CHEMISTRY OF 2*H*-ISOINDOLES: RECENT DEVELOPMENTS

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Abstract. *In this review, new synthetic methods for the preparation of 2H-isoindoles based on ring closure reactions, isoindoline aromatization and ring transformations are discussed. The resulting 2H-isoindoles can be isolated or* in situ *trapped with dienophiles to give the corresponding Diels-Alder adducts.*

Contents

1. Introduction

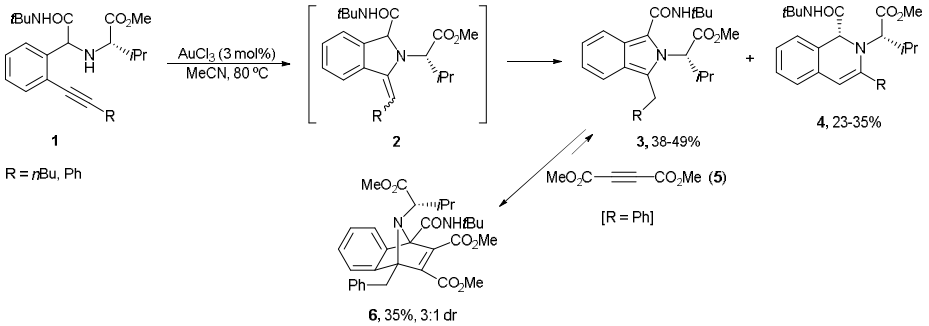
Properties and reactivity of 2*H*-indoles have attracted considerable attention in the last 50 years.[1-3] The isoindole structure can be found in natural products and bioactive compounds with a pharmacological profile such as antimicrobial, anthelmintic, insecticidal, cyclooxygenase isoenzyme (COX-2), thrombin inhibitor and anticancer activity.[4-6] Isoindole derivatives and oligomers are very important compounds in material science[7-11] and as photosensitizers for photodynamic therapy.[12] Isoindole are rather unstable compounds because of the *o*-quinoid structure and are frequently trapped as latent dienes in intermolecular Diels-Alder (DA) reactions.

Several methodologies for the synthesis of isoindoles have been described in the literature, based mainly on (a) ring-closure reactions, (b) ring transformations, (c) aromatizations, and (d) substituent modifications.[3] In this review article, recent advances in the last 20 years on isoindole chemistry will be considered.

2. Synthesis by ring-closure reactions

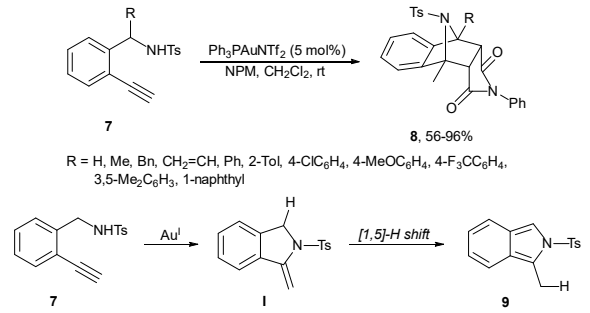
2.1. Alkynes cyclization

Aromatic compounds bearing an acetylenic unit and nitrogen moieties have been cyclized mainly under transition metal-catalyzed conditions to give different indole derivatives including isoindoles.[13] Intermolecular hydroamination of alkynes **1**, obtained by four-component Ugi reaction, was performed by Dyker and co-workers[14] under $AuCl_3$ catalysis to give isoindole **3** derived from the 5-*exo*-*dig*-products **2** by isomerization under the acidic reaction conditions (Scheme 1). Dihydroisoquinolines **4** were also obtained by a 6-*endo*-*dig* cyclization in 23-35% yield. The chiral isoindole **3a** was allowed to react with dimethyl acetylenedicarboxylate (DMAD) **5** providing cycloadduct **6** in 35% yield as a 3:1 mixture of diastereomers. However, this compound partially decomposed under flash chromatography purification.



Scheme 1. Isoindoles **3** from acetylenic compounds **1**.

$Ph_3PAuNTf_2$-catalyzed cycloisomerization-[1,5]-hydride migration-DA reaction of 2-ethynylbenzyl-sulfonamides **7** provided the corresponding isoindole *endo*-cycloadducts **8** by reaction with *N*-phenylmaleimide (NPM) (Scheme 2).[15] This one-pot three-step cascade reaction takes place under very mild reaction conditions in CH_2Cl_2 at room temperature (rt). On the basis of deuterium labelling experiments, it has been proposed the initial formation of intermediate **I**, which after [1,5]-hydride transfer gave the isoindole **9**. Various dienophiles such as DMAD **5**, naphthoquinone, tetracyanoethylene and methyleneindolinone were also successfully employed.

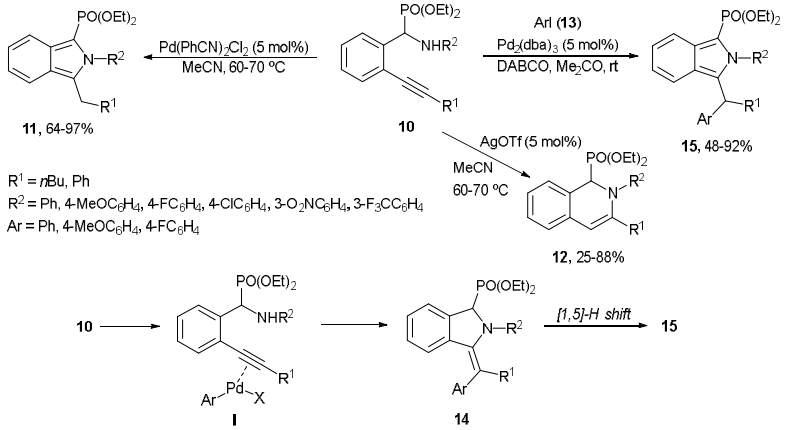


Scheme 2. Gold-catalyzed cascade of benzylsulfonamides **7** to isoindole cycloadducts **8**.

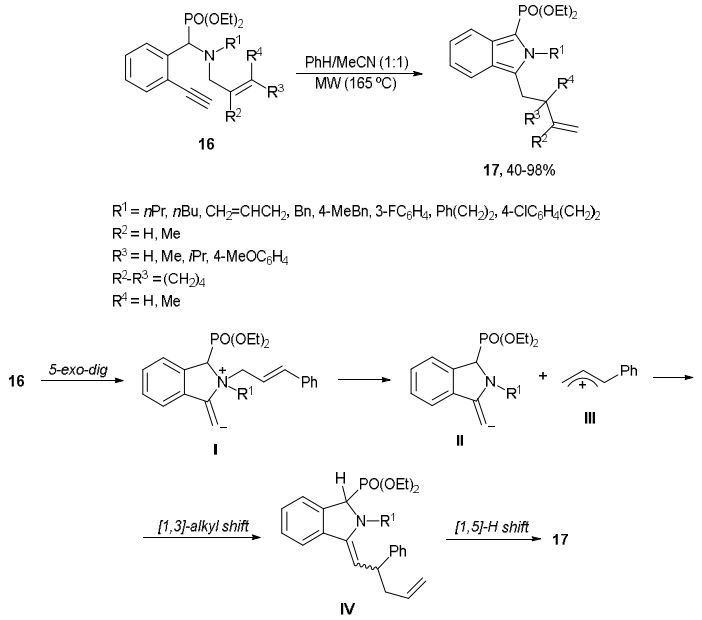
Intramolecular hydroamination of acetylenic α-amino phosphonates **10**, under Pd-catalysis, provided by a 5-*exo-dig* cyclization isoindoles **11**.[16] Regiodivergent[17] 6-*endo-dig* cyclization to dihydroisoquinolines **12** resulted under AgOTf catalysis. The starting compounds **10** were prepared by $FeCl_3$-catalyzed reaction of 2-alkynylbenzaldehydes with amines and diethyl phosphate.[16] After cyclization of compounds **10** to intermediate **I**, a subsequent [1,5]-H shift took place giving products **11**.[16] On the other hand, in the presence of aryl iodides **13** a [1,3]-aryl shift in intermediate **I** resulted compounds **14**, which after final aromatization provided isoindoles **15** (Scheme 3).[18]

Dieltiens and Stevens[19] reported a metal-free entry to phosphonylated isoindoles **17**, related to compounds **11**, by 5-*exo-dig* cyclization of *N*-allyl amino phosphonates **16** followed by a [1,3]-alkyl shift and final aromatization under microwave (MW) heating (Scheme 4). In this case, it was proposed that after the hydroamination to give intermediate **I**, the [1,3]-alkyl shift produces the anion **II** and cation **III**, which reacted at the phenylated position to yield intermediate **IV** precursor of isoindoles **17**.

Steven's group reported[20] a $AuCl_3$-catalyzed synthesis of 1-cyanoisoindoles **19** from *N*-allylic aminonitriles **18** (Scheme 5). In this case, under MW irradiation no conversion could be detected. In the proposed mechanism, after intramolecular hydroamination promoted by the Lewis acid, intermediate **I** resulted from this 5-*exo-dig* cyclization followed by the [1,3]-alkyl migration to form **II** and 1,5-prototropic aromatization to yield product **19**.



Scheme 3. Phosphonylated isoindoles **11** and **15** from acetylenic α-amino phosphonates **10**.

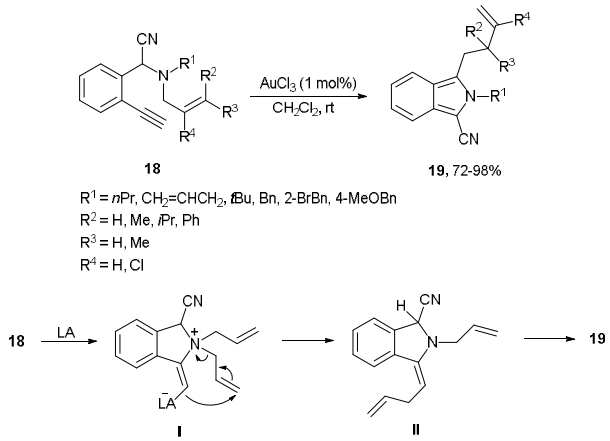


Scheme 4. Phosphonylated isoindoles **17** from acetylenic α-amino phosphonates **16**.

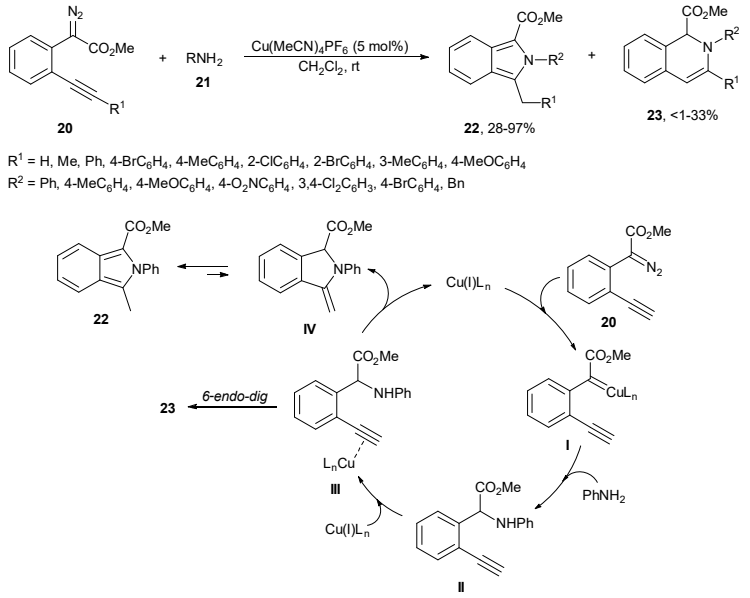
Acetylenic systems bearing a diazoacetate unit at the *ortho*-position **20** underwent metal-catalyzed C–N bond formation through a metal carbene precursor in the presence of primary amines **21** followed by hydroamination generating isoindoles **22** (Scheme 6).[21] This sequential process can be carried out with $Cu(MeCN)_4PF_6$ as catalyst under mild reaction conditions. In the proposed mechanism, the Cu(I) carbene **I** is generated from **20**, which reacts with aniline to give intermediate **II**. Subsequently, the amino group attacks the activated triple bond of intermediate **III** in a 5-*exo-dig* manner to provide intermediate **IV** precursor of the isoindole **22**. Cyclization of intermediate **III** in a 6-*endo-dig* manner forms dihydroisoquinolines **23** with yields in the range of <1-33%.

Herndon and co-workers[22] reported the synthesis of naphthalene derivatives **29** through the coupling of electron-deficient alkynes **26**, Fischer carbene complexes **25** and benzaldehyde hydrazones **24** *via* isoindole

intermediates **27** (Scheme 7). The reaction of hydrazones **24** with carbene complexes **25** gave isoindoles **27**, which in the presence of dienophiles afforded azanorbornenes **28** by a regioselective DA reaction. These cycloadducts **28** underwent a nitrene extrusion reaction to form the aromatic products **29** using dioxane as solvent. However, in the presence of a polar solvent such as ethanol, Michael addition products **30** were isolated.



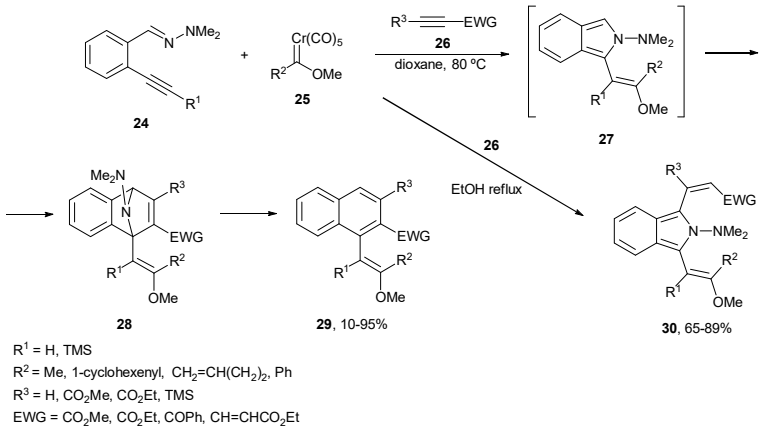
Scheme 5. 1-Cyanoisoindoles **19** from acetylenic aminonitriles **18**.



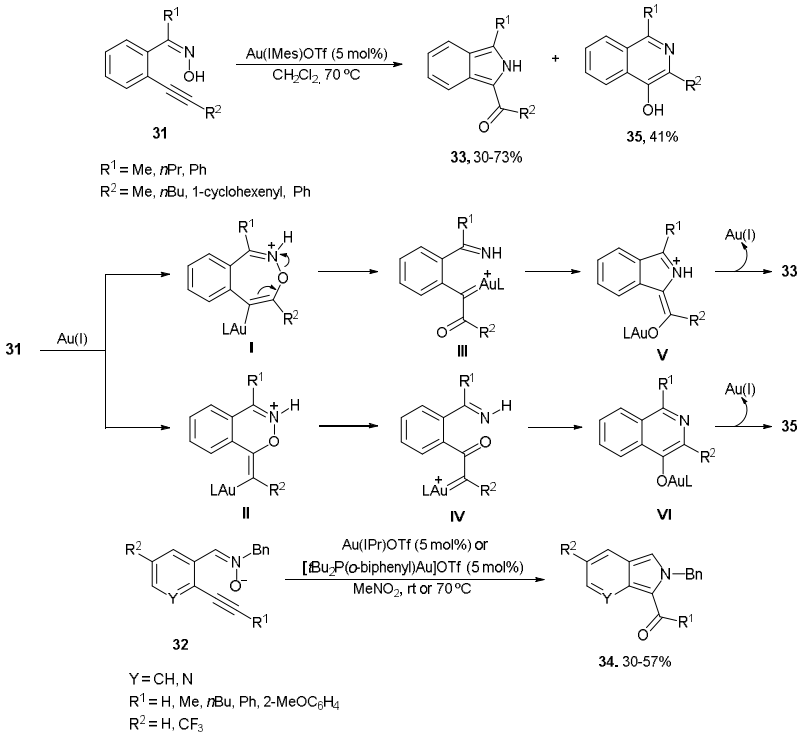
Scheme 6. Isoindoles **22** from acetylenic phenyldiazoacetates **20**.

Acetylenic *Z*-ketoximes **31** or nitrones **32** underwent a gold-catalyzed redox cascade cyclization leading to isoindoles **33** and **34**, respectively (Scheme 8).[23] In the presence of [1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene)Au]OTf [Au(IMes)OTf], *o*-alkynylaryl ketoximes **31** in dichloromethane at 70 ºC provided the corresponding isoindoles **33** in good yields, except in the case of **31** (R^1=Me, R^2=Ph and R^1=R^2=Ph), which gave 4-hydroxyisoquinolines **35** as well. These results were

rationalized based on the formation of intermediate **I** or **II** through a 7-*endo-dig* or 6-*exo-dig* cyclization, respectively, followed by a redox process to give the Au-carbenoid **III** or **IV**, respectively, giving the five and six-membered products by intermediacy of **V** and **VI**, respectively. Nitrones **32** experimented cyclization using either [1,3-bis-(2,6-diisopropyl)imidazol-2-ylidene)Au]OTf [Au(IPr)OTf] or [tBu$_2$P(o-biphenyl)Au]OTf in $MeNO_2$ giving exclusively isoindoles **34** in moderate yields by a similar mechanism than *Z*-oximes.



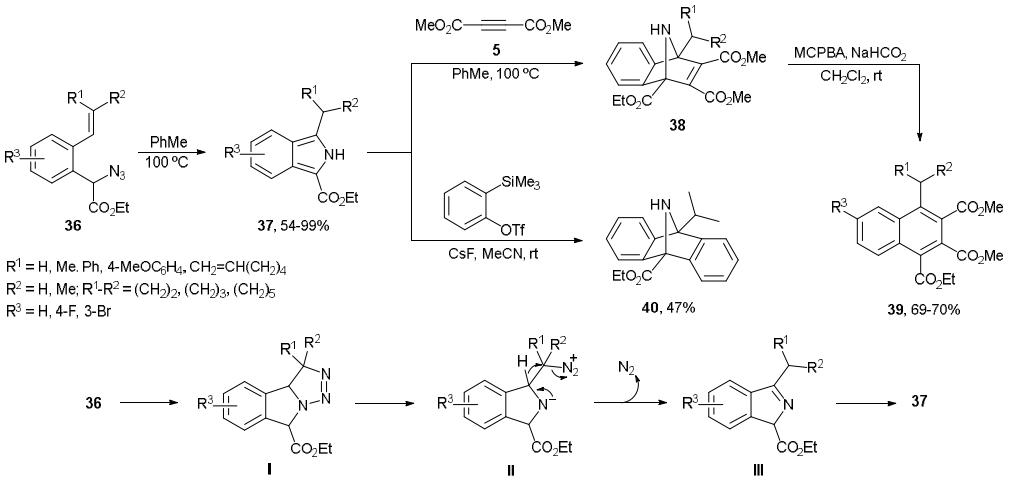
Scheme 7. Synthesis of naphthalene derivatives **29** by intermediacy of isoindoles **27**.



Scheme 8. Isoindoles **33** and **34** from *Z*-oximes **31** and nitrones **32**, respectively.

2.2. 1,3-Dipolar cycloadditions

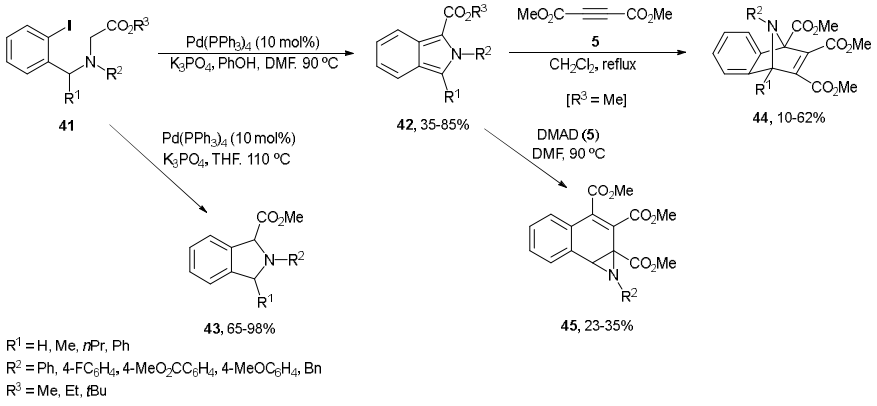
α-Azido carbonyl compounds bearing a 2-alkenylaryl moiety at the *ortho*-position **36** gave under thermal conditions isoindoles **37** (related to compounds **22** in Scheme 6) *via* 1,3-dipolar cycloaddition of azides onto alkenes (Scheme 9).[24,25] This process took place in toluene at 100 ºC either starting from azides **36** or by reaction of the mesylate precursor of **36** with NaN_3 in dimethylformamide (DMF) to form the crude azides **36**. In the proposed mechanism, the formation of triazoline **I** followed by subsequent elimination of nitrogen in intermediate **II** and [1,5]-H shift in intermediate **III** gave product **37**. The obtained isoindoles **37** were allowed to react with DMAD **5** to give cycloadducts **38**, which were transformed into 1,2,3,4-tetrasubstituted naphthalenes **39** after final oxidative deamination in very good overall yields. The cycloaddition with benzyne took place at room temperature affording cycloadduct **40** in 47% yield.



Scheme 9. Synthesis of naphthalenes **39** and bicycle **40** from isoindoles **37**.

2.3. Intramolecular α-arylation of α-amino esters

Solé and Serrano[26,27] described the synthesis of 1-isoindolecarboxylic acid esters **42** by Pd-catalyzed intramolecular arylation of α-(2-iodobenzylamino) esters **41** (Scheme 10). Using $Pd(PPh_3)_4$ with K_3PO_4 and a catalytic amount of phenol in DMF at 90 ºC, isoindoles **42** were formed, whereas working without phenol in THF at 110 ºC isoindolines **43** were obtained.[27]

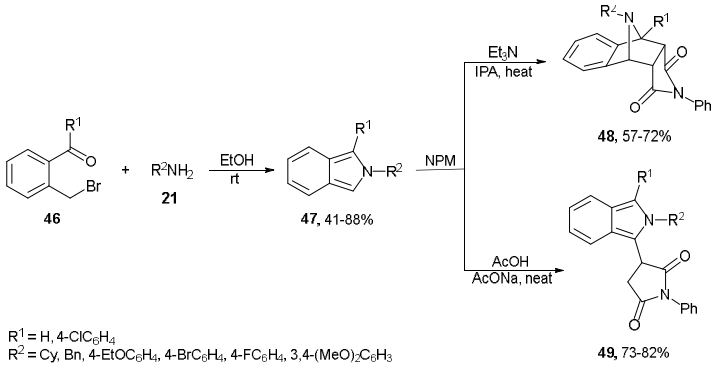


Scheme 10. 1-Isoindolecarboxylic acid esters **42** from α-(2-iodobenzylamino) esters **41**.

When isoindole derivatives **42** were allowed to react with DMAD **5**, the corresponding adducts **44** were mainly obtained in dichloromethane, but also aziridines **45** were prepared working in DMF.[26]

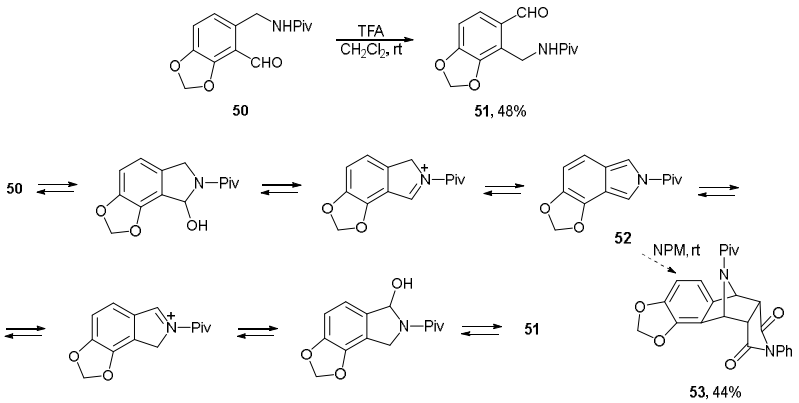
2.4. Cyclization of benzylamines

1-Substituted isoindoles **47** have been prepared from 2-(bromomethyl)benzaldehyde or benzophenone **46** and primary amines **21** in EtOH at room temperature (Scheme 11).[28] Under isopropanol reflux and in the presence of Et_3N isoindoles **47** reacted with NPM to give cycloadducts **48**. However, under AcOH reflux and NaOAc as base Michael adducts **49** were obtained.



Scheme 11. 1-Substituted isoindoles **47** from 2-(bromomethyl)benzaldehyde or benzophenone **46** and DA reactions.

Under acidic conditions *o*-(pivaloylaminomethyl)benzaldehyde substituted by methylenedioxy group **50** underwent a rearrangement reaction leading to the regioisomers **51** (Scheme 12).[29] The proposed mechanism for this transformation involves the formation of an isoindole **52** as key intermediate, which was trapped with NPM to give cycloadduct **53**.



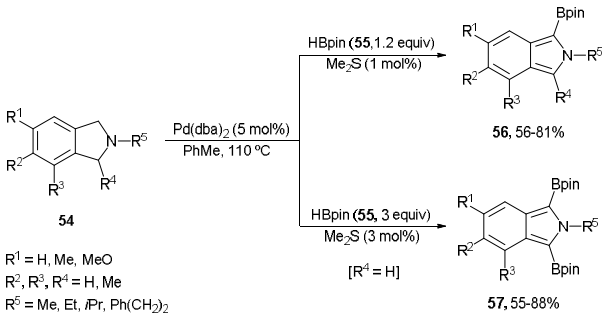
Scheme 12. Rearrangement of *o*-(pivaloylaminomethyl)benzaldehyde **50** to **51** through intermediacy of isoindole **52**.

3. Synthesis by aromatization processes

A general method for the synthesis of isoindoles is the aromatization of isoindolines.[3,30] These saturated heterocycles can be prepared by different cyclization strategies such as (a) amination of dihalides, (b) intramolecular hydroamination, (c) DA reactions, (d) [2+2+2] cyclotrimerization of alkynes and (e) cyclocarbonylative Sonogashira reaction, which have been recently reviewed.[30]

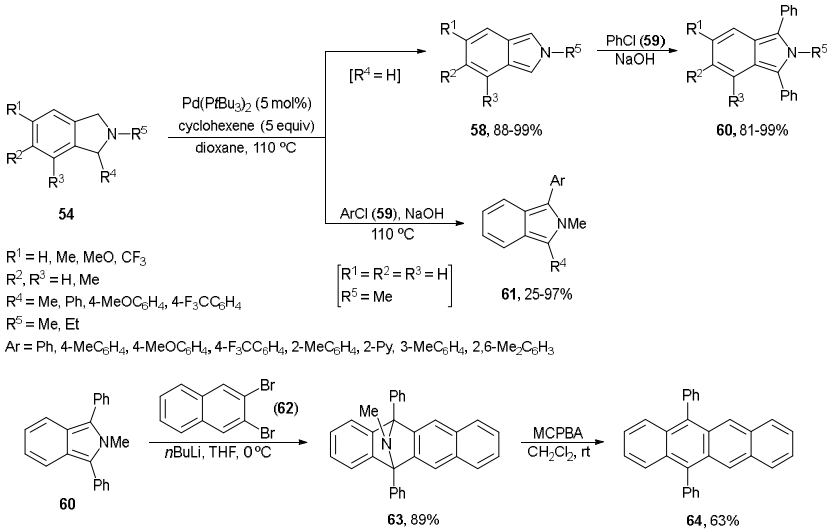
3.1. C–H functionalization of isoindolines

1-Borylisoindoles **56** were prepared *via* Pd-catalyzed dehydrogenation/C–H borylation of isoindolines **54** (Scheme 13).[31] The reaction of *N*-substituted isoindolines **54** with 1.2 equivalents of pinacolborane (HBpin) **55** took place first by dehydrogenation to isoindole followed by C–H borylation, which was accelerated by the presence of Me_2S. The second borylation was also achieved working with three equivalents of HBpin **55** starting from isoindolines **54** (R^4=H) to provide doubly borylated isoindoles **57**. These borylated isoindoles can be submitted to Suzuki-Miyaura coupling with aryl iodides.



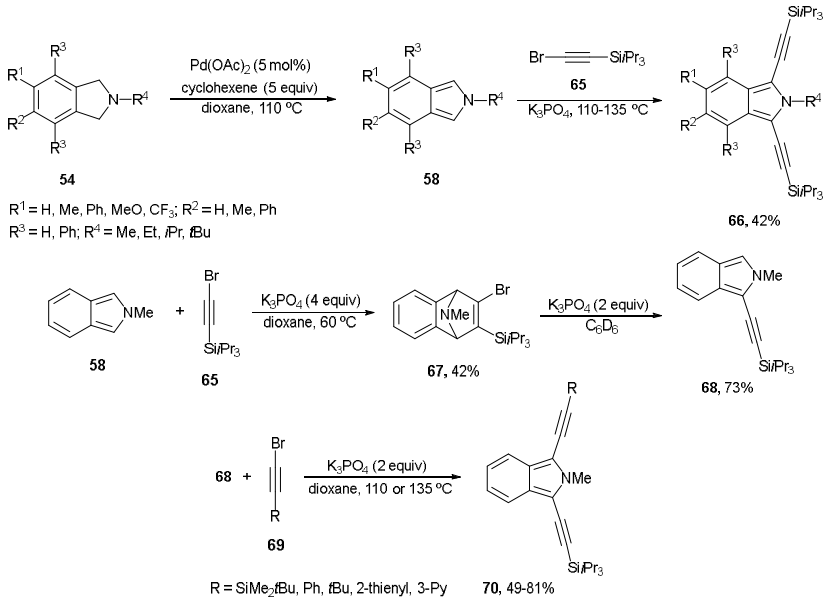
Scheme 13. Borylated isoindoles **56** and **57** from isoindolines **54**.

Aryl substituted isoindoles have been obtained by a dehydrogenative/C–H arylation process starting from isoindolines **54** performed by the same group (Scheme 14).[32] In this case, the first dehydrogenation step allowed to isolate isoindoles **58** or to perform *in situ* the C–H arylation step adding phenyl chloride **59** to provide diarylated isoindoles **60**. When monosubstituted isoindolines were used, the one-pot dehydrogenation/C–H arylation with aryl chlorides **59** gave *N*-methyl isoindoles **61**. DA reaction of *N*-methyl 1,3-diphenylisoindole **60** with naphtalyne generated *in situ* from 2,3-dibromonaphthalene **62**, afforded bicyclic amine **63**, which was converted into 5,12-diphenyltetracene **64** by treatment with *meta*-chloroperbenzoic acid.



Scheme 14. Arylated isoindoles **60** and **61** from isoindolines **54**.

The Suginome's group[33] has carried out the synthesis of 1,3-dialkylated isoindoles **66** by reaction of isoindoles **58** with (bromoethyhyl)triisopropylsilane **65** (Scheme 15). In the absence of transition metal, first the [4+2] cycloaddition takes place first to give **67**, followed by ring opening with elimination of HBr to yield the monoalkylated isoindole **68** without formation of a cycloadduct. Unsymmetrical 1,3-dialkinylisoindoles **70** can be prepared *via* alkynylation of monoalkylated isoindole **68** with bromoalkynes **69**. A one-pot synthesis of isoindoles **66** was carried out starting from isoindolines in good yields. The triisopropyl group in compound **66** was desilylated with tetra-*n*-butylammonium fluoride and also submitted to desilylative Sonogashira coupling with aryl iodides in the presence of AgF. Photophysical properties of alkynylated isoindoles showed strong fluorescence of compounds **66**.



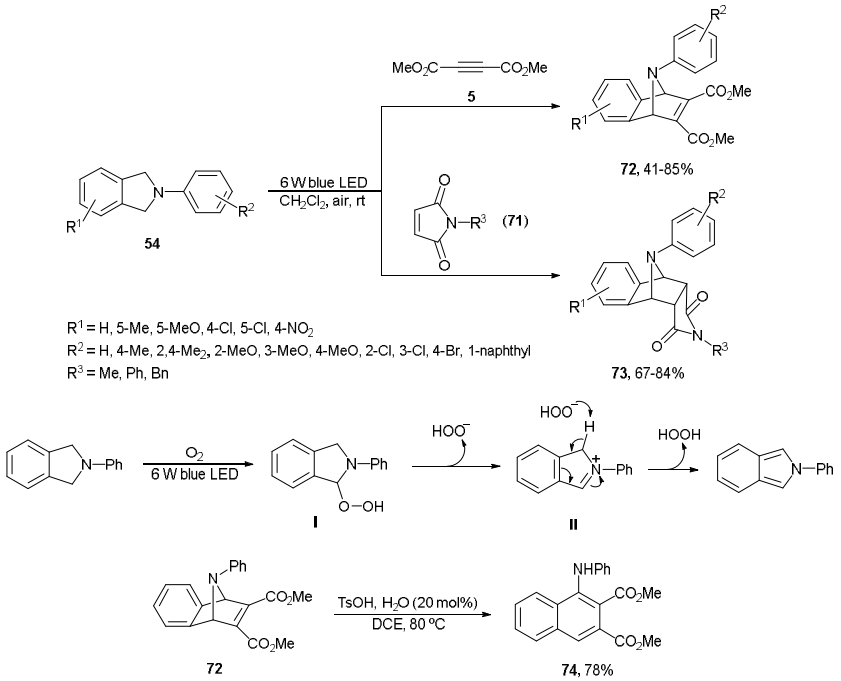
Scheme 15. Alkynylated isoindoles **66**, **68** and **70** from isoindolines **54**.

Transition metal-free isoindole formation from isoindolines in the presence of air has been carried out using visible-light which enables an intermolecular DA reaction under mild reaction conditions.[34] Thus, the reaction of isoindolines **54** with DMAD **5** or maleimides **71** took place with 6 W blue LED in dichloromethane at room temperature to give products **72** and **73** in excellent diastereoselectivity and high yields (Scheme 16). A plausible mechanism for forming *N*-phenylisoindole from *N*-phenylisoindoline involves the formation of hydroperoxide **I** in the presence of oxygen. Elimination of hydrogen peroxide ion from **I** provides iminium **II** which isomerizes to *N*-phenylisoindole. Treatment of cycloadduct **72** (R^1=R^2=H) with *p*-TsOH afforded 1-naphthylamine derivative **74** in 78% yield.

3.2. [1,5]-Hydride shift

Gold-catalyzed [1,5]-H shift of *N*-propargylisoindolines **75** and subsequent DA reaction with dienophiles has been reported by Gong and co-workers.[35] The *in situ* generated *N*-allylisoindoles such as **76** gave cycloadducts **77**, **79**, **81**, **83** and **84** in good yields and diastereoselectivities working in 1,2-dichloroethane (DCE) at 60 ºC (Scheme 17). This two-step procedure gave *endo*-cycloadducts **77** with maleimides **71** and products **79** with dimethyl fumarate **78**. However, dimethyl maleate **80** provides product **81** as a 1:1 mixture of diastereomers. Benzylidene malononitrile **82** showed less reactivity giving **83** in 52% yield and DMAD **5** reacted with isoindoles **76** after cooling down the temperature to 20 ºC providing products **84**. On the basis of deuterium labelling experiments a plausible mechanism showed in Scheme 17 was proposed. The [1,5]-H shift gives intermediate **I**, which undergoes a reversible protonation and

deprotonation sequence under the assistance of Tf_2N^- forming the σ-gold complex **II** and finally the *N*-allylisoindole **76**.



Scheme 16. Isoindoles by visible light oxidation of isoindolines **54** and *in situ* DA reaction.

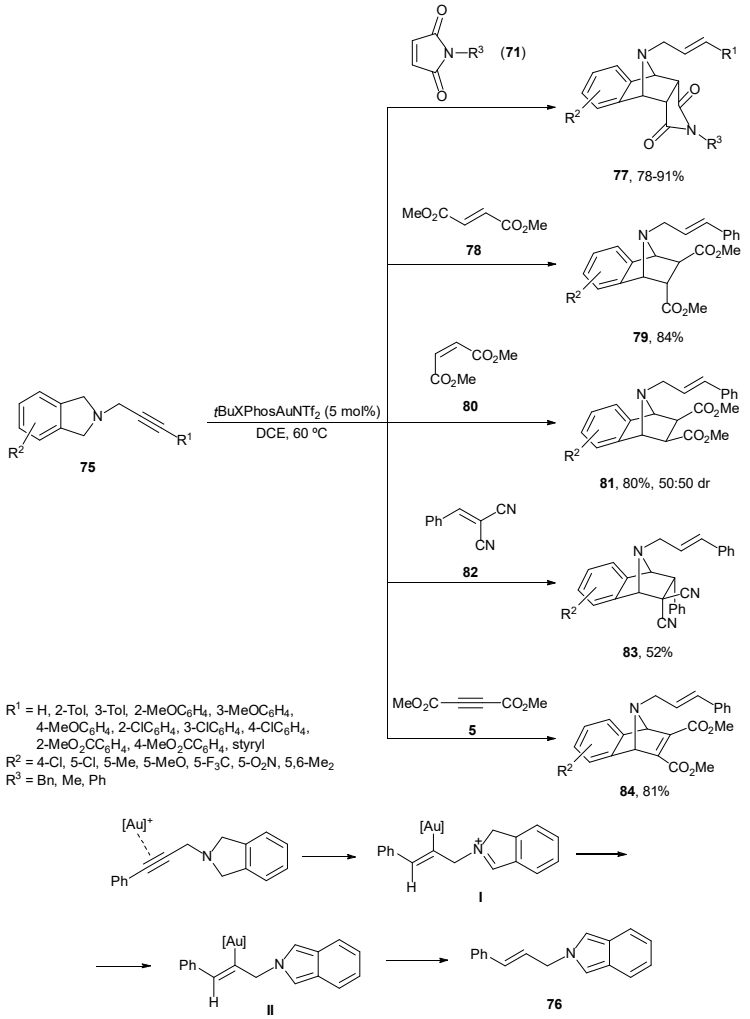
Diphenyl phosphoric acid (DPP) **86** promoted the [1,5]-H shift of isoindolines **85** to provide isoindoles **87** which were also trapped by DMAD **5** and maleimides **71** giving cycloadducts **88** and **89**, respectively (Scheme 18).[35] In the proposed mechanism, after protonation of the benzylic alcohol, deprotonation takes place to give intermediate **I**. Then [1,5]-H shift process occurs providing the iminium cation intermediate **II**, which undergoes deprotonation to isoindole **87**. On the other hand, when the more acidic *p*-TsOH was used instead of DPP **86** in the presence of DMAD **5** as dienophile, 1-naphthylamine derivative **90** was obtained by protonation of the cycloadduct **88** and isomerization.

The Cu(I)-catalyzed three component-coupling of an alkyne, an aldehyde and an amine[36] has been applied to the synthesis of isoindole **95** by Ma and co-workers.[37] The coupling of isoindoline **91** with cyclohexanecarbaldehyde **92** and 1,1-dimethylpropargyl alcohol **93** gave isoindole **95** by an unexpected Cu(I)-catalyzed *E*-stereoselective reduction of the *in situ* formed propargyl amine **94** *via* [1,5]-H shift (Scheme 19). The corresponding isoindole **95** was trapped by addition of *N*-methylmaleimide (NMM) at -10 ºC to provide cycloadduct **96** in 70% overall yield.

4. Synthesis by ring transformation

Retro DA reactions have been used for the synthesis of moderate stable isoindoles. Swager and co-workers[38] reported the synthesis of 4,5,6,7-tetrafluoroisoindole **99** by reaction of azabicycle **97** with 3,6-(di-2-pyridyl)-1,2,3,4-tetrazine **98** at room temperature (Scheme 20), adapted from the Warrener's methodology[39] described by Gribble.[40] This process takes place *via* a DA reaction and subsequent thermally allowed electrocyclic fragmentation.[40] This isoindole **99** was transformed into tetracenes **102** by DA reaction with naphthalynes resulting from dibromonaphthalenes **100** to give products **101**, which were aromatized by deamination with an aqueous solution of NaOH to furnish products **102** in 15-35% overall yield. These fluorinated tetracenes **102** have good solubility in common organic solvents and crystallize with antiparallel,

cofacial, stacked column superstructures and **102** (R^1=H, R^2=*n*-C_8H_{17}) exhibited a slipped parallel π-stacking arrangement in crystals. They are promising candidates for the use in organic electronics.

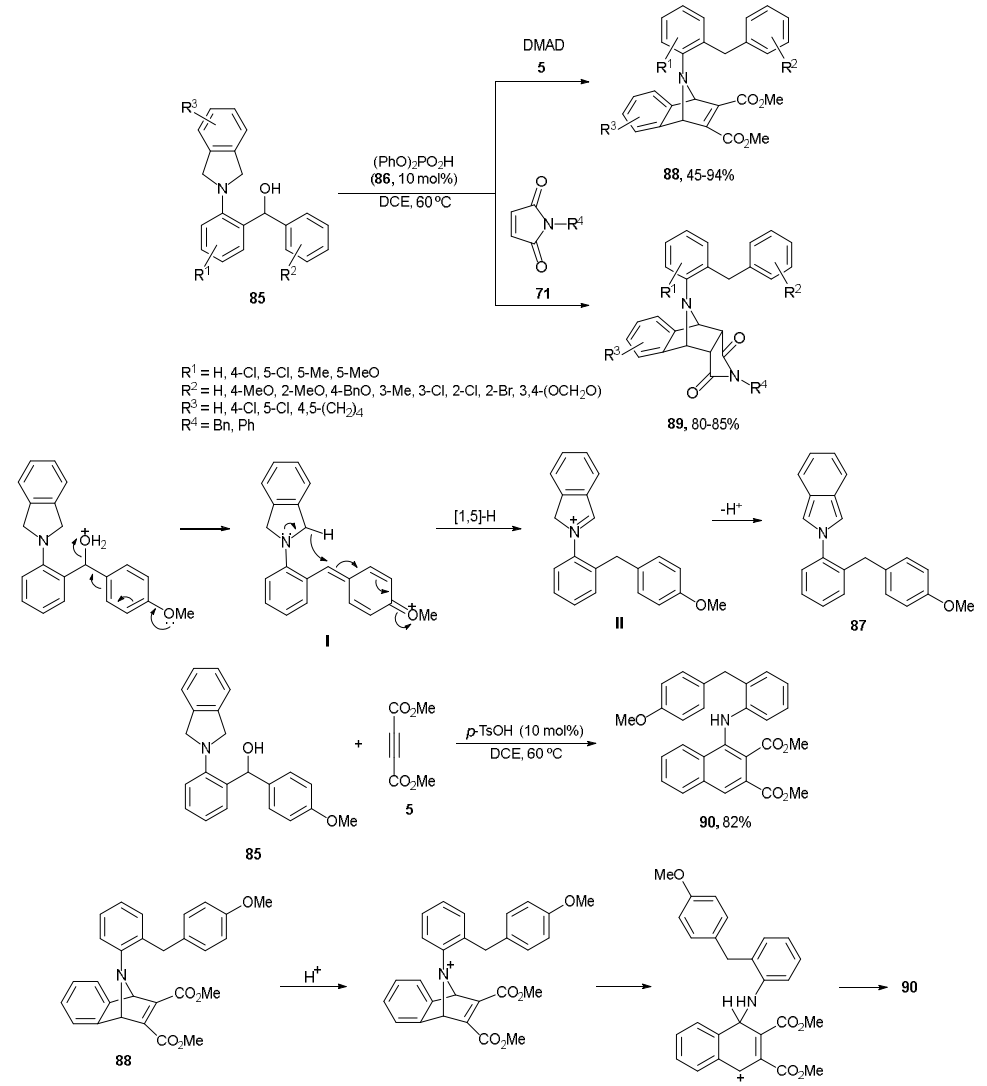


Scheme 17. *N*-Allylylic isoindoles **76** from isoindolines **75** trapped in DA reactions.

Oxadisilole-fused isoindoles **105** and **106** have been prepared using Warrener's methodology starting from azabicycles **103** and **104**, respectively, by Lee and co-workers (Scheme 21).[41] The resulting isoindoles **105** and **106** were allowed to react with different dienophiles such as DMAD **5** and benzynes giving cycloadducts in good yields (48-98%). Some representative examples have been submitted to a deamination process by treatment of benzyne cycloadduct **107** with trifluoroacetic acid at room temperature to provide *p*-quinone **108**. In the case of cycloadduct **109** additional treatment with AcOH at 100 ºC gave quinone **110** in 45% yield.

Rincón and Plumet[42] applied the Warrener's methodology to the preparation of *N*-Boc-protected isoindole **112** using the azabicycle **111** and the tetrazine **98** (Scheme 22). This isoindole **112** was trapped by different alkynyl and vinyl sulfones **113** to provide cycloadducts **114-116** in moderate to good yields.

Bicyclopyrroles **117** have been transformed into the corresponding stable isoindoles **118** performing the retro-DA reaction using supercritical carbon dioxide avoiding oxidation of isoindoles when high-boiling solvents were used (Scheme 23).[43] Oxidative decomposition of isoindoles was prevented by adding ethylene gas as an oxygen scavenger increasing the isolation yield of **118** (R=X=H) with 68-81% yields.

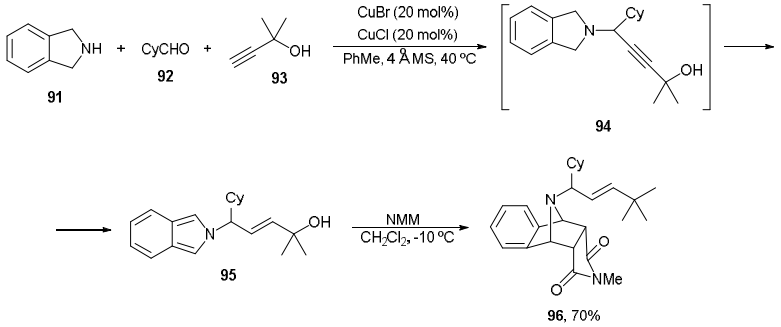


Scheme 18. Isoindoles **87** from isoindolines **85** trapped in DA reactions.

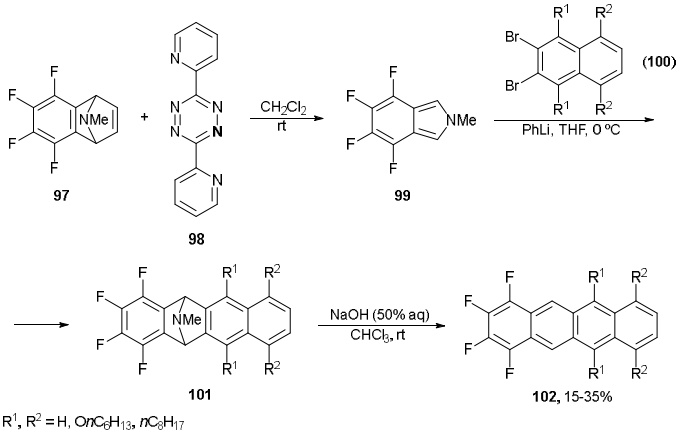
5. Other methodologies

Recent advances in isoindole chemistry are related to the transformation of nucleophilic isoindoles into electrophilic isoindolinium *via* protonation of the *in situ* generated isoindoles. Wang and co-workers[44] reported the reaction of 2-(bromomethyl)benzaldehydes **46** with triptamines **119** to give isoindoles **120**, which were treated *in situ* with trifluoroacetic acid giving isoindolines **121** by a Pictet-Spengler-type cyclization in good yields (Scheme 24).

A Pd-catalyzed Heck-type dearomative [4+2] annulation of isoindoles **122** with internal alkynes **123** provided polycyclic pyrrolidines derivatives **124** in good yields (Scheme 25).[45] This process has been carried out with *N*-(2-bromo)- and also with (2-iodo)aryl isoindoles **122**. In the proposed mechanism, after the initial oxidative addition of the aryl iodide to Pd(0), the arylpalladium species **I** is formed. Then, the insertion of the internal alkyne provides an alkenylpalladium intermediate **II** followed by an intramolecular Heck reaction with the carbon-carbon double bond closed up to the ester group of the isoindole delivering intermediate **III**. The subsequent aromatization produces the benzylic palladium species **IV**, which undergoes β-hydride elimination to the final product and the catalytic species is regenerated by K_2CO_3.



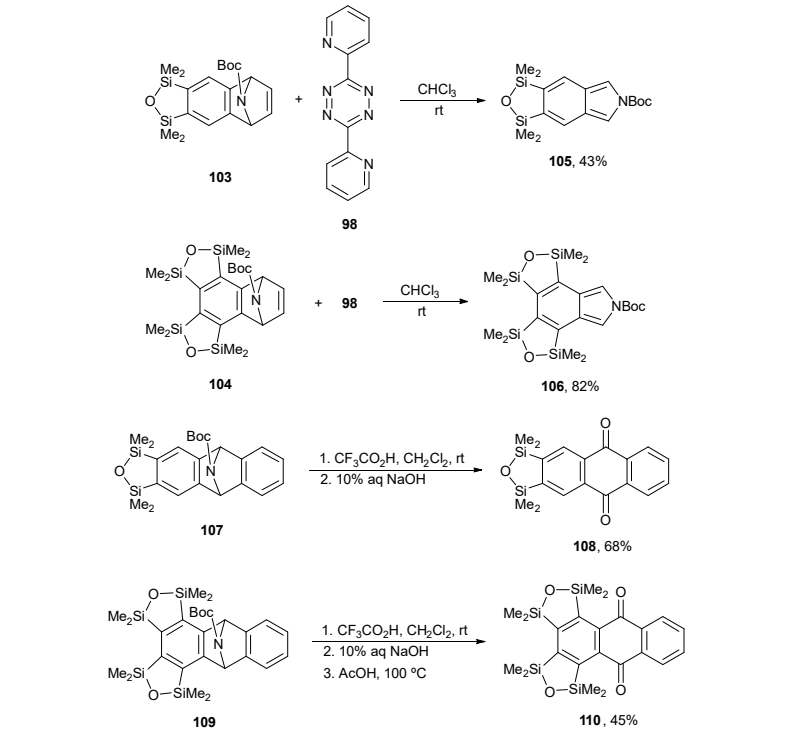
Scheme 19. Isoindole **95** formed by a three component-coupling of isoindoline **91**, cyclohexanecarbaldehyde **92** and 1,1-dimethylpropargyl alcohol **93**.



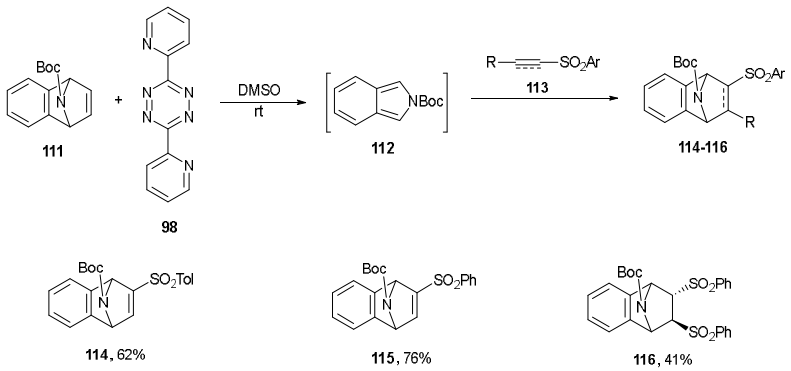
Scheme 20. 4,5,6,7-Tetrafluoroisoindole **99** from azabicycle **97** and tetrazine **98**.

6. Conclusion

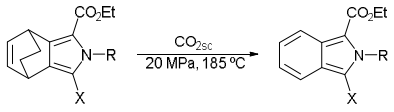
In the present review, recent developments for the synthesis of 2*H*-indoles indicate that four strategies have been mainly employed. Intramolecular cyclization of *o*-alkynyl benzylamine derivatives under Au, Pd and also under metal-free conditions are important methodologies based on hydroamination reactions followed by aromatization. Acetylenic diazoacetates reacting with amines under Cu-catalysis to give similar derivatives are alternative starting compounds. Aromatization process starting from isoindolines and [1,5]-hydrogen shift of *N*-propargyl isoindolines are mediated by Lewis or Brønsted acids. Concerning ring transformation Warrener's methodology is still an interesting strategy. Other methodologies allowed the intramolecular α-alkylation of isoindoles bearing a tryptamine and by an intermolecular Heck-type [4+2] annulation. In many cases it is possible to isolate relative stable isoindoles and alternatively have been trapped by a DA reaction.



Scheme 21. Ozadisilole.fused isoindoles **105** and **106** by Warrener's method.

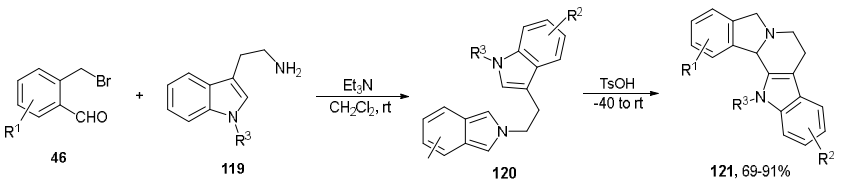


Scheme 22. *N*-Boc-isoindole **112** by Warrener's method.



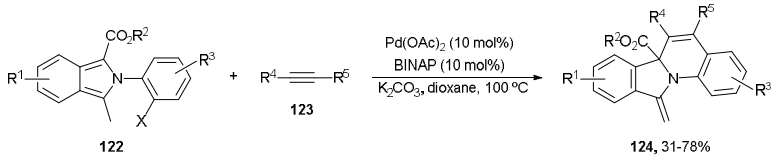
R = H, Bn
X = H, Ph, CN, CHO

Scheme 23. Isoindoles **118** by retro-DA reaction of bicyclopyrroles **117** in supercritical CO_2.

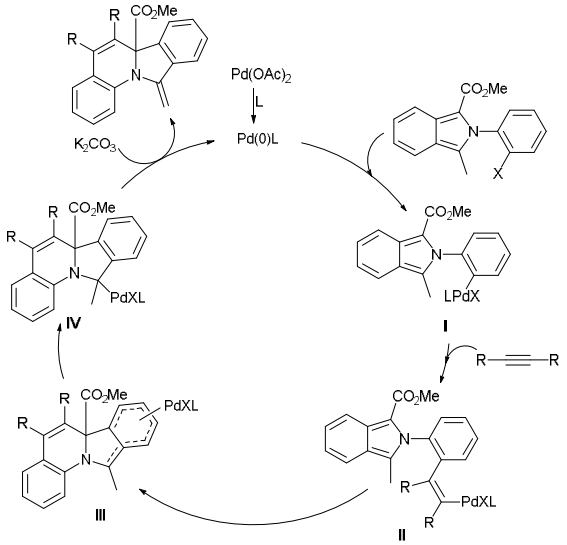


R^1 = H, 4-Cl, 5-Cl, 4-F, 5-F
R^2 = H, 5-Me, 5-MeO, 5-Cl
R^3 = H, Me

Scheme 24. Isoindolines **121** by intramolecular 1-alkylation of isoindoles **120**.



X = Br, **I**
R^1 = H, 4-Me, 5-Me, 4-Cl, 5-Cl
R^2 = Me, Et, *i*Pr
R^3 = H, 4-Me, 4-F, 4-Cl, 4-Br, 3-Me, 3-F, 3-Cl, 3-Br
R^4 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4
R^5 = Me, *n*Bu
R^4 = R^5 = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-NCC_6H_4, 4-$MeO_2CC_6H_4$, 2-thienyl, Et, *n*Pr, *n*Bu



Scheme 25. Dearomative annulation of isoindoles **122** with alkynes **123** under Pd-catalysis.

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