene, under hydrogen

pressure, gave 1-methyl-2-phenylisoindoline **111** in 70% yield (Scheme 40).



Scheme 40 Hydroamination N-(2-ethynylbenzyl)aniline.

Asymmetric hydroamination was obtained by Tomioka et al. reacting aminoalkenes **112** with chiral bisoxazoline and LDA in toluene at 0°C (Scheme 41).[127] The substituents on the amine and olefin moieties played a fundamental role on the reaction efficiency and enantioselectivity. Indeed, the reactions of N-methyl or N-allyl aminoalkenes with a phenyl group on the double bond afforded the isoindolines derivatives **113** with high yields and enantiomeric excesses, while the reactions performed with a terminal alkene derivative generated the cyclization product **114** in 33% yield with 43% ee.

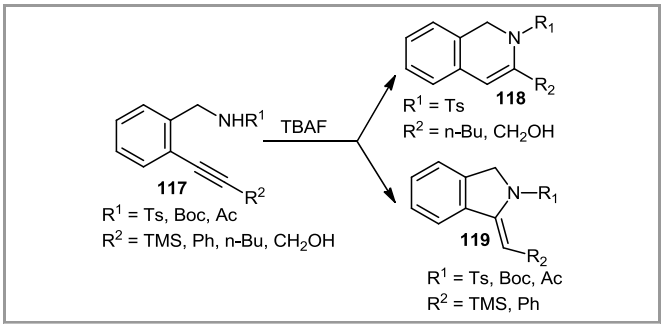


Scheme 41 Asymmetric hydroamination of aminoalkenes.

In 1999, Domínguez *et al.* described the first example of base-promoted cyclization of *N*-acetyl 2-ethynylbenzylamine **115** affording the corresponding 1-methyleneisoindoline **116** with 87% of yield (Scheme 42).[128] However, this protocol could not be applied to molecules containing hindered substituents at the benzylic position.

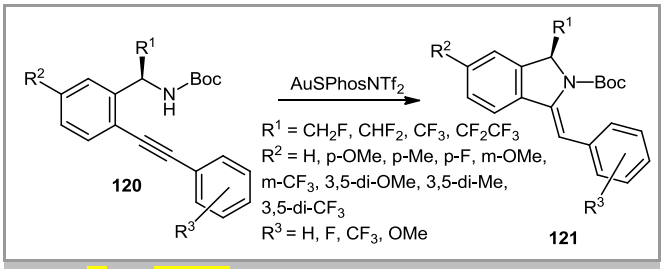
Scheme 42 NaH-promoted intramolecular hydroamination of *ortho*-ethynylbenzylamide.

A few years later Sakamoto and co-workers reported an extensive study on the TBAF-promoted intramolecular hydroamination of several *o*-alkynylbenzylamine derivatives.[96] Interestingly, the authors found that substrates **117** bearing alkyl-substituted triple bond gave preferentially 6-*endo-dig* ring closure, affording 1,2-dihydroisoquinolines **118** as main product, whereas benzyl amides having a TMS- or aryl-substituted triple bond yielded only alkylideneisoindolines **119** (Scheme 43).



Scheme 43 TBAF-promoted cyclization of *ortho*-alkynylbenzylamine derivatives.

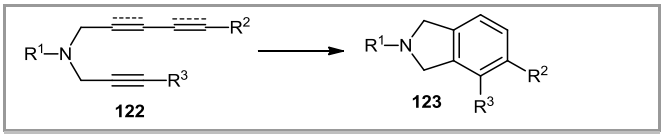
Moving to transition metal-catalyzed reactions, the only relevant example in the field of hydroaminations was reported by Catalán et al.[129] in 2013. The authors described the synthesis of many alkylideneisoindolines **121** by gold(I)-promoted intramolecular hydroamination of enantiopure *ortho*-alkynylbenzyl carbamates **120** bearing a fluorinated alkyl substituent at the benzylic position (Scheme 44).



Scheme 44 Gold catalyzed intramolecular hydroamination.

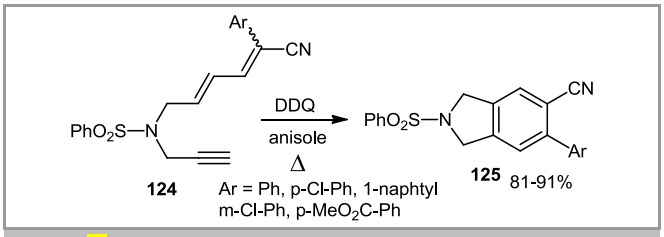
3.3 Diels-Alder and related reactions

Isoindolines functionalised on the benzene ring can be generated via intramolecular Diels-Alder (IMDA) cycloadditions and related reactions (Scheme 45).



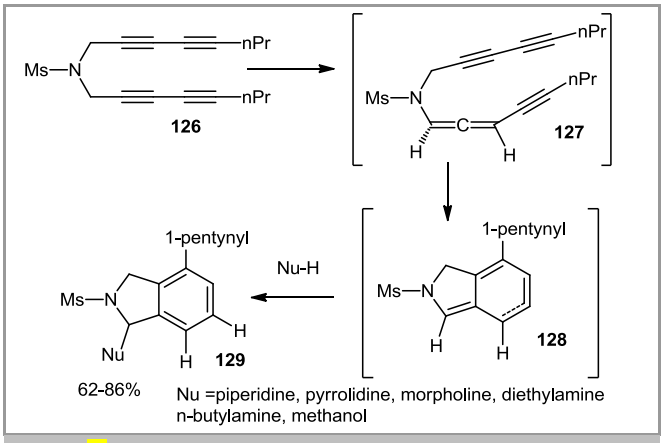
Scheme 45 Intramolecular Diels-Alder reactions.

For this purpose Back and co-workers investigated the reactivity of N-pentadienyl-N-propargyl derivatives **124** in order to develop a synthetic approach to isoindoline with diverse substituents on the aromatic moiety.[130] Indeed, when N-dienyl-N-(propargyl)benzenesulfonamides **124** were subjected to IMDA cycloaddition in refluxing anisole with DDQ, the corresponding isoindolines **125** were obtained in excellent yields (Scheme 46).



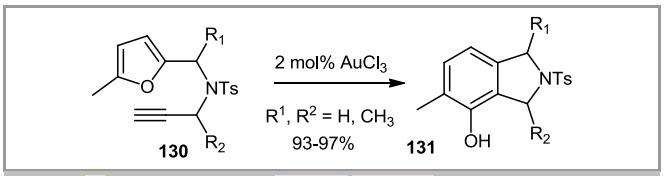
Scheme 46 IMDA approach to isoindolines.

More recently, Wang et al. reported the first case of pentadehydro-Diels-Alder (PDDA) reaction applied to the synthesis of 1-functionalised isoindolines **129**.[131] The reaction took place with the initial isomerization of tetrayne **126**, followed by rapid PDDA cyclization of **127** and trapping of the intermediate **128** with nitrogen or oxygen nucleophiles (Scheme 47). The product yields were related to the substituent on the N-isoindoline atom and to the structure of the nucleophilic reagent employed. Primary, secondary amines and methanol together with methansulfonamide resulted to be the best substrates yielding the isoindoline nuclei in high quantity.



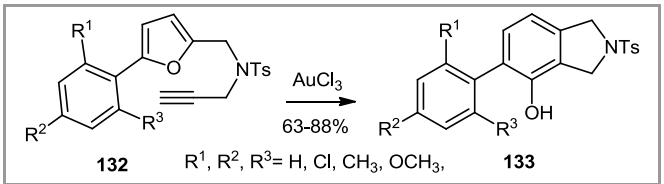
Scheme 47 Pentadehydro-Diels-Alder based synthesis of isoindolines.

The first example of gold-catalyzed formal intramolecular Diels-Alder reaction of N-tosylated furanynes **130** was described by Hashmi and co-workers in 2000 (Scheme 48).[132] When 2 mol% of $AuCl_3$ were employed, the cyclization took place successfully, whereas no reaction was observed with $AgNO_3$, $Hg(CLO_4)_2$, $Pd_2dba_3{\cdot}CHCl_3$, $Pd(PPh_3)_4$, $Rh(PPh_3)Cl$, $FeCl_3$ and $InCl_3$.



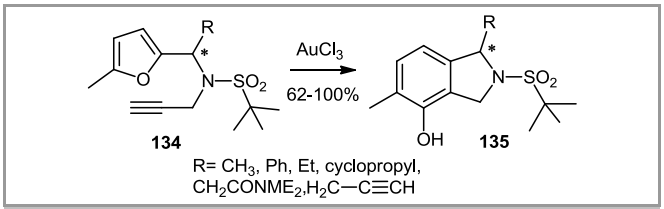
Scheme 48 First example of gold catalyzed cyclization of N-tosylated furanyne.

Subsequently the same authors extended their protocol to the reactions of sterically hindered aryl furanynes (Scheme 49).[133] Their results clearly indicated that benzene ring bearing two or three substituents such as chlorine, methyl or methoxy groups, did not influence the gold catalyzed cyclization, since 5-arylisoindolines **133** were obtained in good yields.



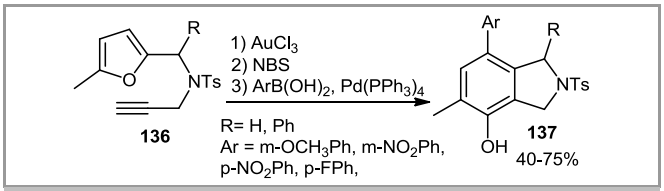
Scheme 49 Gold catalyzed cyclization of aryl functionalised furanynes..

Moreover, the presence of various (Br, CH_2Cl, CH_2OAc, CH_2OPiv) substituents on the furan ring proved to be well tolerated in the gold-catalyzed reactions.[134] Two years later, Hashmi et al. reported the synthesis of isoindolines **135** possessing a chiral centre at the 1-position starting from enantiomerically pure sulfonamides **134** (Scheme 50).[135]



Scheme 50 Gold catalyzed cyclization of chiral sulphonamides.

Finally, the same group developed a one pot sequence for the synthesis of 4-arylated isoindolines starting from N-tosylated furanyne substrates **136**, followed by electrophilic bromination with N-bromosuccinimide (NBS) and palladium catalyzed Suzuki coupling. The reactions proceeded with good overall efficiency and showed broad substrate scope (Scheme 51).[136]



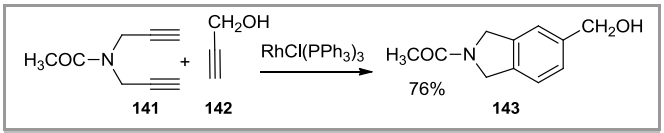
Scheme 51 One pot sequence to arylated tosilindolines.

3.4 [2+2+2] Cycloaddition reactions

Transition metal catalyzed [2+2+2] cyclization of three π-systems has been widely investigated as a valuable synthetic tool for the synthesis of aromatic rings.[137] In particular the reaction between suitable α,ω-diynes **138** and alkynes can be used for the preparation of isoindoline scaffolds (Scheme 52).

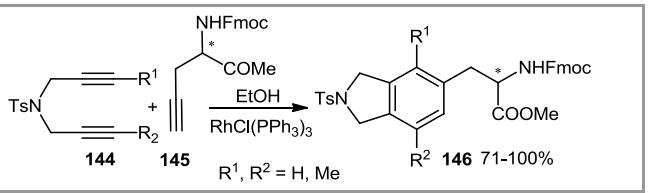
Scheme 52 Synthesis of isoindolines via cycloaddition reactions.

During the past half-century rhodium-based catalysts have been one of the most commonly used catalysts for [2+2+2] cycloaddition of alkynes.[138] One of the first example of rhodium catalyzed cyclization was reported in 1982 by Grigg and co-workers who used Wilkinson's catalyst $[(PPh_3)_3RhCl]$ in the co-cyclization of diynes **141** with excess of monoacetylene.[39a] In particular, dipropargyl acetamide was converted into the corresponding isoindoline with 76% yield (Scheme 53). The reaction showed good chemoselectivity with no detectable trimerization of the monoacetylene.



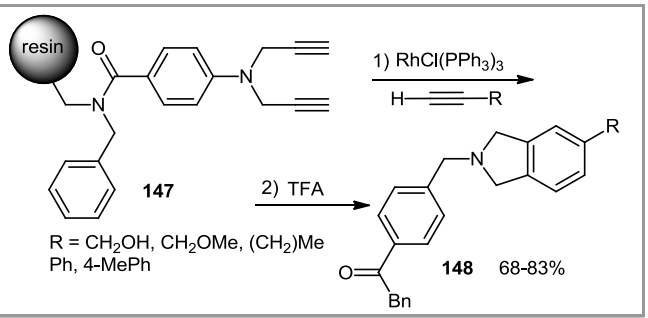
Scheme 53 Grigg's first example of cycloaddition between dipropargyl acetamide and 2-propynol.

The same catalyst was used by Roglans and co-workers in [2+2+2] cycloadditions between N-tosylated diynes **144** and alkynes **145** bearing a phenylalanine protected amino acid group (Scheme 54).[44] The reactions were carried out in an environmentally friendly solvent such as ethanol and afforded the functionalised isoindolines **146** with high yields.



Scheme 54 Cycloadditions between N-tosylated diynes and functionalised alkynes.

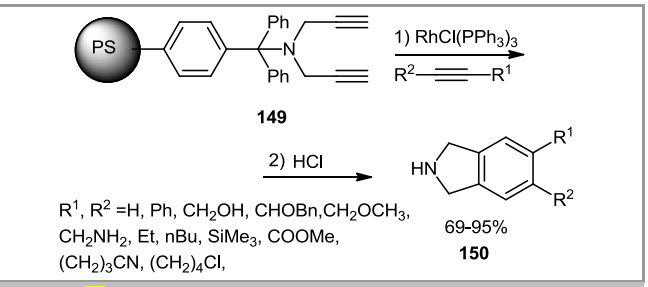
Solid-phase reactions technique was applied to the synthesis of isoindolines via [(PPh3)3RhCl]-catalyzed cyclization between resin supported dipropargyl amines and alkynes **147** (Scheme 55).[139]



Scheme 55 Synthesis of isoindolines via solid-phase reactions.

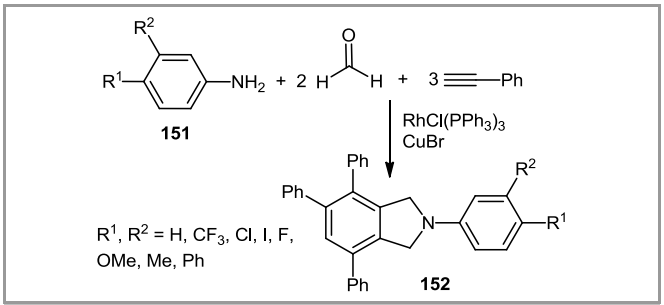
Products were cleaved from the resin by treatment with TFA. Terminal alkynes gave better yields than internal ones, possibly due to steric factors.

A few years later, Deiters at al. reported the [(PPh3)3RhCl]-catalyzed cycloaddition of polystirene-supported 1,6-diynes and alkynes **149**.[47] The corresponding isoindolines **150** were obtained in excellent yields after deprotection with diluted HCl (Scheme 56). The experimental conditions used for these solid-supported cyclotrimerization reactions were compatible with a variety of functionalities such as alkyl chains, hydroxyl and alkoxy groups, aromatic rings, cyano and silyl groups, chlorine and esters.



Scheme 56 Cycloaddition of polystirene-immobilized 1,6-diynes and functionalised acetylenes.

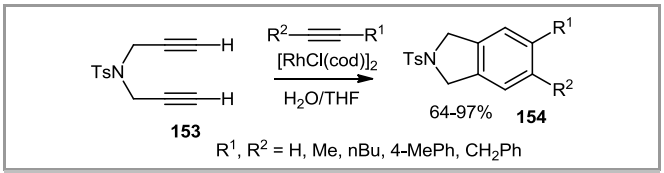
Li and Bonfield developed a multicomponent [2+2+2] cycloaddition promoted by Wilkinson's catalyst.[140] One-pot reactions of a primary amine with 2 molecules of formaldehyde and 3 molecules of phenyl acetylene produced substituted isoindolines derivatives **152**. (Scheme 57).



Scheme 57 Synthesis of isoindolines via one-pot multicomponent [2+2+2] cycloaddition reactions.

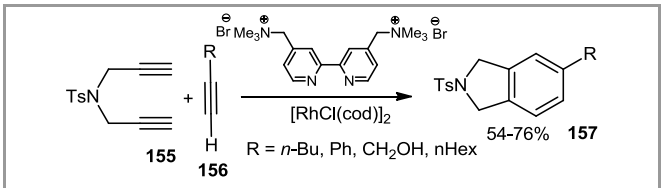
Very recently [(PPh3)3RhCl]-promoted [2+2+2] co-cyclization has been successfully applied to the synthesis of heat shock protein 90 inhibitor AT 13387, currently used in clinical trials for treatment of gastrointestinal cancers.[141]

Wilkinson's complex is not the only rhodium species that can catalyse the intramolecular [2+2+2] cycloaddition reactions of alkynes and diynes. For instance Wu and co-workers reported that [RhCl(cod)]2 was able to promote the [2+2+2] cyclotrimerization of terminal dipropargyl tosylamide **153** and alkynes at room temperature in water/THF mixed solvent (Scheme 58).[142]



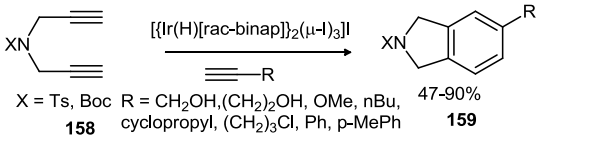
Scheme 58 [RhCl(cod)]2 promoted selective cycloaddition of 1,6-diynes and monoynes leading to isoindolines.

Another simple procedure for the [2+2+2] cycloaddition of α,ω-diynes and alkynes in water was described by Tsai and co-workers.[51] The authors reported that [RhCl(cod)]2-2,2'-bipyridyl complex, bearing two quaternary ammonium moieties, can be used for the synthesis of N-tosyl isoindoline derivatives **157** in good yields (Scheme 59).



Scheme 59 Rhodium(I)cationic 2,2-bipyridyl-catalyzed [2+2+2] cycloadditions.

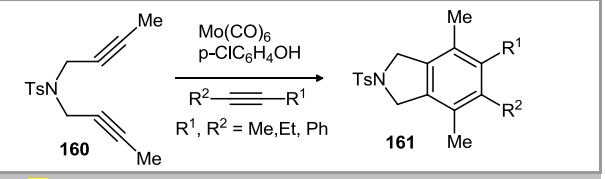
In addition to rhodium-based catalysts, other transition metals complexes are able to catalyse [2+2+2] cycloaddition reactions. Michelet and co-workers[80a,143] reported the synthesis of isoindoline scaffolds via [2+2+2] cycloaddition of dipropargyl amides and alkynes employing the stable and practical ionic triply iodo-bridged iridium-catalyzed [{Ir(H)[rac-binap]}2(μ-I)3]I in isopropyl alcohol. (Scheme 60). A number of functional groups were tolerated including chlorine, alcohol, ether, cyclopropyl and phenyl.



Scheme 60 Iridium(III) catalyzed approach to the synthesis of isoindolines.

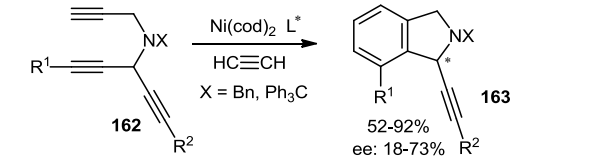
The same group developed[80b] a solvent free iridium(III)- catalyzed cycloaddition between α,ω-diynes and terminal alkynes which provided access to isoindolines with good yields. Michelet et al. reported[78c] also a solvent and ligand free ruthenium trichloride-catalyzed [2+2+2] cycloaddition of diynes and functionalised alkynes. The commercially available, cheap and easy to handle $RuCl_3 \cdot nH_2O$ showed high catalytic activity and selectivity towards the synthesis of N-tosyl and N-Boc isoindoline derivatives.

Mori et al. used Mortreux's catalyst, derived from $Mo(CO)_6$ and p-chlorophenol, for cotrimerization reactions of diyne **160** and internal alkynes to prepare poly-substituted isoindolines in moderate yields (Scheme 61).[144]



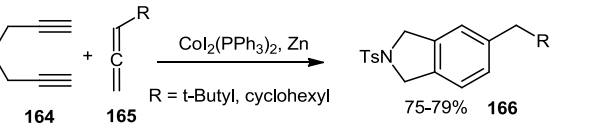
Scheme 61 [2+2+2] Cocyclization promoted by $Mo(CO)_6$-p-ClPhOH.

The same authors reported a catalytic asymmetric synthesis of isoindolines via nickel(0) catalyzed [2+2+2] cocyclization of triynes **162** and excess acetylene (Scheme 62). $Ni(cod)_2$ and a chiral ligand promoted the synthesis of isoindolines **163** with good yields an enantiomeric excess.[145]



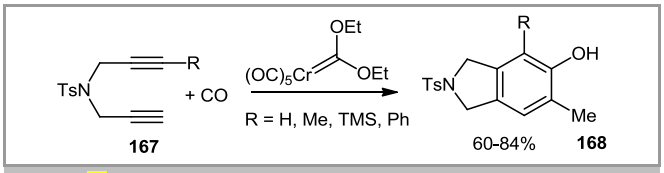
Scheme 62 Synthesis of isoindolines via nickel(0) catalyzed [2+2+2] cocyclization between triynes and acetylene.

Cheng and co-workers described[65] the first example of regio and chemoselective [2+2+2] cycloaddition reactions between 1,7-heptadiynes **164** and allenes **165** in the presence of $CoI_2(PPh_3)_2$/Zn system. N-tosylated isoindolines were obtained in satisfactory yields as depicted in Scheme 63.



Scheme 63 [2+2+2] cycloaddition of 1,6-eptadiynes with allenes.

Finally, a different approach to isoindolines was described by Mori et al.[146] The reaction between nitrogen-containing acetylenes **167**, and a chromium carbene complex under carbon monoxide atmosphere, produced isoindolines through a [2+2+1+1] cocyclization. The experimental reaction conditions were optimised for 4-methyl-N,N-di(prop-2-yn-1-yl)benzenesulfonamide (Scheme **64**, R = H) and then extended to internal diynes which generated isoindolines **168** having three substituents on the aromatic ring in good yields.

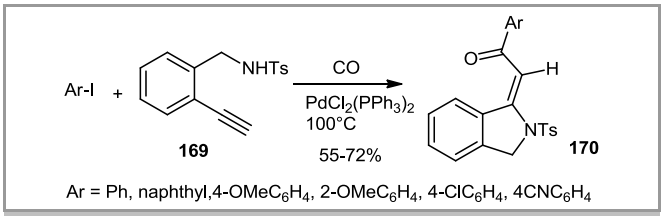


Scheme 64 Synthesis of isoindolines using chromium carbene complex.

3.5 Tandem carbonylative Sonogashira-cyclization reactions

The only example of palladium-catalyzed tandem carbonylative Sonogashira-cyclization reaction applied to the synthesis of alkylideneisoindoline ring was reported very recently by Aronica et al.[147] 2-Ethynylbenzylamine could not be used directly as substrate, since its reaction with iodobenzene did not give any isoindoline product, although a total consumption of reagents was observed. As a consequence the authors protected the amine moiety with *tert*-butyloxycarbonyl (Boc) and tosyl (Ts) groups. When *N*-(2-ethynylbenzyl)-4-methylbenzenesulfonamide **169** was used, the reaction took place with complete chemo- and stereoselectivity resulting in the exclusive formation of the five-membered isoindolines derivatives **170** with an (*E*) configuration (Scheme 65).

The protocol could be extended to iodoarenes characterised by different functional groups such electron donating (2-OMe, 4-OMe, 2-naphtyl) or electron withdrawing (2-Cl, 4-CN) substituents. A quantitative conversion of the reagents was detected in all cases affording the corresponding (*E*)-1-carbonylmethyleneisoindoline pure products with good yields (55-72%).



Scheme 65. Synthesis of alkylideneisoindolines via tandem carbonylative Sonogashira-cyclization reactions

4 Conclusions

In this review we highlighted the most significant synthetic strategies described in the literature for the synthesis of phathalans and isoindolines via cyclization reactions. The majority of this methods require O- or N-functionalised compounds. Two principal cyclization pathways can be involved: i) a benzene ring possessing the suitable substituent may undergo a cyclization reaction which forms the pirrolidine and the furan ring; ii) a polyunsaturated ether or amine derivative can rearrange generating the heterocyclic nucleus. Many of these transformations require a transition metal catalyst or have to be promoted by acid or basic reagents. In a few cases solid-phase techniques have been also applied to the synthesis of both heterocycles.

Considering that isoindolines and 1,3-dihydoisobenzofuran have been recognized as privileged structure due to their

presence in many bioactive molecules, we hope that this short review can stimulate further research in the field of the synthesis of these compounds such as the investigation on the use of milder experimental conditions and of heterogeneous metal catalysts in order to improve the "greenness" of these processes.

Funding Information

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Biosketches

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