UNIVERSITÀ DEGLI STUDI DELL'INSUBRIA
Dipartimento di Scienza e Alta Tecnologia

Dottorato di Ricerca in Scienze Chimiche – XXVI ciclo

SYNTHESIS AND FUNCTIONALIZATION OF INDOLE SKELETON COMPOUNDS VIA NITROSOARENE-ALKYNE CYCLOADDITIONS

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Ph.D. dissertation by
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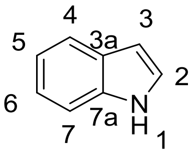
List of abbreviations

Ar	aryl (substituted aromatic ring
aq	aqueous
Bn	benzyl
Boc	tert-butoxycarbonyl
br s	broad singlet (spectral)
Bz	benzoyl
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
Cp	cyclopentadienyl
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DMAP	*N,N*-4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDP	petroleum ether
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
GC	gas chromatography
Hz	Hertz
h	hours
IR	infrared spectroscopy
J	coupling costants (NMR)
mol	moles
Me	methyl
MeOH	methanol
MS	mass spectrometry
NMR	nuclear magnetic resonance
m/z	mass to charge
n-BuLi	*n*-butyllithum
o-	ortho
Oxone®	potassium peroxymonosulfate
PG	protecting group
Ph	phenyl
ppm	parts per million (NMR)
r.t	room temperature
TBAF	tetra-n-butylammonium fluoride
TEA	(Et_3N) triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

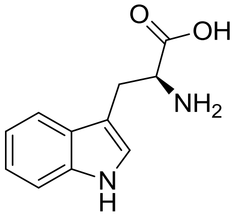
GENERAL INTRODUCTION

1 INDOLES

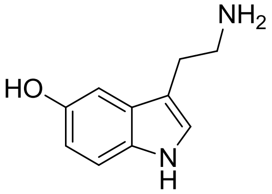
In 1866, Baeyer and Knop, in the course of a study of the structure of indigo, reduced isatin and obtained two products, $C_8H_7NO_2$ and C_8HN_7O (dioxindole and oxindole), which they regarded as hydroxyl derivatives of C_8H_7N; they named the latter "*indole*". The work was continued by Baeyer and Emmerling, who proposed in 1869 the formula which is generally accepted[1]:



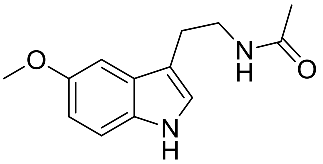
Since then, indole and its myriad of derivatives capture the attention of organic chemists. Indoles are indeed one of the most important and abundant classes of *N*-heterocycles, being present in the form of innumerable natural products and bioactive compounds[2]. The indole ring appears in the amino acid tryptophan (**1**) and metabolites of tryptophan, like serotonin (**2**) (one of the key neurotransmitters) and melatonin (**3**) (involved in controlling the natural daily cycle of hormone release in the body), are important in the biological chemistry of humans and animals[3].



(1) ***L-tryptophan***

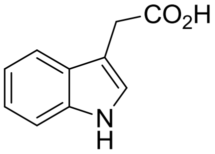


(2) ***serotonin***

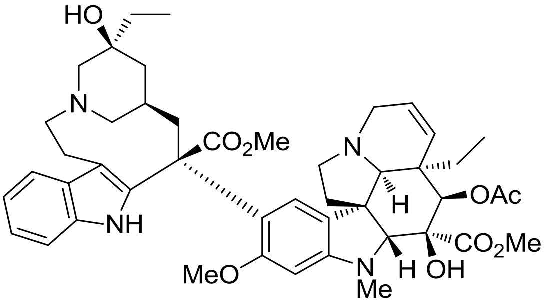


(3) ***melatonin***

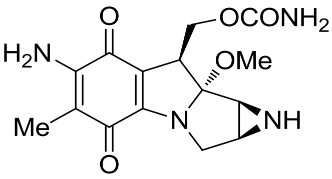
Other natural compounds containing the indole skeleton range from small structures like indole-3-acetic acid (**4**) (plant growth hormone) to complex alkaloyds such as the clinically used anticancer agents vinblastine (**5**) and mitomycin C (**6**), and the antihypertensive alkaloid reserpine (**7**).



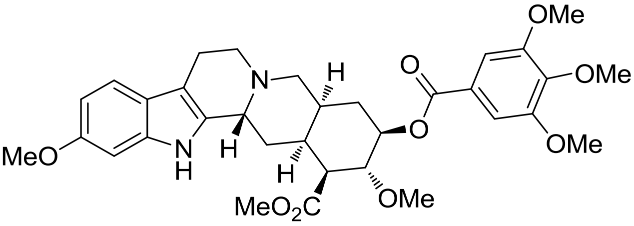
(4) indol-3ylacetic acid



(5) vinblastine

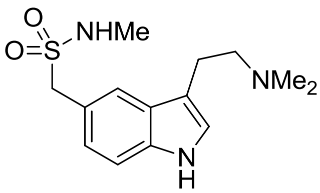


(6) mitomycin C

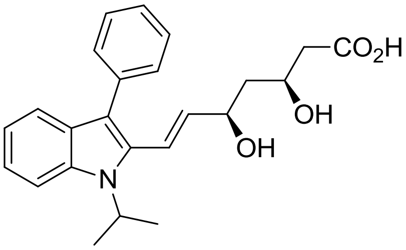


(7) reserpine

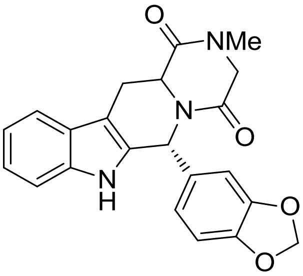
Indole motif could also be found in a number of important synthetic drugs, including sumatriptan (**8**), tadalafil (**9**), and fluvastatin (**10**)[4].



(8) ***sumatripan***



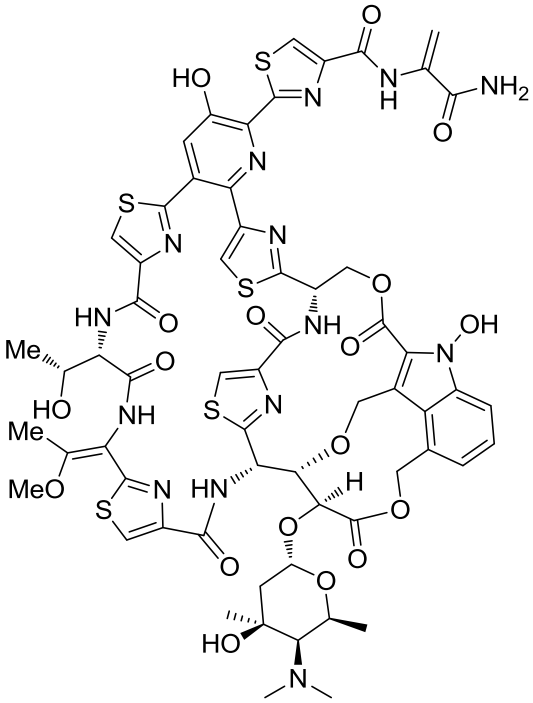
(9) ***tadalafil***



(10) ***fluvastatin***

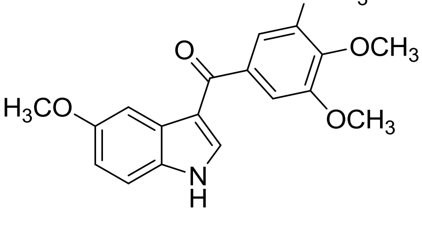
A class of indole derivatives which have received considerable attention in recent years are *N*-hydroxyindoles[5]. The biological role of *N*-hydroxyindoles is still an area of active investigation since they have been shown to possess biological activity in certain cases, recently a new class of inhibitors of human LDH-A enzyme was identified in a series of *N*-hydroxy-2-carboxy-substituted indoles[6]. In addition, biologically inactive indoles have been rendered biologically active when their *N*-hydroxyindole analogues were examined.[7]

There are only few naturally occurring *N*-hydroxyindoles, maybe this is due to their instability to isolation. Furthermore, most of them show a stabilizing group on the indole nucleus. One of the most impressive naturally-occurring molecules that feature the *N*-hydroxyindole unit is the nocathiacin I[8](**11**), an antibiotic isolated from *Nocardia sp*.[9] and the fungus *Amicolaptosis sp*.[10], exhibiting strikingly potent activity in vitro and in vivo against Gram-positive bacteria.[9a, 10]



(11) ***nocathiacin I***

3-Aroylindoles are another class of indole derivatives, known as bioactive compounds with interesting properties[11]. Some synthetic compounds as BPR0L075 (6-methoxy-3-(3',4',5'-trimethoxy-benzoyl)-1H-indole) (**12**) showing 3-aroylindole unit were discovered as potent antitubulin agents[12]. 3-Aroylindoles were differently prepared by classic synthetic approaches by acylation of preformed indole substrates[13a-b] and very recently by Pd-Cu[13c] and Cu[13d] catalyzed coupling reactions. Not many indolization procedures are known to afford directly 3-acylindoles starting from commercially available reactants[14].



12 – BPR0L075

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CHAPTER 1 – INDOLE SYNTHESES

1 Introduction

The synthesis of indole derivatives has been and continue to be a topic of research interest from well over a century[1]. Naturally occurring and synthetic indole containing molecules produced by many synthetic approaches have important uses and potential as drugs with a broad spectrum of applications in many therapeutic categories, including non-steroidal anti-inflammatory, antimigraine, antidepressant, antineoplastic, anticancer and many others. Libraries based on the indole scaffold have been developed to address the need for novel drugs with increased and enhanced potency. Indoles are currently prepared by numerous and varied synthetic approaches, both intramolecularly and intermolecularly[2]; particularly attractive but few in numbers are reactions that directly produce indoles by annulations of commercially available *N*-aromatic precursors as in the Fisher indole synthesis[3].

In order to describe the indole synthesis using benzenoid as precursors, we can indentify four bond disconnections, depending on the bond formed during the process (Figure 1.1).

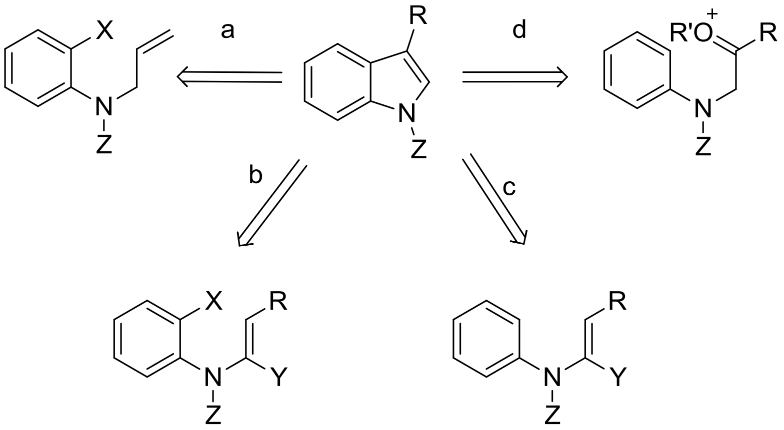
disconnection "a"(C3-C3a) disconnection "b"(C2-C3) disconnection "c"(N-C2) disconnection "d"(N-C7a)

Figure 1.1 - Bond disconnections for indoles synthesis from benzenoid precursors

1.1 *Disconnection “a”*

Disconnection “a” involves formation of the C3-C3a bond and requires aniline derivatives with a nitrogen substituent appropriate for such reactions. Some of those cyclizations also need an *o*-substituent, frequently halogen. The retrosynthetic transformations corresponding to the most important of this group of syntheses are shown in Scheme 1.1.

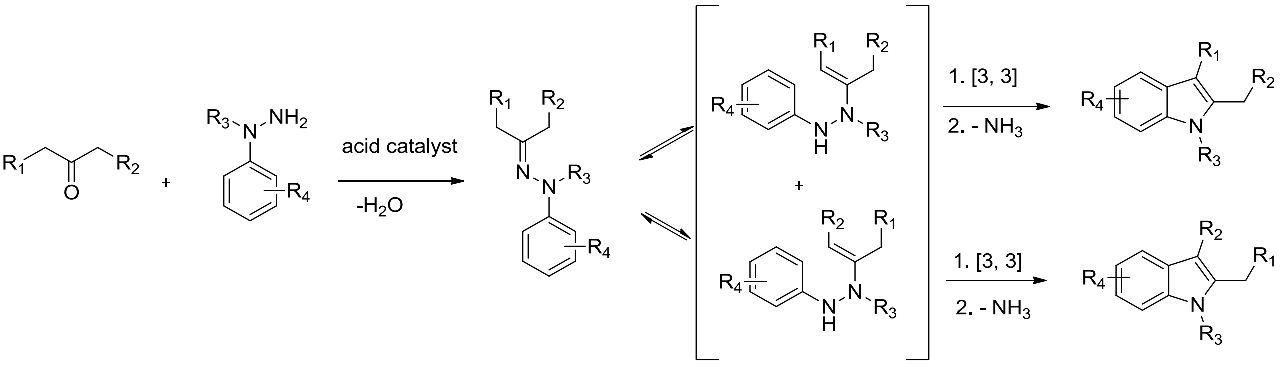
Disconnection “a”



Scheme 1.1

1.1.1 *Fischer Indole Synthesis*[3, 4]

The first indolization of an arylhydrazone was effected by Fischer and Jourdan in 1883[5], treating pyruvic acid and 1-methylphenylidrazone with alcoholic hydrogen chloride. Since its discovery, it has become the most important method to prepare substitute indoles[6].



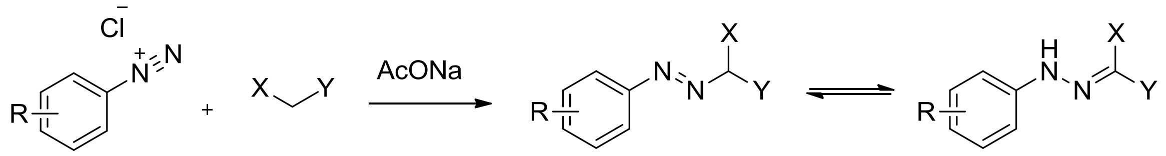
Scheme 1.2

The Fischer indole synthesis provides a simple, efficient method for the transformation of enolizable *N*-arylhydrazones into indoles. It involves *ortho*-substitution *via* sigmatropic rearrangement. The reaction generates an imine of an *o*-aminobenzyl ketone which cyclizes and aromatizes by loss of ammonia.

Advantage of the Fischer reaction includes the toleration of a wide range of functional groups around the aromatic ring and lack of requirement for a functional group to form the new C-C and C-N bonds.

1.1.1.1 Synthesis of N-arylhydrazones

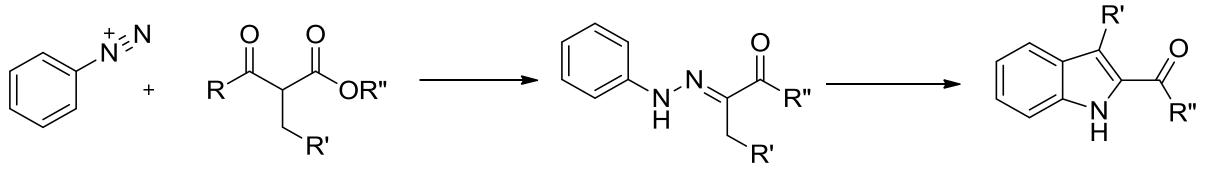
N-arylhydrazones are often prepared via condensation of an arylhydrazine with an enolizable ketone. However, since few arylhydrazines are commercially available, they are generally prepared according to the Japp-Klingemann procedure[7]. Aryl diazonium salts, in turn obtained from the appropriate anilines, are treated with an active methylene or methine compound under acidic or basic conditions to form an azo derivative, which, under basic, acidic or thermal conditions, is converted to the hydrazone (Scheme 1.3).



X, Y = COR, COOR, CN

Scheme 1.3

If a β-ketoester (Scheme 1.4, **a**) is used, deacylation is followed by indole formation to afford an indole-2-carboxylate ester[8a]. If, instead of an ester, the reaction is carried with a salt of β-ketoacid (Scheme 1.4, **b**), decarboxylation provides 2-acylindole[8b]. The Japp-Klingemann reaction was also applied with malonates to prepare 2-alkoxycarbonyl-5-methoxyindoles[9].



a - R" = alkyl
b - R" = H

a - R" = O-alkyl
b - R" = alkyl

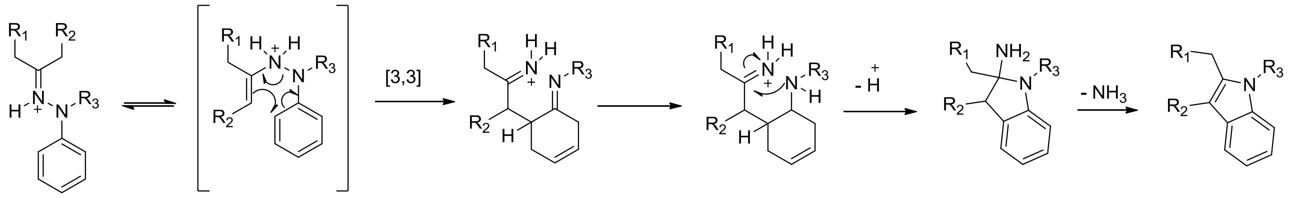
a - R" = O-alkyl
b - R" = alkyl

Scheme 1.4

1.1.1.2 Mechanism

The currently accepted mechanism of the Fischer indole synthesis was originally proposed by Robinson in 1924[10]. There are five separated steps: 1) coordination of the Lewis acid to the imine nitrogen; 2) tautomerization of the hydrazone to the corresponding ene-hydrazine; 3) disruption of the aromatic ring by a [3,3]-sigmatropic rearrangement; 4) rearomatization *via* a proton shift and formation of the 5-membered ring by a favored 5-*exo-trig* cyclization; 5) loss of an ammonia molecule to finally form the indole system (Scheme 1.5).

The mechanism is not ionic, but concertated. In strong acids, the rate-determining step is deprotonation to form the ene-hydrazine, whereas under weakly acidic conditions tautomerization is sufficiently rapid that the [3,3]-sigmatropic rearrangement is rate determining[11]. If the ketone is unsymmetrical, the tautomerization can occur at both position, resulting in a mixture of indole regioisomers.



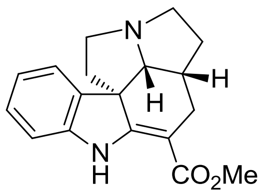
Scheme 1.5

Investigations on the effects of *ortho*-substituents on the regiochemistry and rate of Fischer indole cyclizations demonstrated that the hydrazone undergoes cyclization to the more electron-rich aromatic ring[12].

1.1.1.3 Synthetic Applications

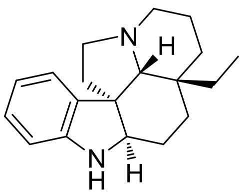
The Fischer indole synthesis has been largely applied to access a wide range of indoles and derivatives of biological and medicinal interest.

(±)-Deethylibophyllidine (**13**) was synthesized by J. Bonjoc and co-workers using the Fischer indole synthesis as one of the key steps[13]. (+)-Aspidospermidine (**14**)[14], (±)-Peduncularine (**15**)[15] and Tryptostatin A (**16**)[16] are only few examples of indole alkaloids obtained by Fischer indole synthesis.



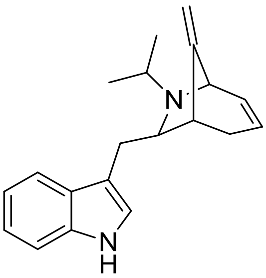
(±)-Deethylibophylline

13



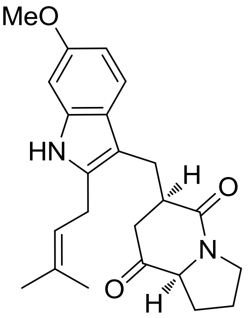
(+)-Aspidospermidine

14



(±)-Peduncularine

15

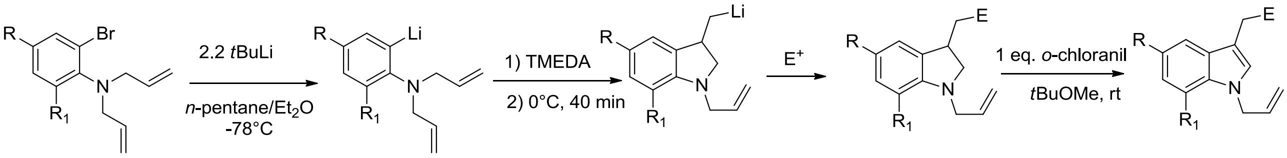


Tryprostatin A

16

1.1.2 Bailey-Liebeskind Indole Synthesis

Bailey[17] and Liebeskind[18] developed an indole ring-forming reaction involving anionic cyclization onto an *N*-allyl unit. The obtained indoline anion can be treated with an electrophile and oxidized with chloranil (2,3,5,6-tetrachloro-*p*-benzoquinone) to the indole.



Scheme 1.6

1.1.3 Bischler-Möhlau Indole Synthesis[19]

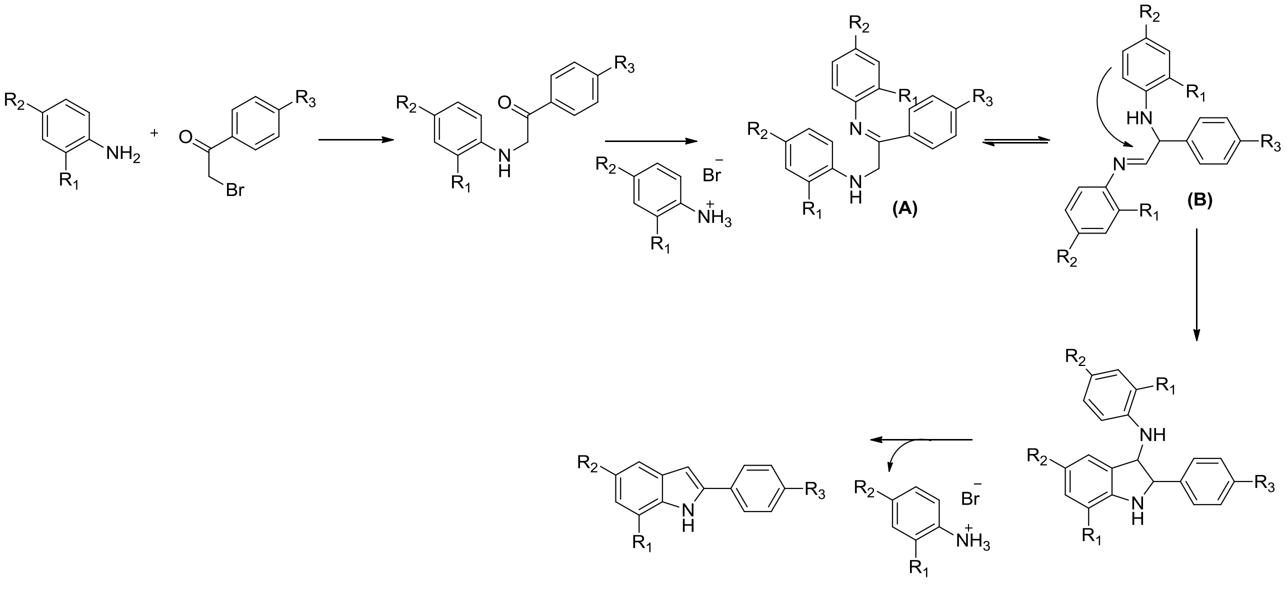
The Bischler (or Bischler–Möhlau) indole synthesis consists in a monoalkylation of an aniline with phenacyl bromide that lead to a 2-substitued indole after rearrangement mechanisms.

Disconnection “a”

Perhaps owing to the harsh reaction conditions that it requires, the original method of the Bischler reaction has received relatively little attention. Recently, milder methods have been developed, including the use of lithium bromide as a catalyst and an improved procedure involving the use of microwave irradiation. Variations of the Bischler synthesis that allow the preparation of 2,3-unsubstituted indoles by cyclization of acetals are known, although they are of limited scope[20].

1.1.3.1 Mechanism

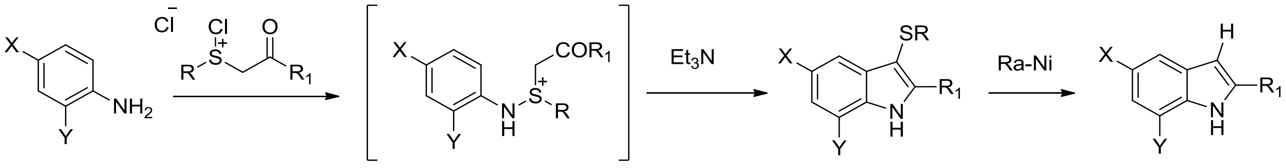
The first step involves monoalkylation of anilines with phenacyl bromides, followed by treatment with an aniline hydrobromide as a catalyst, which forms an imine. Because of the high temperatures required, which favor thermodynamic control, the more stable imine tautomer (Scheme 1.7, **B**) predominates. Its cyclization and the loss of the initial aniline lead to the final indole compound. The tautomerization of (**A**) to (**B**) explains the apparent migration of the aryl group to the indole C-2 position. If the starting aniline is *N*-substituted, this tautomerism is not possible and 3-arylindoles are obtained[21].



Scheme 1.7

1.1.4 Gassman Indole[22] and Oxindole[23] Synthesis

In its simplest form, Gassman indole synthesis involves a one-pot reaction in which hypohalite, a β-carbonyl sulfide derivative, and base are added sequentially to an aniline to yield 3-thioalkoxyindoles in good to excellent yield. Raney-nickel reduction then produces the desulfurized indole.

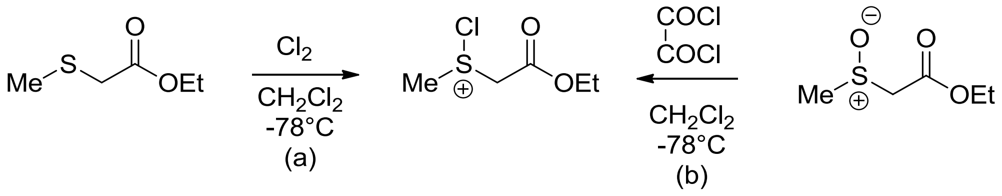


Scheme 1.8

The Gassman reaction proceeds under very mild conditions: all of the steps can be run below 0°C and no acid or strong base is needed.

The chlorosulfonium salt is typically generated from ethyl methylthioacetate and chlorine (Scheme 1.9, path a),which is difficult to dispense accurately on a small scale.

With reference to the limitation above, Wright and co-workers developed a modification (Scheme 1.9, path b) that allows to obtain the chlorosulfonium salt using sulfoxides as starting materials[24].



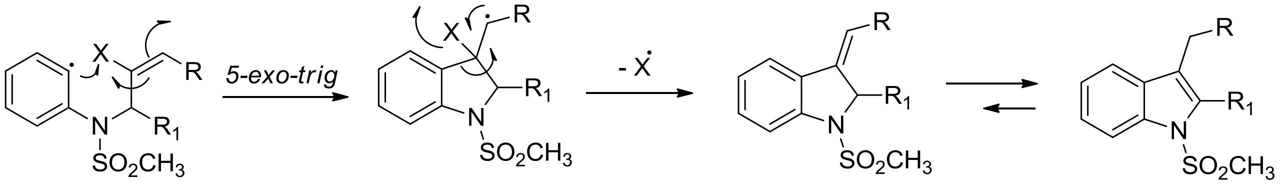
Scheme 1.9

1.1.5 Murphy Indole Synthesis[25]

The Murphy indole synthesis allows to afford indole derivatives by cyclizations of aryl radicals onto vinyl halides, followed by elimination of halide radical and tautomerism of the resulting product.

1.1.5.1 Mechanism

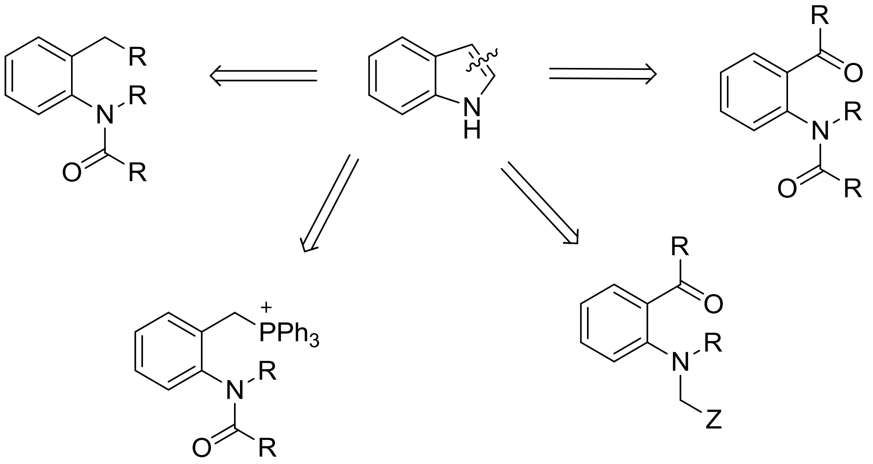
The reaction proceeds with a simple addition-elimination mechanism, which involves *5-exo-trig* cyclisation of an aryl radical (obtained from the corresponding arenediazonium salt or aryl iodide) into a substituted olefin to give alkyl radical. If X is a good radical leaving group, β-elimination should occur leading to the exocyclic alkene, that can tautomerise to its more stable aromatic indole (it should possess a strong driving force) (Scheme 1.10).



Scheme 1.10

1.2 *Disconnection "b"*

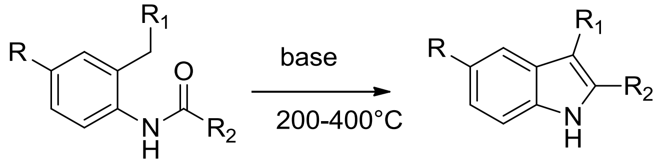
Category "b" cyclizations effect closure of the C2-C3 bond, included three variations of the intramolecular aldol condensation and reductive coupling of *o,N*-diacylanilines.



Scheme 1.11

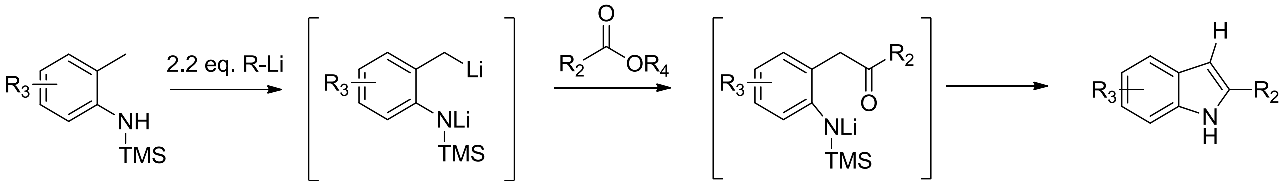
1.2.1 Madelung Indole Synthesis

The intramolecular cyclization of *N*-acylated-*o*-alkynilines to the corresponding substituted indoles in the presence of a strong base and at high temperature is known as the Madelung indole synthesis[26].



Scheme 1.12

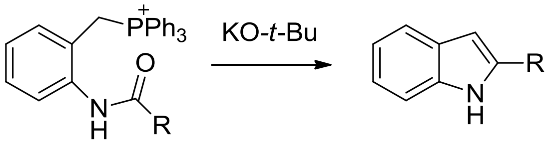
These conditions are so harsh that they are applicable only to indoles with the most inert substituents. Cyclization can be achieved at lower temperatures by using alkyllithium reagents as the base. These conditions are applied, for example, in the *Smith indole synthesis*[27], that involves an organolithium reagent to metalate substituted *N*-TMS-*o*-toluidines. The resulting benzylic anion reacts with non-enolizable esters or lactones to afford *N*-lithioketamine intermediates that first undergo intermolecular heteroatom Peterson olefination to give indolines, and then tautomerize to the corresponding 2-substituted indoles[28,29].



Scheme 1.13

Alkyllithium reagents were used also by Houlihan and co-workers, treating *N*-(alkylphenyl)alkylamide with 2 or 3 equivalents of *n*-butyllithium or lithium diisopropyl-amide in tetrahydrofuran, at temperatures between -20 and +25°C[30].

Another variation of the Madelung cyclization involves the installation of a functional group on the *o*-methyl group which can facilitate cyclization. For example, a triphenylphosponio substituent converts the reaction into an intramolecular Wittig condensation (Scheme 1.14). The required phosphonium salts can be prepared by starting with *o*-nitrobenzyl chloride or bromide[31].

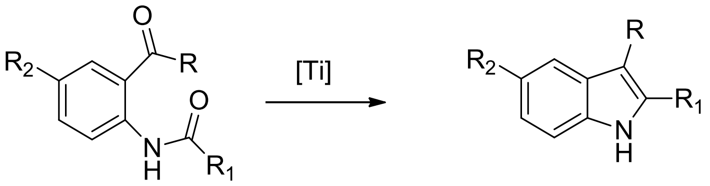


Scheme 1.14

1.2.2 Fürstner Indole Synthesis

Disconnection "b"

The Fürstner indole synthesis is the titanium-induced reductive cyclization of oxo-amides leading to an indole ring[27]. When suitably substituted aromatic compounds are treated with low-valent titanium reagents of the formal oxidation states 0, +1 and +2, the respective indoles are obtained by formation of their C2-C3 bond.



Scheme 1.15

The reductive cyclizations of oxo-amides are not restricted to titanium reagents, other strong electron donors like SmI_2, zirconium, niobium and tungsten afforded the respective indoles. The reduced reaction rate and higher cost make these reagents less attractive than titanium.

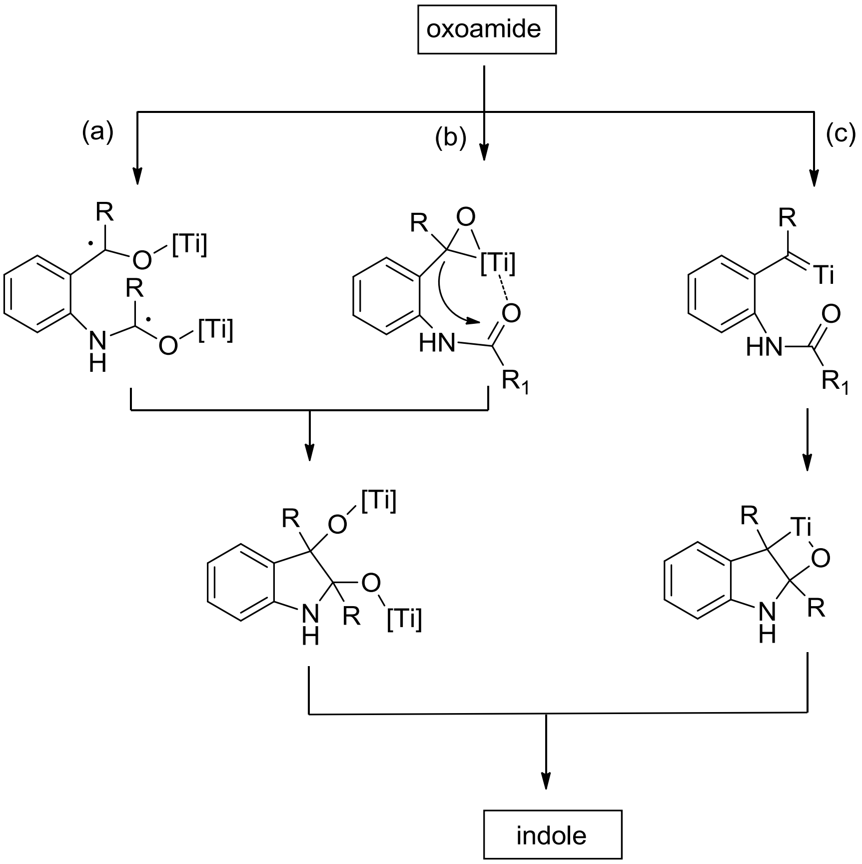
The Fürstner indole synthesis is a general reaction for simple indoles, including highly strained esamples[32] and it's particularly useful for the preparation of 2-aryindoles[33].

An improvement over the original procedure is the so-called "instant" method that uses $TiCl_3$–Zn, and these newer conditions have been employed to synthesize a variety of bi-, ter-, and quaterindoles [34].

1.2.2.1 Mechanism

The authors have considered three major pathways for the intramolecular alkylidenation of amides, that might lead to the formation of aromatic indoles: (i) radical anions formed upon single electron-transfer (s.e.t.) from [Ti] to both the ketone and to the amide function (Scheme 1.16, path a); (ii) titanium carbenes (Scheme 1.16, path c); and (iii) titanium dianions obtained by the input of two electrons into the ketone without any electron transfer to the amide (ester) group (Scheme 1.16, path b).

Electrochemical investigations support this mechanistic interpretation. Thus, the kinetically favored formation of a five-membered ring, the reactivity of the reacting sites, the high oxophilicity of titanium, as well as the aromatic of the final product all contribute to the success of this type of transformation[35].



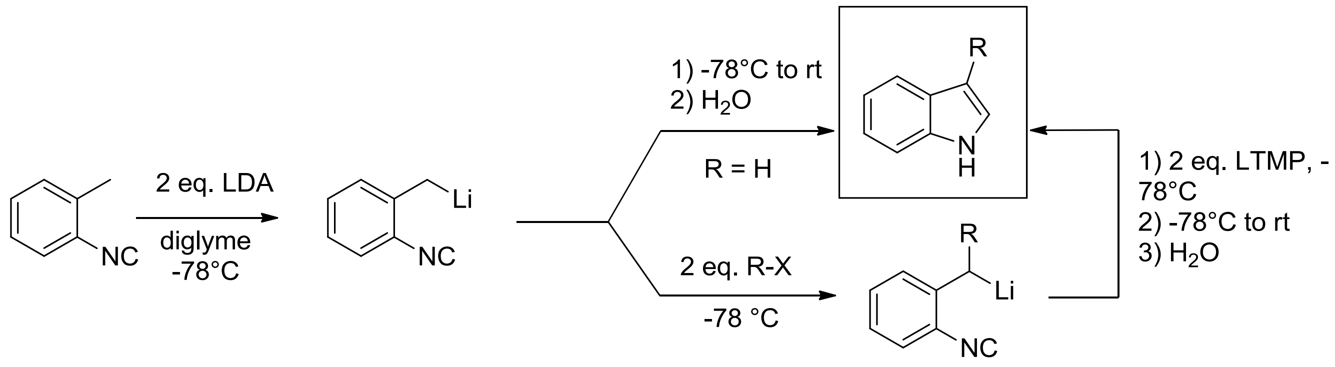
Scheme 1.16

1.2.3 Saegusa Indole Synthesis

The cyclization of *ortho*-lithiated *o*-tolyl isocyanides is a powerful indole synthesis discovered by Saegusa and co-workers in 1977[27].

Lithiation at the methyl group of an *o*-tolyl isocyanide is successfully performed by treatment of the starting material with 2 equivalents of LDA in diglyme at -78°C. The selective lithiation is solvent dependent. The *o*-lithiomethylphenyl isocyanide is allowed to warm up to room temperature to produce, after aqueous workup, indole (R = H) in almost quantitative yield. It can also be elaborated with electrophiles such as alkyl halides and epoxides to give *o*-substituted phenyl isocyanides, from which 3-substituted indoles can be derived[36].

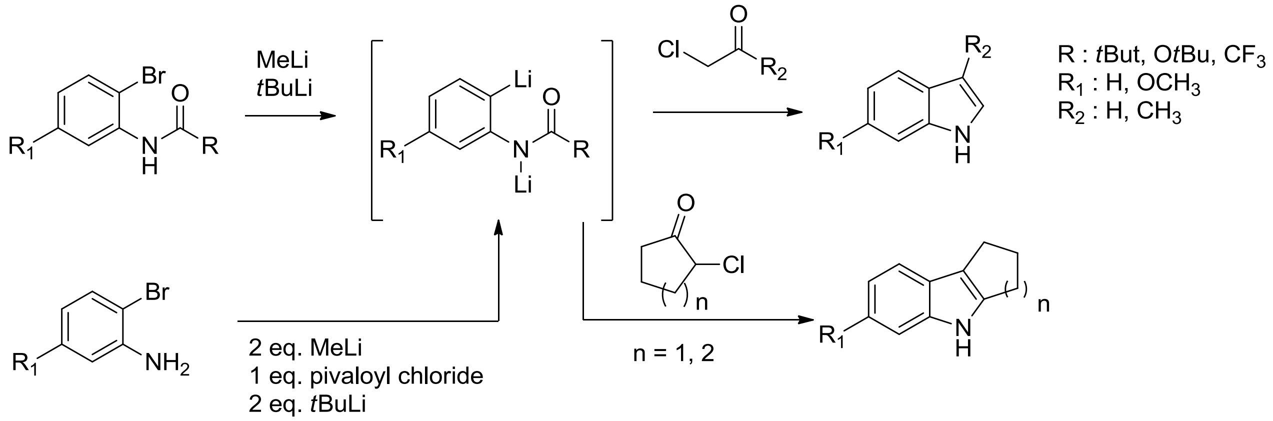
Disconnection "b"



Scheme 1.17

1.2.4 Wender Indole Synthesis

The Wender indole synthesis involves the *ortho*-lithiation of *N*-phenylamides followed by reaction of the resulting dianion with α-haloketones and subsequent ring closure and dehydration[37].



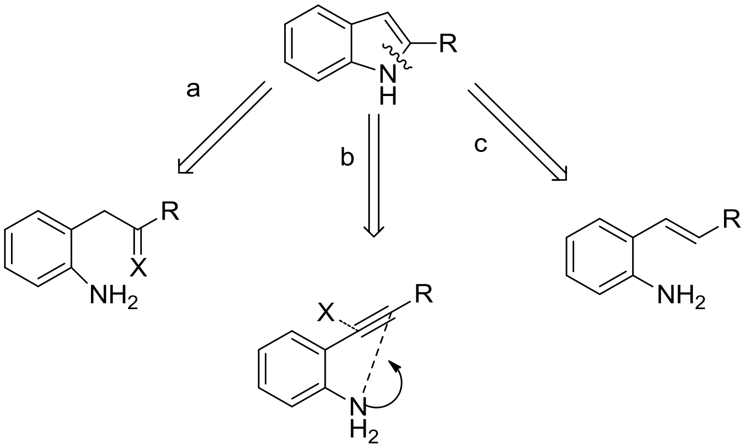
Scheme 1.18

This method has been used for the synthesis of indole itself, 2-substituted indoles, 3-substituted indoles, 2,3-disubstituted indoles and 6-substituted indoles.

The regiochemical outcome of the Wender indole synthesis is determined by the relative nucleophilicities and electrophilicities of the reactants and the regioselectivity realized in their formation. With α-haloketones as biselectrophiles, the annelation process proceeds with complete regiochemical control, the carbanionic center of the dilithium reagent reacts at the carbonyl of the haloketone reactant. Overall regioselectivity is determined, therefore, by the regioselectivity achieved in reactant preparation, which can usually be accomplished by using heteroatom directed deprotonation or site-specific halogen-lithium exchange.

1.3 *Disconnection “c”*

Category “c” cyclizations involve the formation of the N-C2 bond from a preformed intermediate which contanins all the necessary atoms to construct the indole framework. One group of these cyclizations proceeds by addition-elimination at a carbonyl or imine group, as represented in retrosynthetic path “a” (Scheme 1.19). The starting materials are often aromatic nitro compounds, with the cyclization taking place following reductive conversion to the nucleophilic amino group. The carbonyl or imine double bond may be present in the starting material, but it can also be introduced during the synthetic process. Retrosynthetic path “b” involves activation of an acetylene bond to nucleophilic addition (*endo-dig* type). Metal ions, especially Pd^{2+}, are effective catalysts, with Pd^{2+} being removed after cyclization by protonolysis. Retrosynthetic path “c” correspond to reaction between an electrophilic nitrogen species and an adjacent double bond. This pattern is realized synthetically by reductive conversion of *o*-nitrostyrenes to indoles.

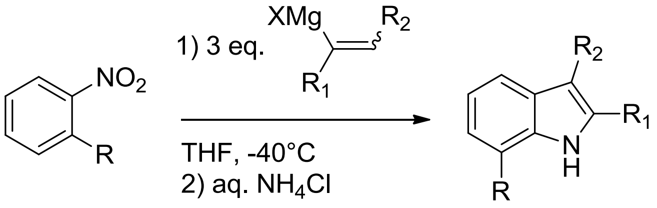


Scheme 1.19

1.3.1 Bartoli Indole Synthesis[38]

In 1989, G. Bartoli et al. described the reaction of substituted nitroarenes with excess of vinyl Grignard reagents at low temperature to afford substituted indoles upon aqueous work-up[39]. The authors found that the higher yields were obtained with *ortho*-substituted nitroarenes, so this reaction has become the simplest way to synthesize 7-substituted indoles.

Disconnection "c"



Scheme 1.20

The necessity of an *ortho*-substituent on the aromatic ring is the limit of the Bartoli indole synthesis, because *o-o'*-unsubstituted nitroarenes follow a completely different pathway when reacting with vinyl Grignard reagents. Bromine, however, should be a transient group, which can enforce the sigmatropic rearrangement, as requested by the mechanism, and is easily removed.

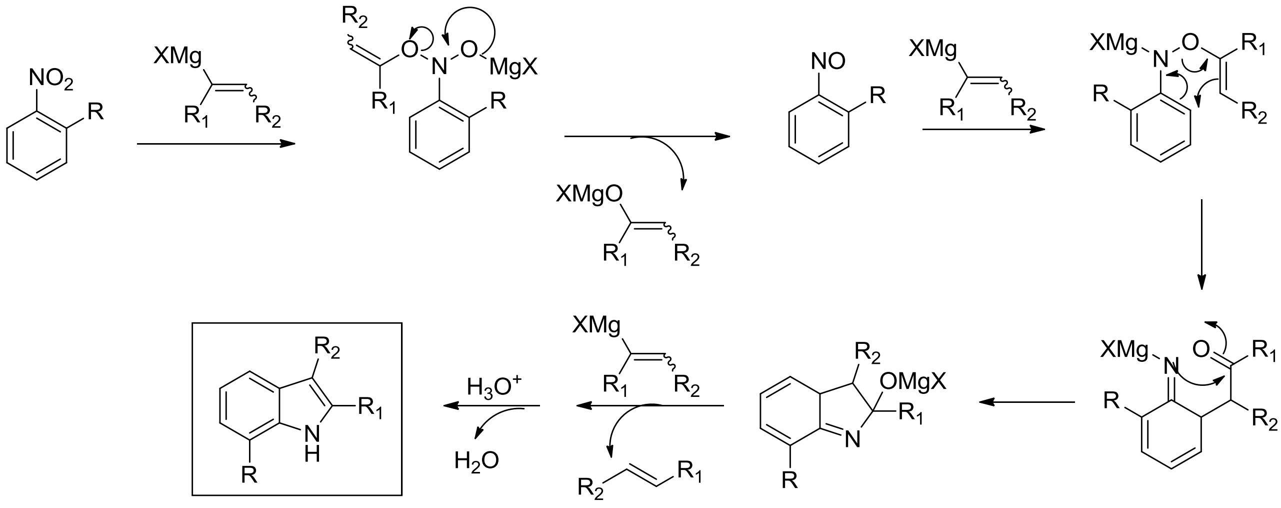
Dobbs proposed a modification of the Bartoli indole synthesis that allows to obtain 7-unsubstituted indoles[40].

Bartoli indole synthesis has been carried out on solid support by Knepper and Brase, this modification allows the suppression of the formation of azo- and azoxy-derivatives arising from the coupling of two nitrosoarene radical anions[41].

Recently, Ishikura and co-workers developed a one-pot methodology to synthesize 3,3'-bisindolylmethanes using the Bartoli indole synthesis[42].

1.3.1.1 Mechanism

The mechanism of the Bartoli indole synthesis is not clear in every detail, but Bartoli and co-workers successfully elucidated the main steps in the process. The first step is the addition of Grignard reagent to the oxygen atom of the nitro group followed by the rapid decomposition of the resulting *O*-alkenylated product to give a nitrosoarene. The nitrosoarene is much more reactive than the starting nitroarene, and it is attacked by the second equivalent of Grignard reagent to give an *O*-alkenyl hydroxylamine derivative, which rearranges in a [3,3]-sigmatropic process. The rearrangement product then undergoes intramolecular nucleophilic attack, and the proton in the ring junction is removed by the third equivalent of the Grignard reagent. Finally, acidic work-up affords the indole[43].

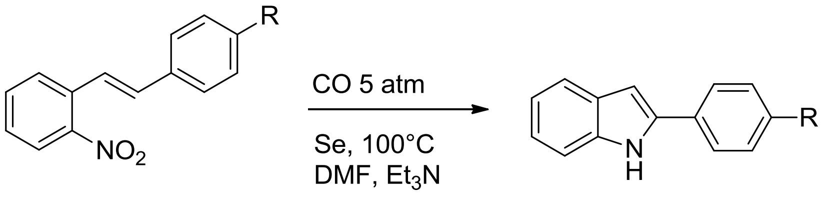


Scheme 1.21

1.3.2 Cadogan-Sundberg Indole Synthesis

This method involves the deoxygenation of *o*-nitrostyrenes or *o*-nitrostilbenes with triethyl phospite and cyclization of the resulting nitrene to form an indole[27]. The indole is almost always accompanied by substantial amounts of the corresponding *N*-ethoxyindole.

Sonoda et al.[44] disclosed that elemental selenium is an efficient catalyst for the carbonylation and the reduction of various organic compounds with carbon monoxide in the presence of a tertiary amine. In particular, it has been found that selenium catalyzed the reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide (Scheme 1.22). Both 2- and 3-substituted indoles can be synthesized in good yields from the corresponding *o*-nitrostyrenes , and indole itself is obtained in 55% yield.



Scheme 1.22

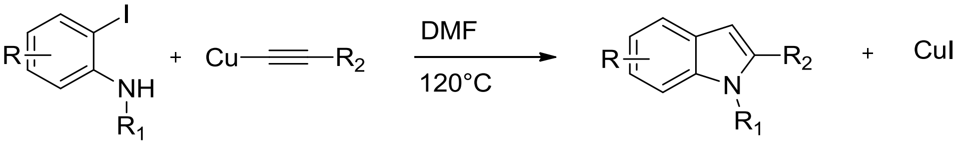
1.3.2.1 Mechanism

Sonoda and co-workers proposed that the reaction catalyzed from selenium, starts with the deoxygenation of 2-nitrostyrenes with SeCO prepared from elemental selenium and carbon monoxide to generate the corresponding short-lived nitrene or nitrenoid species. Intramolecular insertion of nitrene or nitrenoid species into the vinylic C-H bond at the *o*-position of the nitro group proceeds efficiently to produce indoles.

The mechanism concerning the original Cadogan-Sundberg reaction has been poorly understood. Recently, Peet and co-workers discovered , using an ^{18}O labeling experiment, that the oxygen atom in the *N*-ethoxyindole originates from the nitro group of the 2-nitrostilbene, and not from triethyl phospite[45].

1.3.3 Castro Indole Synthesis

Castro et al. were the first to discover the metal-catalyzed cyclization of *o*-alkynylanilines to indoles using copper[46].

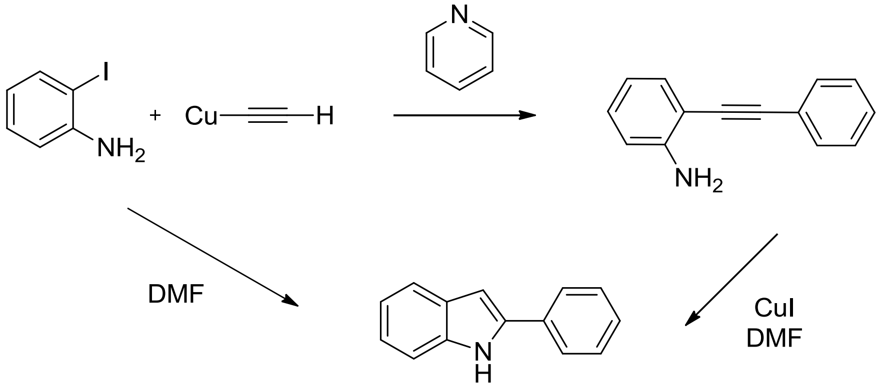


Scheme 1.23

In some cases the Castro cyclization of *o*-alkynylanilines succeeds where the Larock method of Pd-catalyzed coupling of *o*-iodoaniline with alkyne fails.

The course of the reaction is strongly influenced by the solvent. Thus, the acetylides are slightly soluble in dimethylformamide at room temperature, and the system remains visibly heterogeneous throughout. In this milieu the product is exclusively the indole. In contrast, the acetylides are soluble in warm pyridine, and in this solvent, depending upon the nature of the acetylide, the product composition varies from exclusively uncyclized acetylene to mixtures of the acetylene and indole with the latter in preponderance.

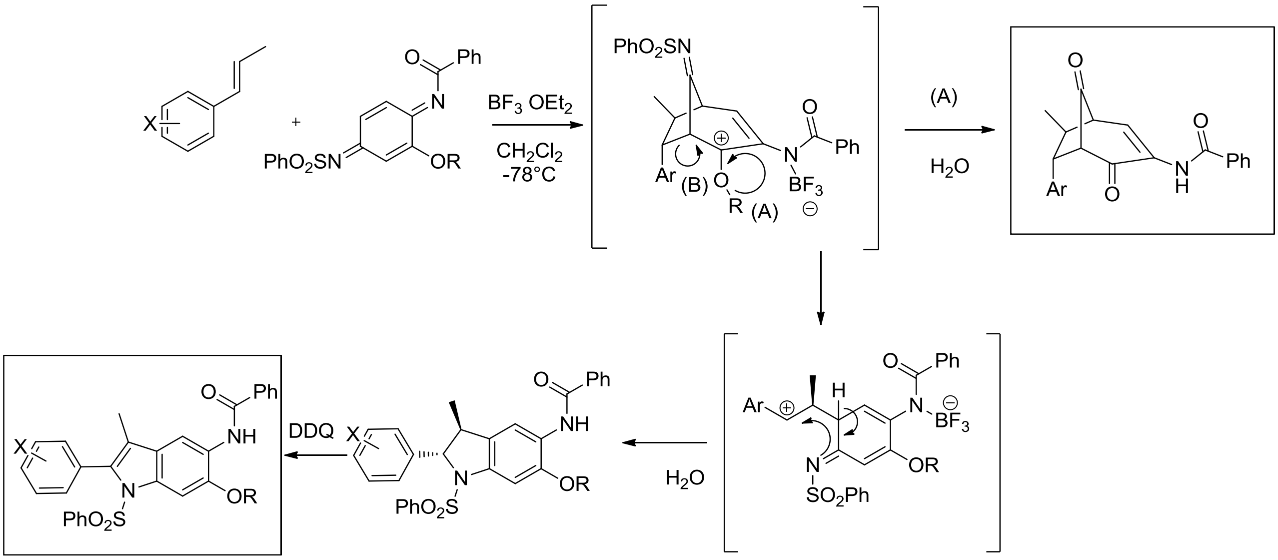
Together with the discussed copper acetylide coupling with *o*-iodoanilines, Castro's discoveries include the CuI-induced cyclization of *o*-alkynyl-anilines to yield indoles (Scheme 1.24).



Scheme 1.24

1.3.4 Engler Indole Synthesis

Engler indole synthesis is based on the Lewis acid-promoted reaction of 2-alkoxy-1-(*N*-benzoyl)-4-(*N*-benzenesulfonyl)-1,4-benzoquinone bisimines and β-methylstyrenes bearing alkoxy substituents (Scheme 1.25, path B); oxidation of the intermediate indolines with DDQ afforded indole derivatives in excellent yield. Starting with neural or electron deficient styrenes, 3-(*N*-benzoylamino)-6-aryl-7-methyl-4,8-dioxobicyclo[3.2.1]oct-2-enes are produced (Scheme 1.25, path A)[47].



Scheme 1.25

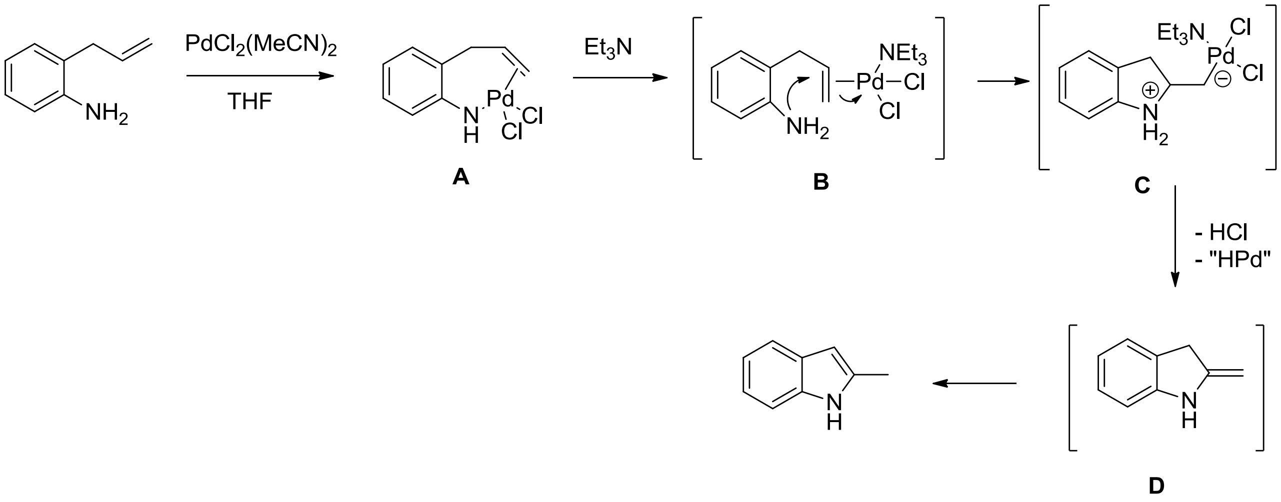
1.3.5 Hegedus Indole Synthesis

Disconnection "c"

After reporting the palladium-assisted amination of simple monoolefins by secondary amines to give tertiary amines, in 1976 Hegedus et al.[48] described an intramolecular version of the reaction in which *o*-allylanilines underwent palladium-assisted cyclization to 2-methylindoles.

1.3.5.1 Mechanism

The reaction of *o*-allylaniline with $PdCl_2$, generated *in situ* by $PdCl_2(MeCN)_2$, affords complex (**A**), which, upon addition of Et_3N, undergoes the displacement of the weakly basic aromatic amine to generate complex (**B**). Nucleophilic attack of the aromatic amine across the coordinated olefin results in the σ-alkylpalladium complex (**C**), which upon elimination of HCl and "HPd" gives compound (**D**). Spontaneous isomerization of the latter affords the observed 2-methylindole.



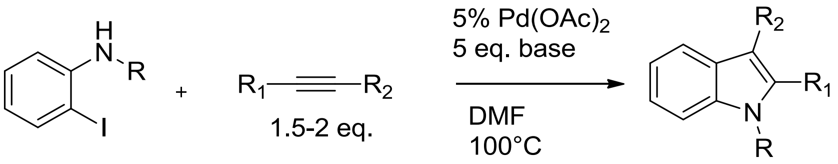
Scheme 1.26

1.3.5.2 Developments

While this chemistry provided a new simple synthesis of indoles under mild conditions, it suffered from requiring stoichiometric amounts of palladium dichloride. Improvements to this method were needed, and in a following report[49], Hegedus et al. described a catalytic version of the process using benzoquinone to reoxidize Pd(0) to Pd(II). In some cases, indoles were formed in higher yield under catalytic conditions than stoichiometric conditions. The source of Pd(II) used was $PdCl_2(MeCN)_2$, as in the stoichiometric process. Neither palladium acetate nor lithium chloropalladate were as effective.

1.3.6 Larock Indole Synthesis

In 1991, Larock reported the synthesis of indoles *via* the Pd-catalyzed coupling of 2-iodoanilines and disubstituted alkynes[50]. In the following years, the scope and limitation of the method were further explored by Larock and co-workers[51]. The one-pot Pd-catalyzed heteroannulation of *o*-iodoanilines and internal alkynes to give 2,3-disubstituted indoles is known as the Larock indole synthesis.



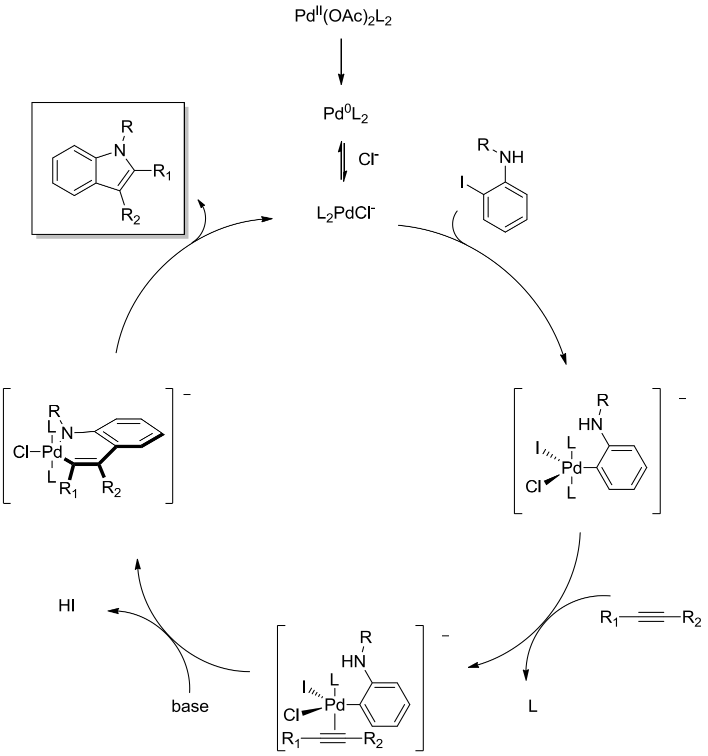
Scheme 1.27

Several factors have been discussed, which affect the reaction. The best condition for the Larock indole synthesis is to use 5 mol % $Pd(OAc)_2$ and either KOAc or K_2CO_3 as the base, with 1 eq. LiCl and 2–5 eq. alkynes. This reaction is very versatile, as indicated by its tolerance of diversified substituents on the alkynes and nitrogen atom of anilines and generally provides a means of preparing complex indole targets in a highly convergent manner. The heteroannulation reaction is regioselective and almost always gives 2,3-disubstituted indoles, where the more sterically hindered group of the alkyne occupies the 2-position of the indole ring. Moreover, the presence of alcohol groups in the alkyne seems to have a particularly strong directing effect, as a result of coordination of the alcohol to palladium during the insertion step.

1.3.6.1 Mechanism

This indole synthesis presumably proceeds via: (**1**) reduction of the $Pd(OAc)_2$ to Pd(0), (**2**) coordination of the chloride to form a chloride-ligated Pd(0) species, (**3**) oxidative addition of the aryl iodide to Pd(0), (**4**) coordination of the alkyne to the palladium atom of the resulting arylpalladium intermediate and subsequent regioselective *syn*-insertion into the arylpalladium bond, (**5**) nitrogen displacement of the halide in the resulting vinylic palladium intermediate to form a six-membered, heteroatom-containing palladacycle, and (**6**) reductive elimination to form the indole and regenerate Pd(0) (Scheme 1.28).

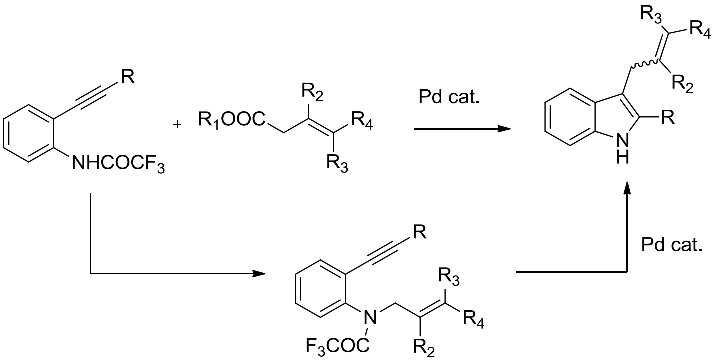
Disconnection “c”



Scheme 1.28

1.3.7 Cacchi Indole Synthesis

Intramolecular version of the Larock indole synthesis is generally known as the Cacchi indole synthesis (Scheme 1.29). Cacchi palladium-catalyzed hydroarylation/cyclization of alkynes bearing nucleophilic and electrophilic centers close to the carbon-carbon triple bond was proved to be a useful tool for the construction of heterocyclic rings[52].



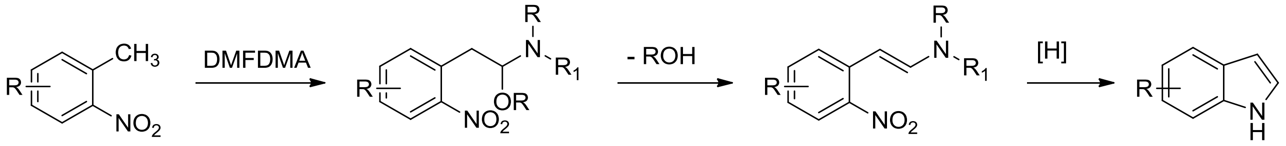
Scheme 1.29

Palladium-catalyzed cyclization of readily available *o*-alkynyltrifuoro-acetanilides with allyl esters provides a valuable route to 3-allyl-indoles[53]. To prove the process actually involves an intramolecular cyclization, the authors developed a stepwise method based on the isolation of the *N*-allyl derivative and its subsequent cyclization.

1.3.8 Leimgruber-Batcho Indole Synthesis

One of the most important and commonly used methods for the preparation of 2,3-unsubstituted indoles is the Leimgruber-Batcho indole synthesis. The reaction tolerates a large range of ring substituents and has been used extensively for the construction of both natural products and pharmaceutically important compounds.

The classical Leimgruber-Batcho indole synthesis involves the condensation of an appropriately substituted *o*-nitrotoluene with dimethylformamide dimethyl acetal (DMFDMA) to give intermediate β-(dimethylamino)-2-nitrostyrene (Scheme 1.30). The increased acidity of the methyl group of the *o*-nitrotoluene allows the simple preparation of this remarkably stable intermediate[54].



Scheme 1.30

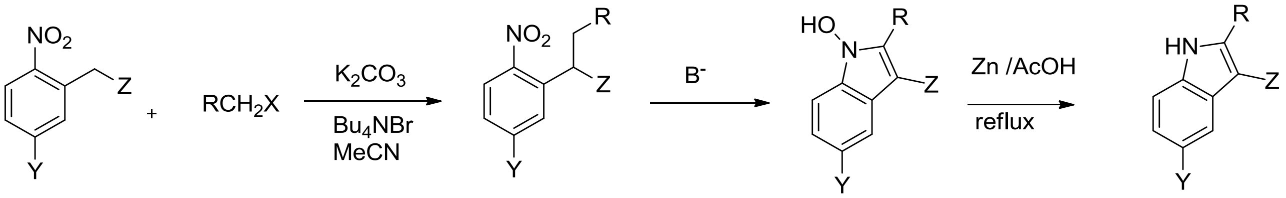
The second step of the synthesis involves reductive cyclization. This last step is usually done with hydrogen over a palladium catalyst or with Raney nickel and hydrazine. Not much is known about the exact sequence of the reduction, but it is possible to obtain *N*-hydroxyindoles by choice of an appropriate reagent. Zinc/NH_4Cl is the preferred reductant for this purpose. Use of $TiCl_3$ give a mixture of the indole and *N*-hydroxyindole. These results suggest that the cyclization can take place at the hydroxylamine reduction level.

In an improved procedure, the formation of nitrostyrene is conducted in the presence of an excess of pyrrolidine, which exchanges with the dimethylamino substituent.

1.3.9 Makosza Indole Synthesis

1.3.9.1 Synthesis of 1-hydroxyindoles and indoles from ortho-nitroarylethanes[55]

The essence of Makosza indole synthesis is a base-catalyzed cyclization of α,β-disubstituted *ortho*-nitroarylethanes to 2,3-disubstituted 1-hydroxyindoles. 1-Hydroxyindoles can be readily reduced to the corresponding indoles in good yields upon treatment with Zn dust in refluxing acetic acid.

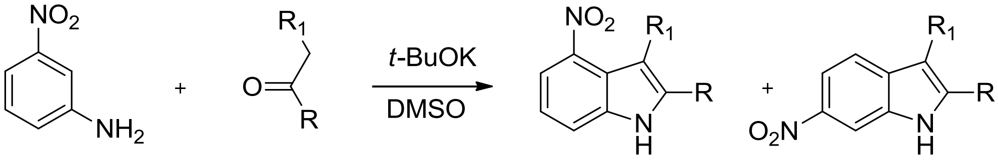


Scheme 1.31

The starting o-nitroarylmethyl derivatives were prepared from the corresponding nitroarenes *via* the VNS (Vicarious nucleophilic substitution) reaction. Alkylation of *o*-nitroarylmethyl derivatives was efficiently carried out in solid-liquid PTC system, and the intermediate specie can be transformed into the desired 2,3-disubstituted 1-hydroxyindoles under various basic conditions which should be properly chosen, depending on the acidity of the substrates. Nitriles undergo smooth cyclization with Et_3N / Me_3SiCl / DMF, methanolic NaOH or even methanolic triethylamine. For the cyclization of less acidic sulfones NaOH / DMSO is the system of choice. Sometimes, the cyclization into 1-hydroxyindole takes place directly during the alkylation of *o*-nitroarylmethyl.

1.3.9.2 One-pot synthesis of 4- and 6-nitroindole derivatives[56]

Base promoted condensation of ketones $RCOCH_2R'$ with 3-nitroaniline results in formation of the corresponding 4- and 6-nitro-2-R-3-R'-indoles. This multistep process apparently includes oxidative nucleophilic substitution of hydrogen in the aromatic ring of the aniline by the enolate anion and subsequent cyclization of the *ortho*-aminoketone intermediate to indoles *via* a Baeyer type reaction.



R = Ph, 2-pyridyl, Me, *t*-Bu, Et
R_1 = H, Me

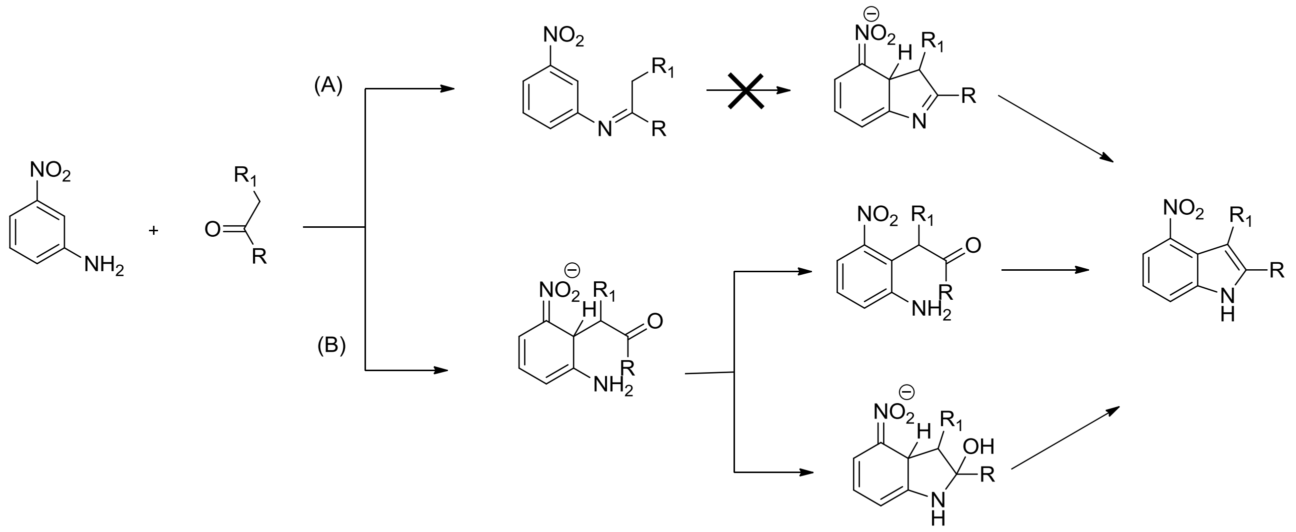
Scheme 1.32

The formation of indoles is a multistep process where one of the steps should be an oxidative nucleophilic substitution of hydrogen (ONSH) with an enolate anion. Two principal pathways appear to be feasible for this transformation:

(A) initial addition of the amino group to the carbonyl group of the ketone, resulting in the formation of an imine which, upon deprotonation, undergoes subsequent intramolecular ONSH to give indoles (Scheme 1.33, path A)

(B) addition of the enolate anion to the nitroaromatic ring resulting in ONSH followed by intramolecular condensation of the ketone so obtained with the *ortho*-amino group *via* a Baeyer type reaction (Scheme 1.33, path B).

Pathway (A) can be excluded because the imine, separately prepared from acetophenone and 3-nitroaniline, under the typical reaction conditions gave a complex mixture of products in which indoles were not detected by TLC. The reaction proceeding via path (B) requires that addition of the enolate anion to the nitroaniline ring takes place mainly in proximity of the amino group. It appears that the produced σ^H are oxidized by atmospheric oxygen.

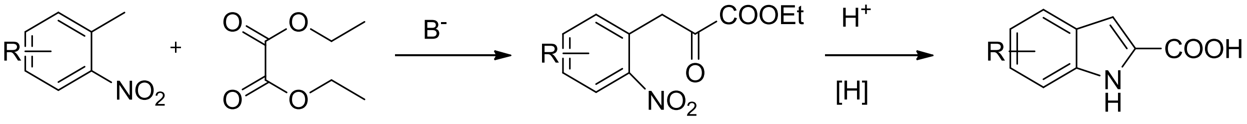


Scheme 1.33

1.3.10 Reissert Indole Synthesis[57]

The Reissert indole synthesis involves base-catalyzed condensation of an *o*-nitrotoluene derivative with an ethyl oxalate, which is followed by reductive cyclization to an indole-2-carboxylic acid derivative.

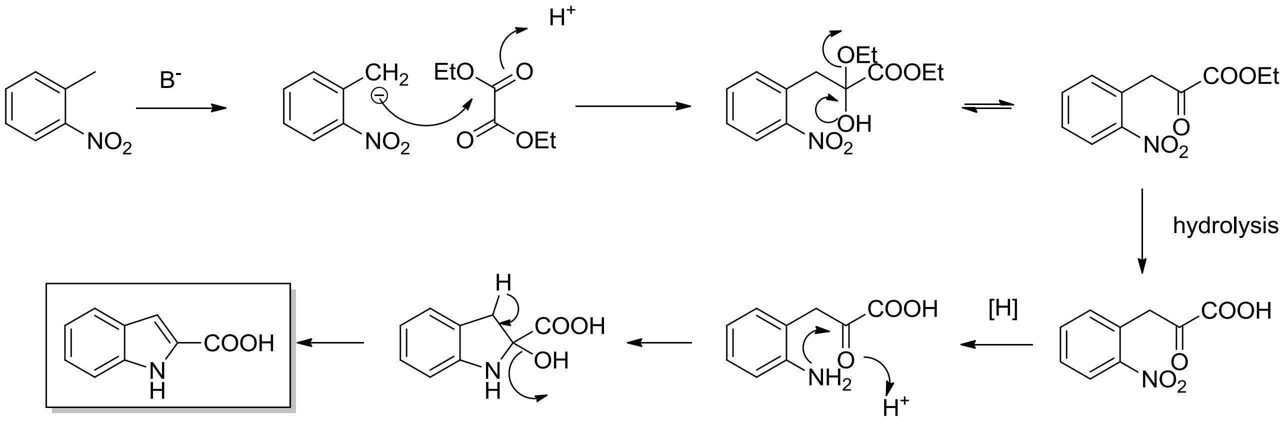
Disconnection "c"



Scheme 1.34

1.3.10.1 Mechanism

Under basic conditions, *o*-nitrotoluene undergoes condensation with ethyl oxlate to provide α-ketoester. After hydrolysis of the ester functional group, the nitro moiety is reduced to an amino fuction, which reacts with the carbonyl group to provide the cyclized intermediate which, by loss of water, aromatizes to the desired indol-2-carboxylic acid.



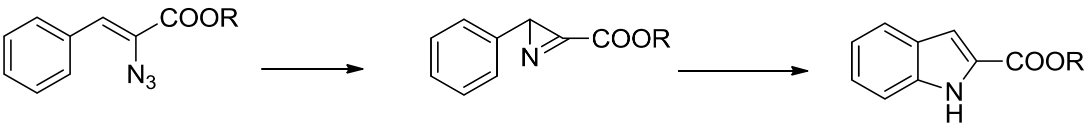
Scheme 1.35

1.4 *Disconnection "d"*

1.4.1 Hemetsberger Indole Synthesis[58]

The Hemetsberger indole synthesis involves the condensation of an aromatic aldehyde with an azidoacetate ester, followed by thermolysis of the resulting α-azidocinnamate. The conditions used for the base-catalyzed condensation are critical since the azidoacetate can decompose by elimination of nitrogen.

While the thermolysis might be viewed as a nitrene insertion reaction, it has been demonstrated that aziridine intermediates can be isolated at milder temperatures[59].

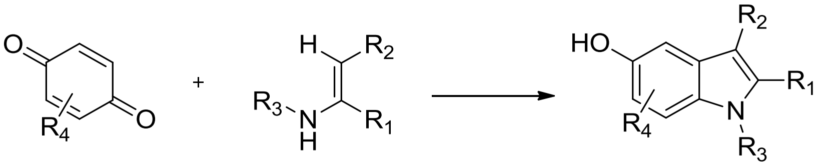


Scheme 1.36

The Hemetsberger protocol has been used to synthesize the ABC rings of nodulisporic acid[60], the thieno[3,2-*g*]indole and thieno[3,2-*e*]indole ring systems[61], and a precursor to CC-1065 and related antitumor alkaloids[62]. Molina *et al*. have described a variation of the Hemetsberger synthesis involving the thermolysis of 2-alkyl- and 2-arylamino-3-(2-azidoethyl)quinolines to give the corresponding pyrrolo[2,3-*b*]quinolines in 39–70% yield[63].

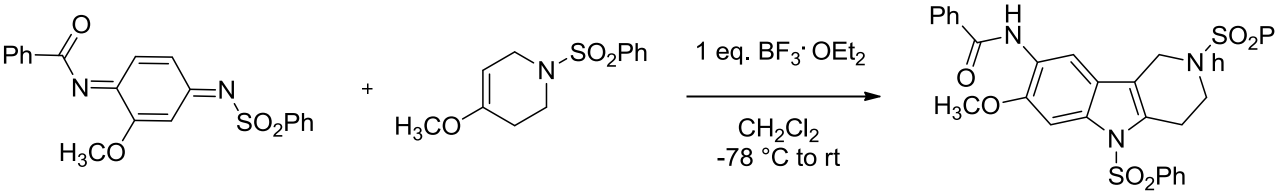
1.4.2 Nenitzescu Indole Synthesis[64]

The Nenitzescu indole synthesis is described as the condensation of 1,4-benzoquinones with 3-aminocrotonates and represents a highly regioselective method for the formation of 1,2,3-trisubstituted-5-hydroxyindoles[65].



Scheme 1.37

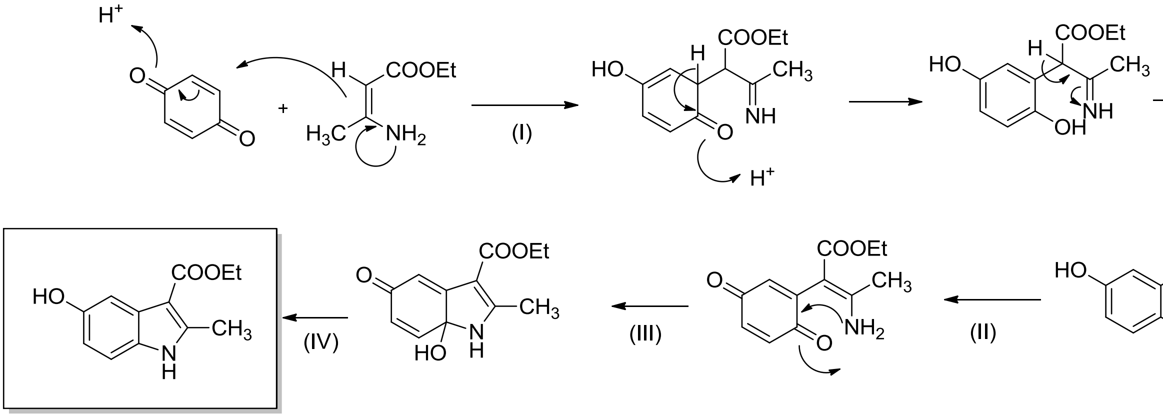
An interesting modification of the Nenitzescu indole synthesis, involving the Lewis acid-directed coupling of enol ethers with benzoquinone mono and bis-imides, was developed by T.A Engler *et al*. for the synthesis of substituted β- and γ-tetrahydrocarbolines (Scheme 38)[66].



Scheme 1.38

1.4.2.1 Mechanism

The mechanism of the Nenitzescu indole synthesis consists of four stages: (I) Michael addition of the terminal carbon of the enamine to quinone; (II) oxidation of the resulting hydroquinone to the quinone; (III) cyclization of the quinone to the carbinolamine and (IV) reduction of the latter to 5-hydroxyindole by the initial hydroquinone adduct. (Scheme 1.39 represents the mechanism for 1,4-benzoquinone and ethyl 3-aminocrotonate).



Scheme 1.39

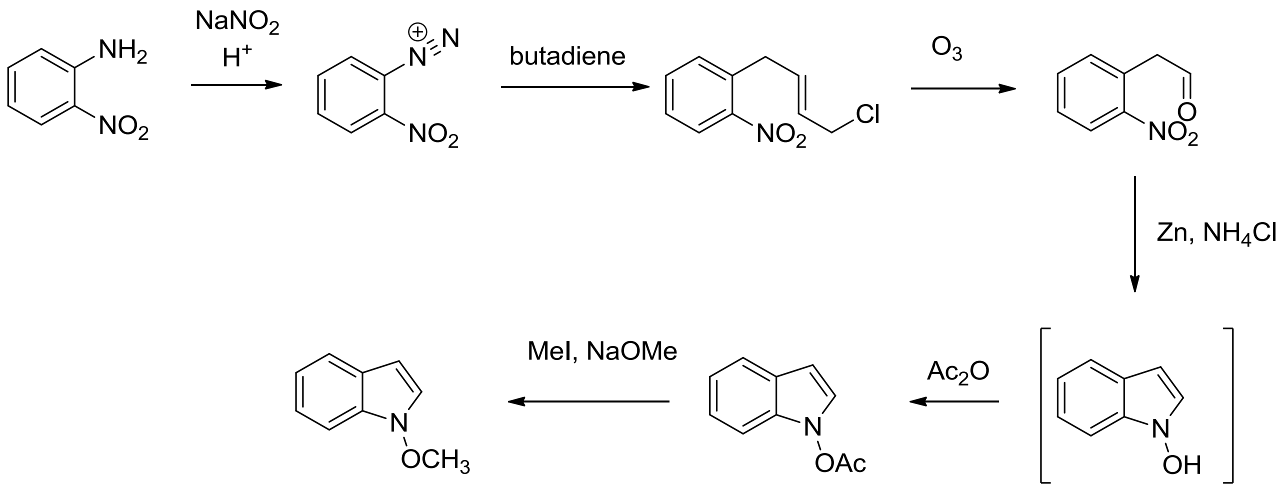
1.5 *Syntheses of N-hydroxy indoles*

Discovering of *N*-hydoxyindole framework in numerous natural products spurred on the development of the synthetic methods leading to this substrate and prompted the study on this rather unknown part of the indole chemistry[67].

The first synthesis of *N*-hydroxyindoles was described by Mousseron-canet and Boca in 1967[68]; however the harsh conditions and irreproducibility of this method rendered it unreliable.

1.5.1 Acheson Synthesis

The first successful synthetic studies on *N*-hydroxyindoles had been reported by Acheson and co-workers in 1974[69] using *o*-nitroaniline as starting materials.



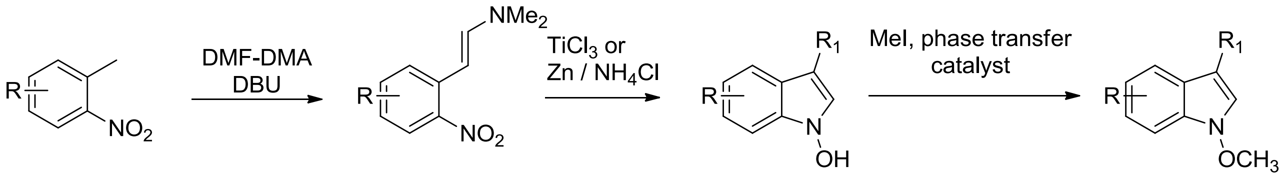
Scheme 1.40

They succeed in the first preparation of *N*-hydroxy-, *N*-acethoxy- and *N*-methoxyindoles, using coupling of diazonium salts with butadiene as a key reaction. With *N*-acetoxyindole in hand, the authors produced some *N*-hydroxyindoles derivatives, stabilized with an electron-withdrawing group at the position 3.

Although Acheson's method is not applicable as a general procedure for the synthesis of *N*-hydroxyindoles, these initial results concerning the general physical properties of those substrates and their unstable nature were really important for the following methods that have been developed.

1.5.2 Somei Syntheses

In 1981, Somei and co-workers reported a second method[70], reacting 2-nitrotoluene with *N,N*-dimethylformamide dimethylacetal (DMF-DMA), followed by reduction on the intermediate nitroenamine with either titanium chloride or zinc and ammonium chloride. Employing the procedure, *N*-hydroxy- and *N*-methoxyindoles were obtained.



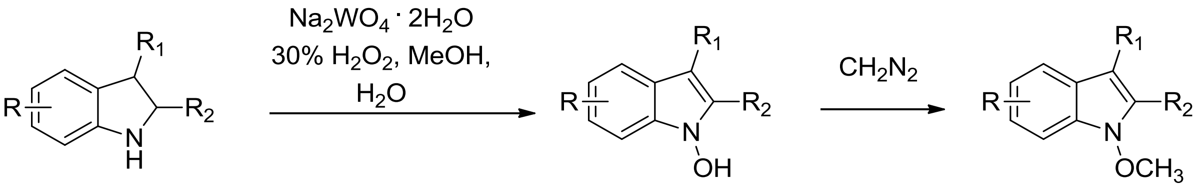
Scheme 1.41

Entry	**R**	**Yield of *N*-hydroxyindole**	**Yield of *N*-methoxyindole**

a	4-NO_2	57 %	97 %
b	4-OCH_2Ph	unstable oil	77 %
c	4-COOMe	65 %, unstable oil	78 %
d	4-NH_2	unstable oil	91 %, unstable oil
e	5-COOMe	26 %	59 %
f	6-CHO	29 %, unstable oil	36 %

Table 1.1 – Examples of *N*-hydroxy- and *N*-methoxyindoles synthesized by Somei[70c]

With the aim to obtain *N*-hydroxyindoles, Somei and co-workers studied the direct oxidation of indoles with various reagents. They succeeded in 1989 in creating a simple and general method for 3-substituted *N*-hydroxyindoles, which involved the oxidation of 2,3-dihydroindoles in methanol-water with 30% acqueous hydrogen peroxide in the presence of a catalytic amount of sodium tungstate dihydrate[71].



Scheme 1.42

The tungstate method employs mild oxidation conditions that could be utilized on a variety of indoline substrates in which the conversion to the *N*-hydroxyindole counterpart is desired.

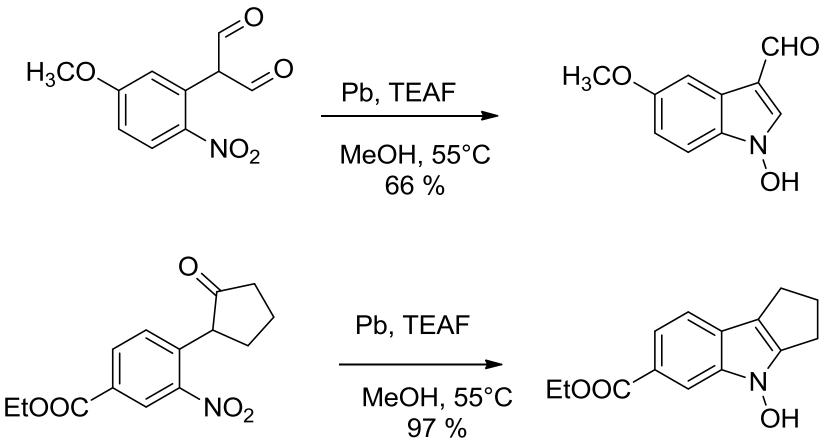
Entry	R	R_1	R_2	Yield of *N*-hydroxyindole	Yield of *N*-methoxyindole
a	H	Me	H	37 %, unstable oil	50 %
b	H	H	Ph	56 %	86 %
c	5-Br	H	H	unstable oil	60 %
d	6-Br	H	H	unstable oil	83 %
e	5,7-diBr	H	H	unstable oil	17 %
f	7-I	H	H	unstable oil	26 %
g	5-OMe	CH_2CH_2NHAc	H	58 %	75 %

Table 1.2 – Examples of *N*-hydroxy- and *N*-methoxyindoles synthesized with the "tungstate method"[71]

In the aftermath of these foundamental techniques for *N*-hydroxyindole formation, a variety of further synthetic methods have been developed with more or less success. More recently, Wong[72] and Nicolaou[73] have reported general syntheses which provide facile and efficient access to a number of substituted *N*-hydroxyindoles.

1.5.3 Wong Synthesis

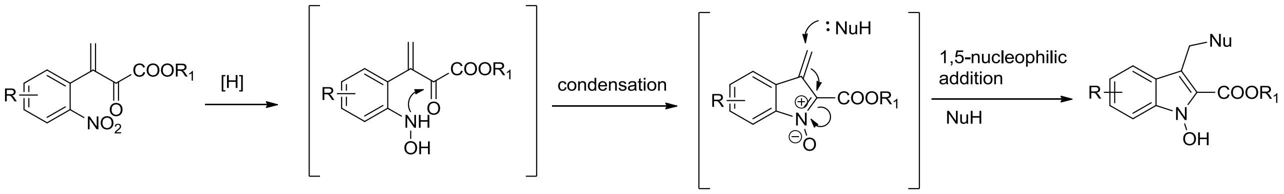
The method introduced by Wong in 2003 utilizes a Pb/triethylammonium formate (TEAF) promoted reductive cyclization of *o*-nitrobenzyl ketones and aldehydes in MeOH to produce substituted *N*-hydroxyindoles in good to excellent yields[72]. These reaction conditions are mild enough to tolerate a wide range of functional groups and avoid further reduction to the indole, a problem that often accompanies the reductive conditions required to generate the postulated reactive hydroxylamine intermediate. It should be noted that the authors report all products to be stable crystalline solids after filtration through a silica gel plug even in the absence of stabilizing electron-withdrawing groups.



Scheme 1.43 - Representive examples of Wong's *N*-hydroxyindole synthesis

1.5.4 Nicolaou Synthesis

In 2005, Nicolaou[73] devised a synthetic procedure which started with the selective reduction of generalized nitro ketoester using $SnCl_2 \cdot 2H_2O$ to hydroxylamine. This was followed by intramolecular condensation into the neighboring ketone to generate the nitrone species which could then be engaged in a 1,5-addition by various nucleophiles to form the desired substituted *N*-hydroxyindoles.

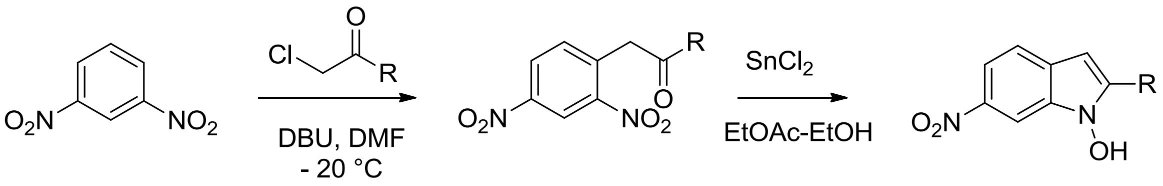


Scheme 1.44

Both Nicolaou's and Wong's methods possess the ability to generate a diverse library of compounds from starting material that can be rapidly accessed *via* standard chemistry.

1.5.5 Wojciechowski Synthesis

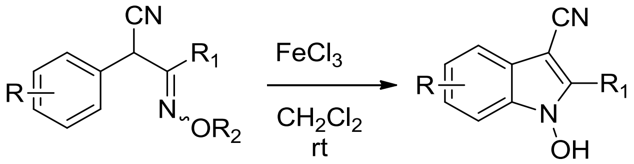
Wojciechowski and co-workers[67]have recently developed a simple methodology for the synthesis of nitroderivatives of *N*-hydroxyindoles from dinitrobenzyl ketones easily available *via* vicarious nucleophilic substitution of hydrogen in 1,3-dinitrobenzene (Scheme 45) or *via* acylation of 2,4- and 2-6-dinitrotoluenes.



Scheme 1.45 - *N*-hydroxyindoles *via* VNS of hydrogen in 1,3-nitrobenzene

1.5.6 Zhao Synthesis of N-alkoxyindoles

N-alkoxyindoles are interesting compounds for their biological activity. A new method for their synthesis was provided by Zhao and co-workers[74]. This group reported the preparation of N-alkoxyindole-3-carbonitrile derivatives under mild conditions by a $FeCl_3$-mediated intramolecular heterocyclization. This process shows a wide functional group tolerance both for electron-withdrawing and electon-donating aromatic substituents. Meta-substituents have the possibility to produce two regioisomeric products. The cyano group has a potential implication in further functionalizations due to a broad versatility.



Scheme 1.46

Zhao and co-workers reported more recently a novel synthesis of 3-indolecarbonitriles, by a Ph(IOAc)$_2$-mediated oxidative carbon-carbon bond formation on *N*-arylenamines[75]. This new method is particularly relevant for the use of environmental friendly conditions via transition-metal free procedure.

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CHAPTER 2 – RESULTS AND DISCUSSION

2 Background : nitroso compounds and alkynes as starting materials

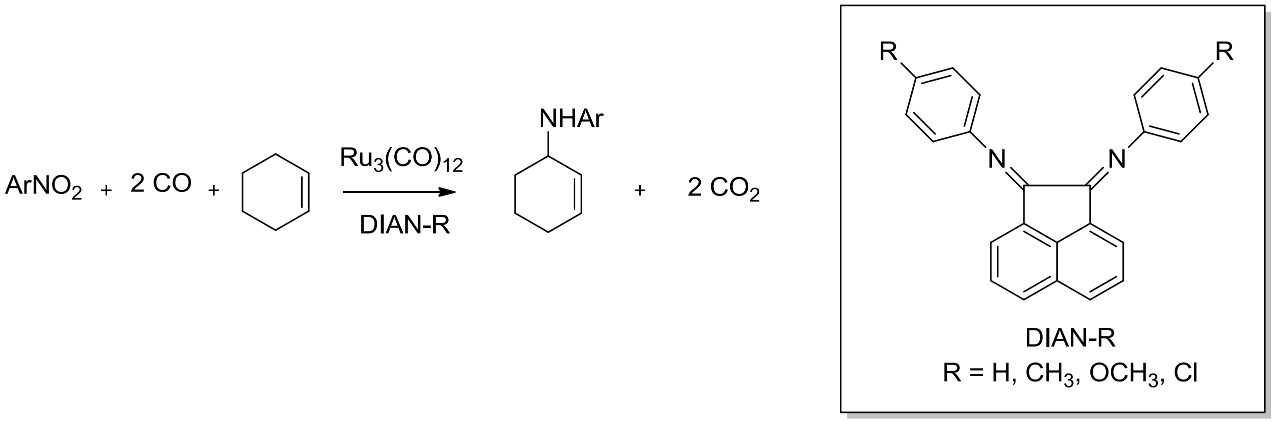
Since Baeyer's first preparation of nitrosobenzene at the end of nineteenth century[1], the nitroso function has been wildely recognized as a useful source to serve nitrogen- and oxygen-containing molecules[2]. The nitroso electrophile appears to be really reactive thanks to the polarization of the nitrogen–oxygen bond and specific structure by the equilibration between monomer and azodioxy dimer. This results in high chemo- and regioselectivity for a lot of transformations using nitroso derivatives, making the control of this equilibrium an essential prerequisite for using nitroso compounds in synthesis reactions. On the other hand, this unique equilibrium could cause various issues in developing selective methodologies[3].

Alkynes are present as active reagents in a large variety of organic reactions. In the last decades they seemed to be really useful starting materials also in the indole synthesis[4].

The first chemist who deeply studied the reactivity between nitrosoarenes and alkynes was Luigi Alessandri (1885-1929). His work was published in the period 1921-1928, completely focused on the reactions between nitrosoarenes and internal or terminal alkynes[5], he reported an alternative path to synthesize nitrones, that were previously obtained only by the reaction of carbonyl compounds and arylhydroxylamines[6].

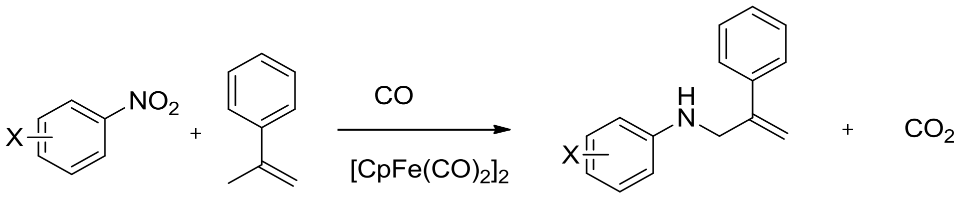
2.1 *From nitro- to nitrosoaromatics*

The carbonylative reduction of nitroarenes in CO atmosphere has been deeply studied and it allowed synthetic chemists to afford many heterocyclic molecules[7]. Cenini and co-workers reported the allylic amination of alkenes by reductive carbonylation of nitroarenes in CO atmosphere catalyzed by Ru[8]complexes (Scheme 2.1).



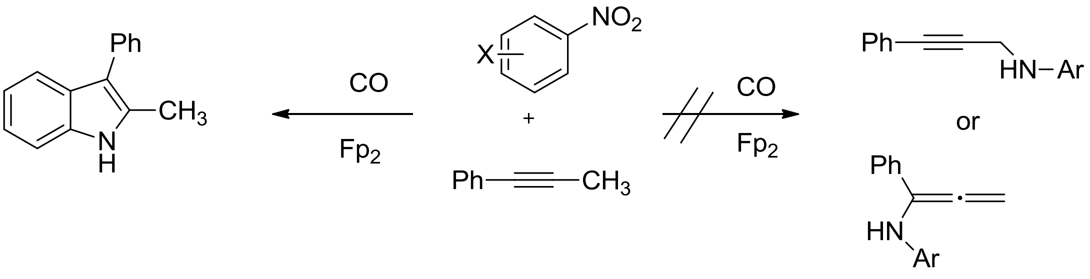
Scheme 2.1

The ability of metal complexes to induce C-N bond formation by the reduction of nitroaromatic compounds with carbon monoxide and the continuing aim to develop direct nitrogenation reactions of hydrocarbons led Nicholas group to study and develop a novel and regioselective, iron-catalyzed synthesis of allylamines by the reductive amination of olefins with nitroaromatics[9].



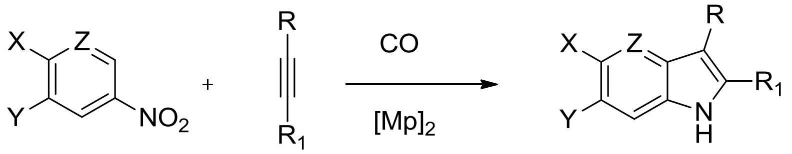
Scheme 2.2

Trying to produce propargyl amines and/or allenyl amines, the corresponding reactions of nitroaromatics and alkynes under a CO atmosphere were investigated. First explorative experiment was carried out using nitrobenzene and 1-phenyl-1-propyne, achieving 2-methyl-3-phenyl indole as the major product. The process was also regioselective for 3-substituted indoles when unsymmetrical alkynes with conjugating substituents were used (Scheme 2.3)[10].



Scheme 2.3

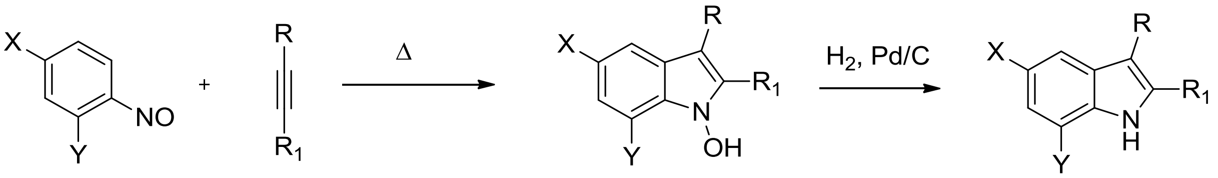
Both Fe- and Ru-cyclopentadienyl derivatives proved to be effective catalysts for the production of 3-phenylindole. Although electron–deficient nitroarenes react more rapidily, both electron-rich and –deficient substrates gave comparable yields of indoles in their reactions with phenylacetylene.



$[Mp]_2 = [(\eta^5\text{–Cp})Fe(CO)_2]_2$, $[(\eta^5\text{–}C_5Me_5)Fe(CO)_2]_2$, $[(\eta^5\text{–}C_5Me_5)Ru(CO)_2]_2$

Scheme 2.4

Given the precedented, metal-promoted deoxygenation of nitro compounds by carbon monoxide[11], it seemed likely that nitrosoarenes, either free or complexed, could be intermediates in the catalytic reductive annulations of nitroarenes to indoles. Reactions between nitrosoarenes and alkynes were examinated under the above conditions, and an uncatalyzed version of the process was also reported[12].

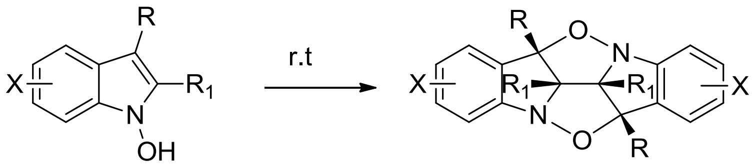


Scheme 2.5

In contrast to the reaction with nitroaromatics, the major products of this annulation process were *N*-hydroxyindoles, produced regioselectively, under mild conditions, with functional group tolerance and with an excellent atom economy. *N*-hydroxyindoles are then efficiently converted to indoles by catalytic reduction.

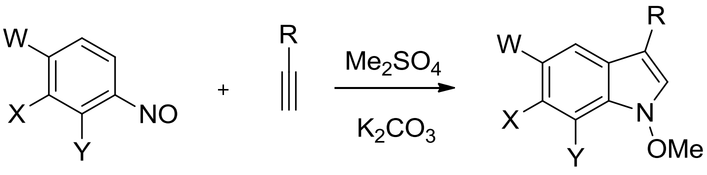
The effective formation of *N*-hydroxyindoles was verified by comparison of the cycloaddition products with authentic samples of *N*-hydroxyindoles prepared by oxidation of the corresponding indolines with the urea/H_2O_2 complex in the presence of $Na_2WO_4 \cdot xH_2O$.

The stability of *N*-hydroxyindoles has been discussed in many reports and was a focus of debate[13]. Some *N*-hydroxyindoles are elusive and easily convert to dehydrodimerization products, known as 1,10-diaza-9,20-dioxakabutane (Scheme 2.6) named after an ancient helmet of the Japanese Army[13a,14]. The first isolation and characterization of this class of compounds was performed by Tedder in the sixties[15] and later confirmed by X-ray diffraction[16].



Scheme 2.6

The labile nature of *N*-hydroxyindoles led to the introduction of some techniques to produce the more stable *N*-methoxy- and *N*-alkoxyindoles. The efficiency of the ArNO/alkyne cycloaddition can be improved significantly by alkylative trapping of the *N*-hydroxyindoles with K_2CO_3-Me_2SO_4 isolating *N*-methoxyindoles as the major products[17].



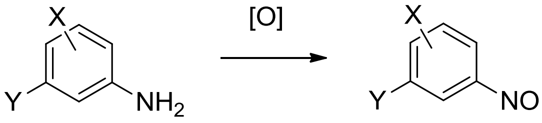
Scheme 2.7

2.2 *Synthesis of 3-arylindoles*

In the aim to study the general application of the synthetic protocol for the preparation of *N-O*-protected hydroxyindoles, a variety of arylalkynes were tested in a wide survey with both electron-rich and electron-deficient nitrosoaromatics.

2.2.1 Synthesis of nitrosoarenes

Nitrosoaromatics (**18a-f**), with a few exceptions, are not commercially available, but are generally synthesized starting from the respective anilines (**17a-f**).



(17a-f) **(18a-f)**

Scheme 2.8 – Synthesis of nitrosoaromatics starting from the corresponding anilines

Nitrosobenzene (X and Y = H, **18g**) is the only purchased substrate. 4-nitro-nitrosobenzene (**18a**) and 4-nitrosobenzoic acid (**18b**) were obtained by oxidation with Oxone® of the corresponding anilines. Dimethyl 2-nitrosoterephthalate (**18f**), 2-nitro- (**18d**), 2-carbomethoxy- (**18e**) and 4-cyano-nitrosobenzene (**18c**) were synthesized using $Na_2WO_4 \cdot 2H_2O$ as oxidant, with or without phase transfer catalysis, depending on the functional group[18].

Entry	X	Y	Reactant	Product	Reaction Conditions	Yield (%)
1	4-NO_2	H	**17a**	**18a**	Oxone®, H_2O, 0°C to rt, 48 h	quant.

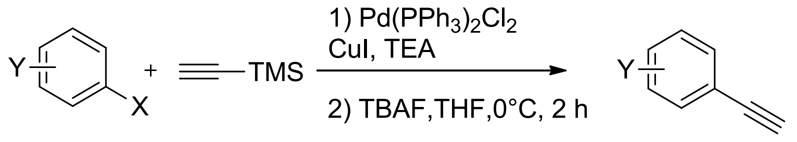
2	4-COOH	H	**17b**	**18b**	Oxone®, CH_2Cl_2, rt, 1 h	quant.
3	4-CN	H	**17c**	**18c**	Na_2WO_4•$2H_2O$, H_3PO_4 85% , H_2O_2 30% , TBAB, CH_2Cl_2-n-pentane (1:1), 40°C, 2.5 h	65
4	2-NO_2	H	**17d**	**18d**	Na_2WO_4•$2H_2O$, H_3PO_4 85% , H_2O_2 30% , TBAB, EtOH, 60°C, 4 h	70
5	2-CO_2CH_3	H	**17e**	**18e**	Na_2WO_4•$2H_2O$, H_3PO_4 85% , H_2O_2 30% , TBAB, EtOH, 60°C, 2 h	92
6	2-CO_2CH_3	CO_2CH_3	**17f**	**18f**	Na_2WO_4•$2H_2O$, H_3PO_4 85% , H_2O_2 30% , TBAB, EtOH, 60°C, 2 h	79

Table 2.1 – Synthesis of nitrosoaromatic from anilines

Aniline (**17f**) was synthesized from aminoterephthalic acid by esterification with methanol in the presence of H_2SO_4 (96%).

2.2.2 Synthesis of arylalkynes

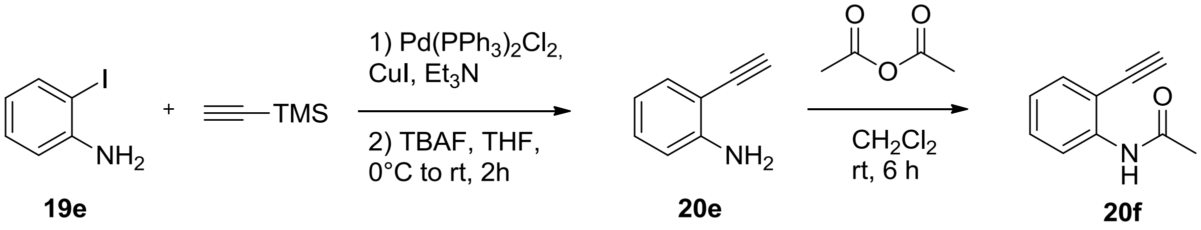
1-Chloro-4-ethynylbenzene[19] (**20a**), 1-ethynyl-4-nitrobenzene[20] (**20b**), 4-ethynyl-1-methoxybenzene[21] (**20c**), and 4-ethynylbenzonitrile[22] (**20d**) were prepared by Sonogashira-type reaction starting from the corresponding commercially available substituted haloarene (bromo- or iodoarene).



(19a-e) **(20a-e)**

Scheme 2.9 – Synthesis of arylalkynes by Sonogashira-type reaction

N-(2-ethynylphenyl)acetamide[23] (**20f**) was synthesized in two steps from 2-iodo-aniline; the first step is the Sonogashira reaction to obtain 2-ethynylaniline (**20d**), which was then acylated with acetic anhydride (Scheme 2.10). Phenylacetylene (**20g**) is the only purchased arylalkyne.



Scheme 2.10

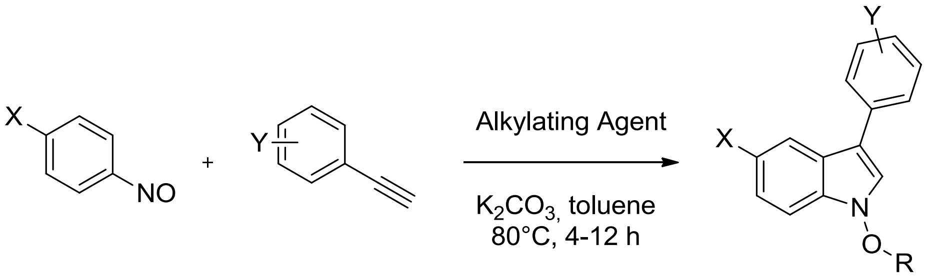
Entry	X	Y	Reactant	Product	Yield (%)
1	I	4-Cl	**19a**	**20a**	69
2	I	4-NO_2	**19b**	**20b**	95
3	I	4-OMe	**19c**	**20c**	70
4	Br	4-CN	**19d**	**20d**	95
6	I	2-NHCOMe	**19e**	**20f**	81

Table 2.2 – Synthesis of arylalkynes

2.2.3 Synthesis of 3-arylindoles under alkylating conditions

In order to avoid the formation of kabutanes as byproducts, alkylating conditions were applied, using K_2CO_3 and differerent protective groups. Generally, nitrosoarenes with EWG substituents react faster than electron-rich nitrosoaromatics and show better yields and regioselectivities. Nitrosoarenes were used as the limiting reagents and the reactions have being carried out with a large excess of the alkyne (from 12- to 15-fold) and the base and the alkylating/acylating agent in a 6-fold excess. Conjugated alkynes were found to be the privileged partners for the cyclization and reactions carried out with unconjugated alkynes and symmetrical internal alkynes (diphenylacetylene, bis-trimethylsilylacetylene and 4-octyne) gave poor yields or no reactions at all.

Terminal alkynes show better yields and all the reactions show exclusively the formation of 3-substituted indoles.



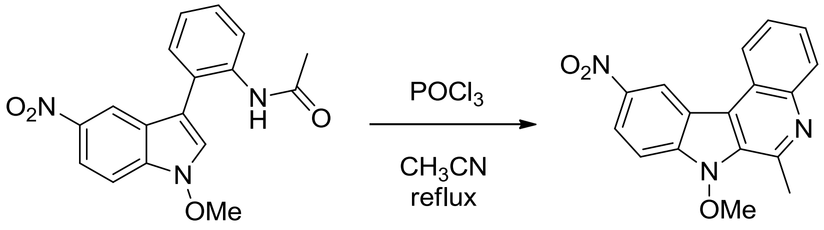
18 (a,c,d) **20 (a,c,d,g)** **21 (a-i)**

Scheme 2.11

Entry	Product	X	Y	R	Alkylating Agent	Yield (%)
1	**21a**	H	4-Cl	Me	Me_2SO_4	29
2	**21b**	H	4-OMe	Me	Me_2SO_4	46
3	**21c**	H	4-CN	Me	Me_2SO_4	39
4	**21d**	NO_2	2-NHCOMe	Me	Me_2SO_4	37
5	**21e**	NO_2	H	Ts	TsCl	32
6	**21f**	NO_2	H	Boc	Boc_2O	65
7	**21g**	NO_2	H	$PhCH_2$	$PhCH_2Br$	77
8	**21h**	NO_2	H	Cbz	CbzCl	53
9	**21i**	CN	H	PhCO	PhCOCl	38

Table 2.3 – 3-arylindoles under alkylating conditions

21d was further functionalized to *N*-methoxy-β-carboline (**22**). The compound was prepared through a Bischler-Napieralski type reaction, compound **21d** was treated with $POCl_3$ and afforded the β-carboline derivative in 91% yield (Scheme 2.12).

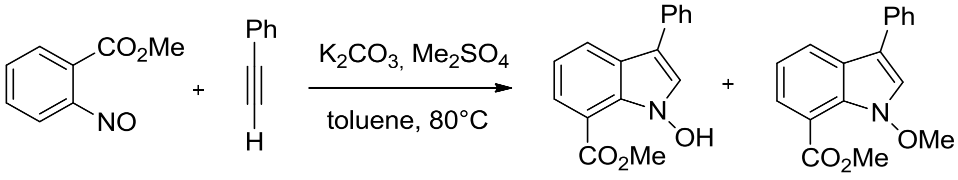


21d **22**

Scheme 2.12

2.2.4 Synthesis of polycyclic compounds

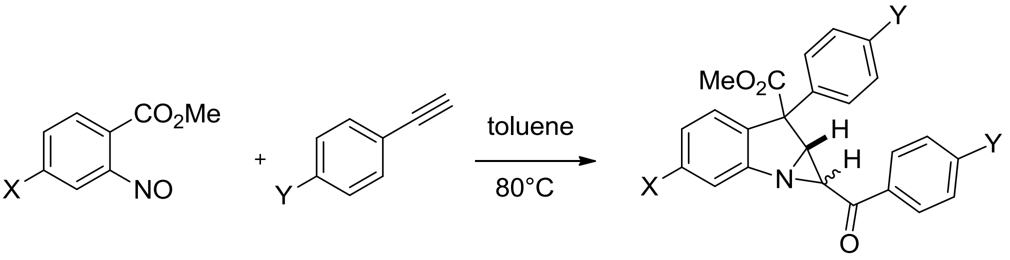
Working with phenylacetylene (**20g**) and *o*-carbomethoxy nitrosobenzene (**18e**), we had the serendipitous formation of a tricyclic byproduct, that allowed us to better understand the mechanism of the cycloaddition reaction. This compound was isolated as the major product and characterized by X-ray diffraction[12]. The reaction was first carried out under stardard alkylating conditions and afforded the *N*-hydroxyindole (**22a**) in 64% yield with only traces of the corresponding *N*-methoxyindole (**22b**) (Sheme 2.13).



18e **20g** **23a** **23b**

Scheme 2.13

The alkylation might be inhibited by the presence of a hydrogen bond between the N-OH group and the carbonyl of the ester group at position 7. The experiment was repeated under non-alkylating conditions and compound **24** resulted the major isolated product (57%) (Scheme 2.14).



18 (e-f) **20 (a-d, g)** **24 (a-f)**

Scheme 2.14

Entry	Product	X	Y	Yield (%)
1	**24a**	H	OMe	64
2	**24b**	H	CN	48
3	**24c**	H	Cl	56
4	**24d+24e**	CO_2Me	H	52 (59/41 *cis/trans*)
5	**24f**	CO_2Me	NO_2	44

Table 2.4

In literature, analogues structures of **24** have been obtained from the reactions of indoline nitrones with alkynes, which proceed via dipolar cycloaddition followed by electrocyclic rearrangement of the intermediate isoxazole[24].

The formation of **24** from the reaction between *o*-carbomethoxy nitrosobenzene and arylacetylenes suggests the intermediacy of an indoline nitrone, trapped by a second molecule of arylacetylene to generate an oxazoline that subsequently rearranges to afford acylaziridine indolines (Scheme 2.15)[25]. This species, in turn, may be derived from migratory rearrangement of a non-aromatic precursor, such as diradical **A** or nitrone **E**. Working with a dicarbomethoxy substituted nitrosoarene it was possible to isolate both the diasteroisomers embodying aziridineindoline ring. These diasteroisomers were characterized and distinguished by coupling costants of the protons on the aziridine ring in ^{1}H NMR (^{3}J*cis* = 7.0 Hz and ^{3}J*trans* = 5.2 Hz). One of these two diasteroismers, **24d**, was characterized by X-ray diffraction and the structure is shown in Figure 2.1.

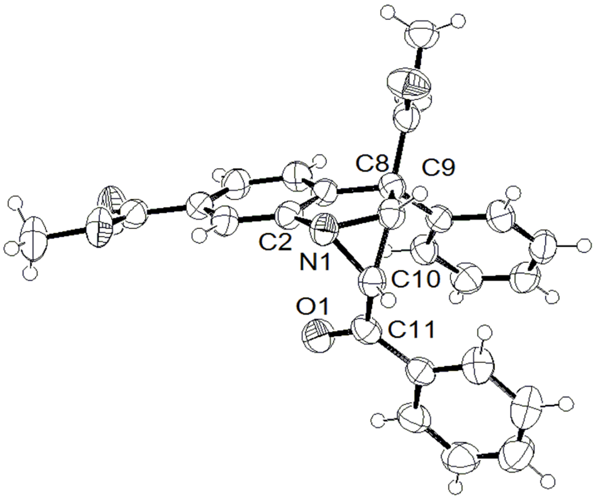
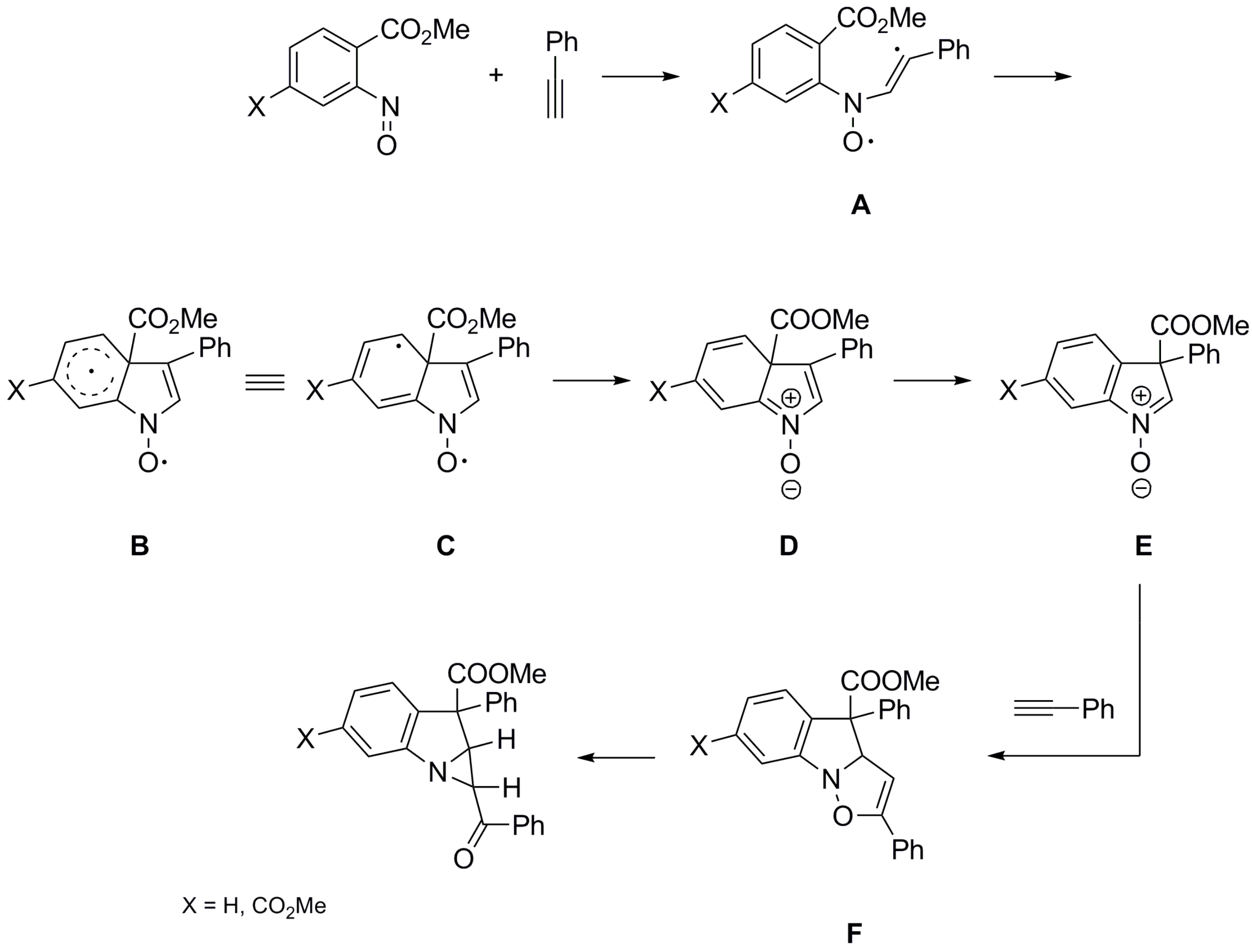


Figure 2.1 – ORTEP drawing of 24d, with partial labeling scheme. Thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms were giver arbitrary radii. Selected bond distances (Å) and angles (°): N1-C2 1.439(2), N1-C9 1.491(2), N1-C10 1.491(2), C8-C9 1.537(3), C10-C11 1.506(3), C11-O1 1.211(2), C2-N1-C9 103.8(2), C2-M1-C10 113.8(2), C9-N1-C10 59.8(1).



Scheme 2.15 – Proposed mechanism

2.3 *Synthesis of 3-aroylindoles*

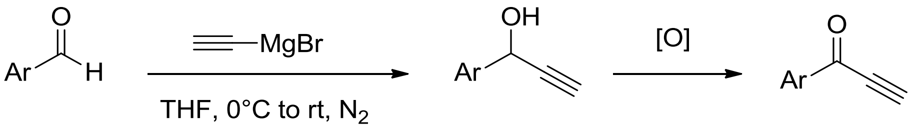
To extend the applications of the nitroso-alkyne cycloaddition we focused on the preparation of 3-aroylindoles. The synthetic path involves the synthesis of aroyl-alkynes as reaction partners of nitrosoarenes. A general drawback for our previous annulation reactions between nitrosoarenes and alkynes was the large excess of alkynes (10-15 fold). Envisioning an unstability of the *N*-hydroxyindoles, our first nitroso-alkyne cycloaddition reaction between 4-nitro-nitrosobenzene (**18a**) and 1-phenyl-prop-2-yn-1-one (**26a**) were run under alkylating conditions, but this strategy was not fruitful and led us to isolate the corresponding *N*-alkoxy-3-aroylindole only in traces. We then determined whether such a large excess of alkyne was strictly necessary to get efficient conversion of nitrosoarenes to target indoles avoiding the degradation to azoxy-derivatives, generally the most relevant side products observed in these reactions. In an attempt to optimize the reaction conditions we used different molar ratio nitrosoarene/alkynone, (e.g. 1:5, 1:12, 1:15), but surprisingly, we found comparable or better yields of indole products running the reactions with a 1:1 nitrosoarene/alkynone molar ratio[26]. In contrast to the *N*-hydroxy-3-arylindoles, *N*-hydroxy-3-aroylindoles are generally more stable and do not undergo dimerization to kabutanes[13a,27] under standard reaction conditions.

2.3.1 Synthesis of aroylalkynes

2.3.1.1 From commercially available aromatic aldehydes

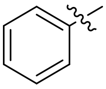
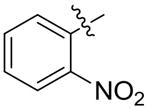
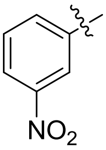
Aroyl-alkynes (**27**) can be generally obtained from the corresponding commercially available aromatic aldehydes (**25**). This two-step process (Scheme 2.16) involves a reaction with ethynylmagnesium bromide and the subsequent oxidation of **26** to the desired ketone. The oxidation can be carried out according to the Jones procedure[28], with the milder manganese dioxide[29] or using Dess-Martin periodinane as oxidant[30].

Jones procedure allowed the use of the crude intermediate alcohol without removing the unreacted aldehyde, where present. The latter would have been directly converted to the corresponding benzoic acid and removed during the final workup. Using manganese dioxide, instead, purification of the secondary alcohol was required. Dess-Martine periodinane provided in most cased better yields, lower reaction times and milder conditions.



25(a-g) **26(a-g)** **27(a-g)**

Scheme 2.16

Entry	Reactant	Ar	Product	Oxidative Method	Overall Yield for (27) (%)
1	**26a**		**27a**	Jones	quant
2	**25b**		**27b**	D. M. Periodinane	quant
3	**25c**		**27c**	Jones	64

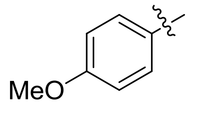
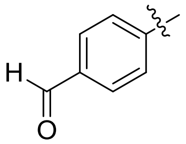
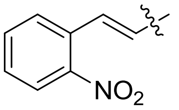
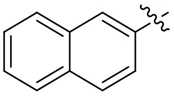
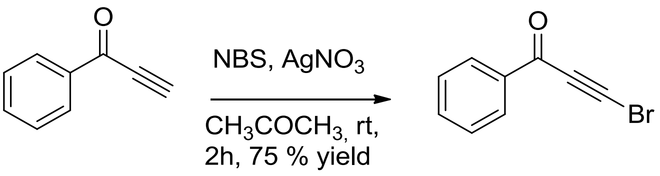
4	**25d**		**27d**	Jones	77
5	**25e**		**27e**	MnO_2	38
6	**25f**		**27f**	D. M. Periodidane	75
7	**25g**		**27g**	Jones	90

Table 2.5 – Synthesis of aroylalkynes from commercially available aldehydes.

Compound **27a** was synthesized from the commercially available 1-phenylprop-2-yn-1-ol (**26a**) instead of the aldehyde. In compound **25e** both the aldehyde functions reacted with ethynylmagnesium bromide and were then oxidized. The yield of the final produc **27e** is lower than the others ynones due to the presence of side products, like the mono-alkylated compound.

Bromination of **27a** using silver nitrate and N-Bromosuccinimide (NBS)[31] gave compound **28**, a internal alkyne that allows the synthesis of 2,3-disubstituted indole.



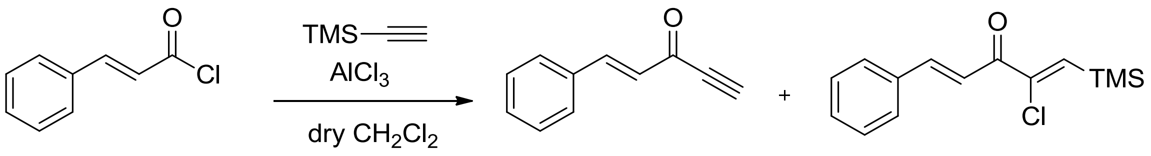
27a **28**

Scheme 2.17

2.3.1.2 From aroylchlorides

Aroylchlorides react with trimethylsilylacetylene in the presence of $AlCl_3$[32]; low temperatures and anhydrous conditions are required.

Starting from cinnamoyl chloride (**29**), (*E*)-1-phenylpent-1-en-4-yn-3-one (**30**) was isolated in 52 % yield running the reaction in anhydrous methylene chloride, together with the adduct (**31**).



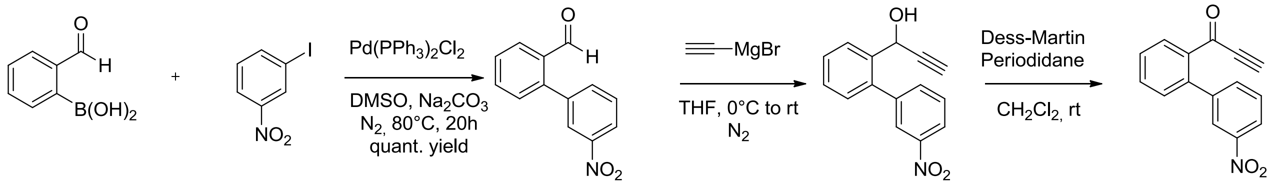
29 **30** **31**

Scheme 2.18

The advantage, compared to the previously described synthesis involving aromatic aldehydes, is the requirement of a single step.

2.3.1.3 From formylphenylboronic acids

(2-Formylphenyl)boronic acid (**32**) can undergo Suzuki Coupling reaction with 1-iodo-3-nitrobenzene (**33**), leading to biphenyl derivative (**34**). The formyl group is then alkylated with ethynylmagnesium bromide and the obtained alcohol (**35**) oxidized as previously reported to give **36** in quantitative yield.



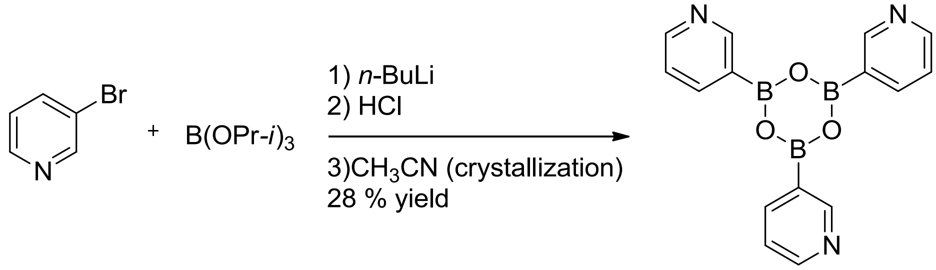
32 **33** **34** **35** **36**

Scheme 2.19

2.3.1.4 Preparation of (E)-1-(1-tosyl-1H-indol-3-yl)pent-1-en-4-yn-3-one

(*E*)-1-(1-tosyl-1H-indol-3-yl)pent-1-en-4-yn-3-one (**44**) was synthesized with a 6-step procedure.

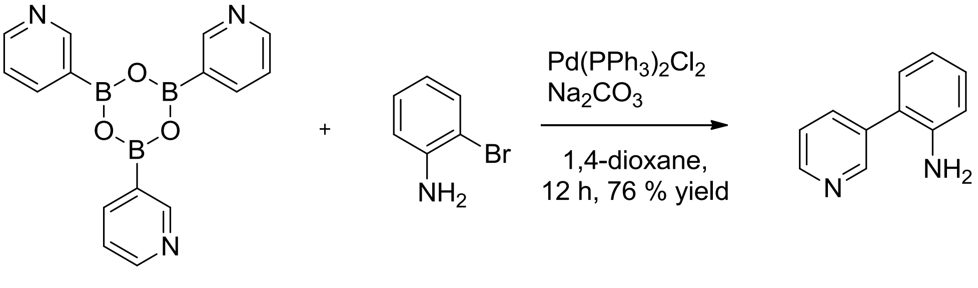
The first reaction is the preparation of 3-pyridylboroxin (**38**) from triisopropyl borate and 3-bromopyridine (**37**) in the presence of *n*-BuLi[33] (Scheme2.20). 3-Pyridylboroxin (**38**) is a useful compound for the introduction of a 3-pyridyl moiety into a molecule by the Suzuki reaction.



37 **38**

Scheme 2.20

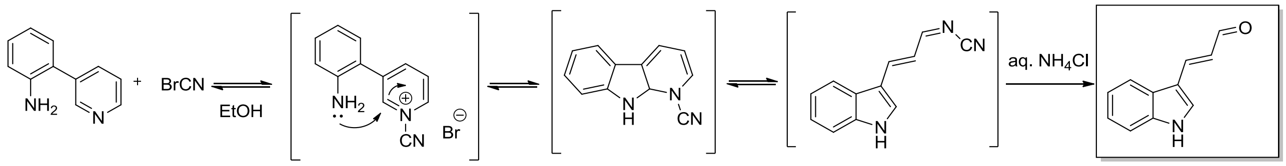
38 was applied in a Suzuki coupling reaction with 2-bromoaniline (**39**) to afford 2-(pyridin-3-yl)aniline (**40**) in good yield [34](Scheme 2.21).



38 **39** **40**

Scheme 2.21

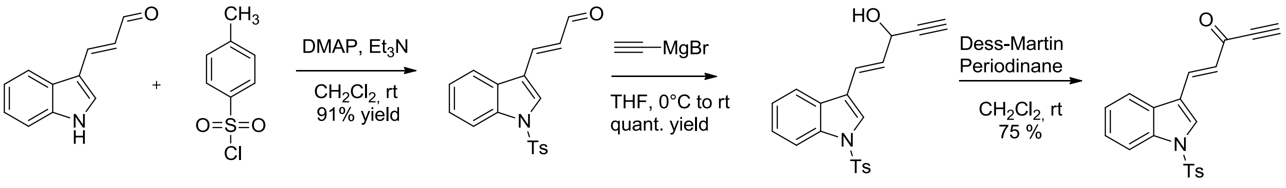
The third step of our synthetic pathway consists of a pyridine ring opening reaction on 2-(pyridin-3-yl)aniline (**40**) to obtain (*E*)-3-(1H-indol-3-yl)acrylaldehyde (**41**). Cyanogen bromide was used as activating agent[35](Scheme 2.22).



40 **41**

Scheme 2.22

(*E*)-3-(1H-indol-3-yl)acrylaldehyde (**41**) was then *N*-protected with 4-toluenesulfonyl chloride and (*E*)-3-(1-tosyl-1H-indol-3-yl)acrylaldehyde (**42**) was treated with ethynylmagnesium bromide to afford the alcohol (**43**) that was finally oxidized to (*E*)-1-(1-tosyl-1H-indol-3-yl)pent-1-en-4-yn-3-one (**44**) (Scheme 2.23).

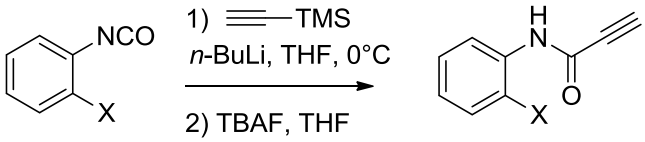


41 **42** **43** **44**

Scheme 2.23

2.3.1.5 Synthesis of propargylamides

Propargylamides (**46a**) and (**46b**) were prepared via interaction of trimethylsilylacetylene with the corresponding isocyanates (**45a**) and (**45b**), followed by desilylation with tetrabutylammonium fluoride (TBAF)[36].



45 (a-b) **46 (a-b)**

Scheme 2.24

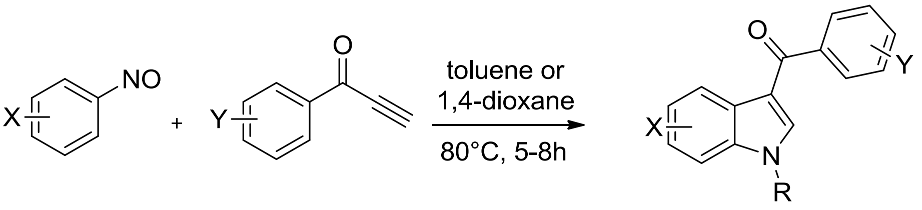
Entry	Reactant	X	Product	Yield (%)
1	**45a**	H	**46a**	54
2	**45b**	I	**46b**	60

Table 2.6

We first tried to synthesize propargylamide **46a** from the reaction between propriolic acid and aniline, screening different activating agents (e.g. HBTU/DIPEA, DCC/DMAP, HOBt/DIPEA/EDC,..), but unfortunately, the right product was not afforded with any of these conditions.

2.3.2 Synthesis of 3-aroylindoles from arylalkynones

Using conjugated alkynones as starting materials the reaction proceeds with the regioselective formation of *N*-hydroxy-3-aroylindoles and/or 3-aroylindoles.



18 (a-c,e) **27 (a-e)** **47 (a-h)**

Scheme 2.25

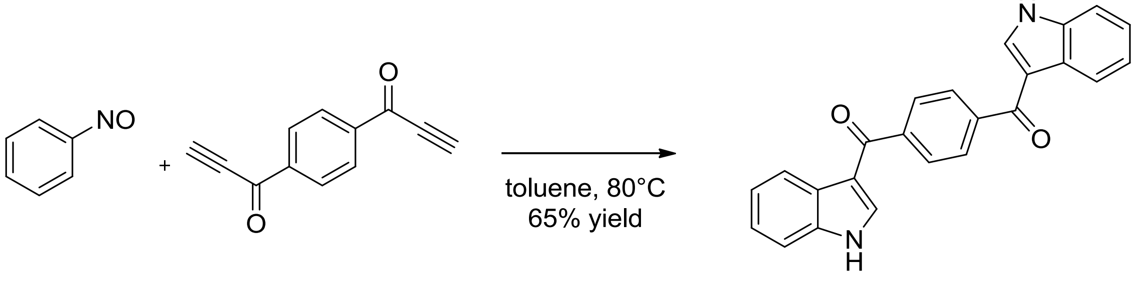
This process shows an excellent atom and step economy. A wide substrate scope was explored by using different substituted nitrosoarenes and arylalkynones affording indole compounds in moderate to excellent yields. Only 3-substituted regioisomers were isolated.

Entry	ArNO	X	Alkynone	Y	Product	R	Yield (%)
1	**18a**	4-NO_2	**27a**	H	**47a**	OH	53
2	**18e**	2-CO_2Me	**27a**	H	**47b**	OH	28
3	**18a**	4-NO_2	**27b**	2-NO_2	**47c**	H	33
4	**18a**	4-NO_2	**27c**	3-NO_2	**47d**	OH	56
5	**18a**	4-NO_2	**27d**	4-OMe	**47e**	OH	37
6	**18a**	4-NO_2	**27e**	4-COC≡CH	**47f**	OH	40
7	**18c**	4-CN	**27e**	4-COC≡CH	**47g**	OH	63
8	**18b**	4-COOH	**27e**	4-COC≡CH	**47h**	OH	43

Table 2.7

Procedures carried out with electron-deficient nitrosoaromatics registered better product yields and shorter reaction times. Only the reaction between **18a** and **27b** gave N-H indole **47c**, which is the only indole with a substituent in position 5 isolated after flash chromatography and not by filtration. All *N*-hydroxy-indoles with a substituent in position 5 were isolated after filtration. Compound **47b,** that has instead a substituent in position 7 was obtained after flash chromatography. 4-Nitrosobenzoic acid (**18b**) is not soluble in toluene, so the reaction was carried out in 1,4-dioxane.

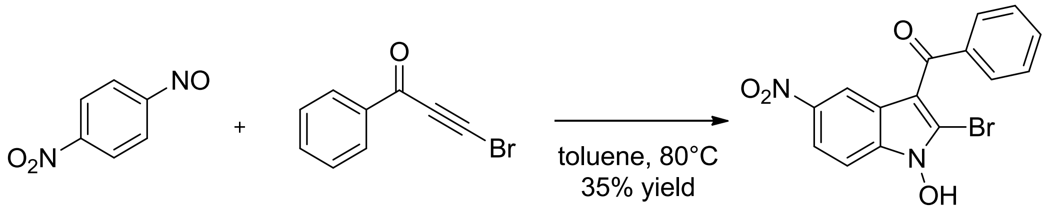
In the reaction between nitrosobenzene (**18g**) and **27e** the corresponding bis-indole (**48**) was achieved as the major product. A plausible explanation is that once formed the 3-aroylindole, it did not precipitate due to its better solubility and the second alkyne functionality reacted with another molecule of nitrosobenzene (**18g**) (Scheme 2.26).



18g **26e** **48**

Scheme 2.26

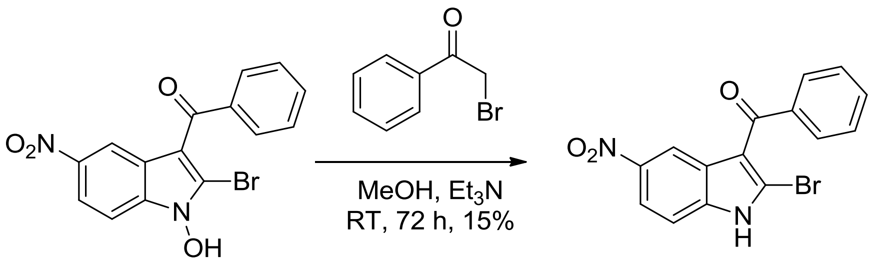
The process was also studied on internal aroylalkyne (**28**) using 4-nitro-nitrosobenzene (**18a**) as nitroarene. Only the regioisomer with the bromine in position 2 of the indole ring (**49**) was isolated in moderate yield (Scheme 2.27).



18a **27** **49**

Scheme 2.27

Since we were looking for a selective reduction procedure that could allow us to reduce the hydroxyl group to form indole derivatives without reducing other functional groups, (**49**) was employed in the reduction process made by α-bromoacetophenone. The corresponding indole (**50**) was isolated and the nitro and carbonyl groups were not reduced (Scheme 2.28).



49 **50**

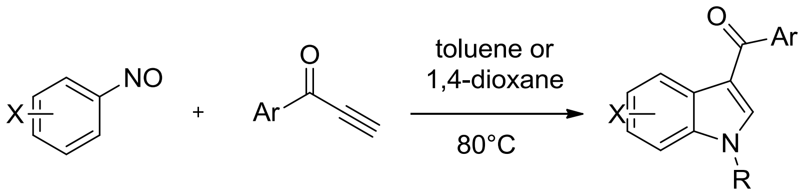
Scheme 2.28

This interesting procedure was first introduced by Somei in 1981[37] and further investigated by Wojciechowski and co-workers[38]. They carried out the reaction on *N*-hydroxyindoles with substituents in position 4 and/or 6, obtaining best results with the substituent in position 4. Positions 2 and 3 did not seem to have a basic role in the run of the procedure.

The reaction was tried on different substrates, all with a substituent in position 5, but **49** is the only one that was successfully reduced. It will be interesting to optimize the procedure also for indoles with a substituent in position 5, since these conditions are less aggressive than, for example, the classic reduction with Zn/AcOH that is usually poorly selective.

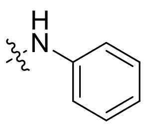
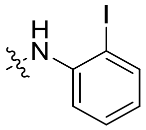
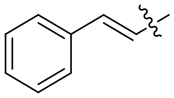
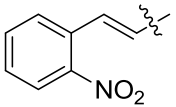
2.3.3 Synthesis of 3-aroylindoles from more complex aromatic alkynones

With the aim to generalize the application of the cycloaddition between nitrosoarenes and alkynones, ethynyl ketones containing polycyclic fragments and different functionality were tested and an extension of the synthetic scope of the reaction was achieved (Table 2.8).



18 (a-d,f) **51-67**

Scheme 2.29

Entry	ArNO	X	Alkynone	Ar	Product	R	Yield (%)
1	**18a**	4-NO_2	**46a**		**51**	OH	14
2	**18c**	4-CN	**46a**		**52**	OH	11
3	**18b**	4-COOH	**46a**		**53**	OH	15
4	**18a**	4-NO_2	**46b**		**54**	OH	22
5	**18a**	4-NO_2	**30**		**55**	OH	61
6	**18a**	4-NO_2	**27f**		**56**	OH	50
7	**18c**	4-CN	**27f**		**57**	OH	33

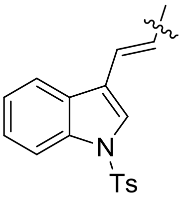
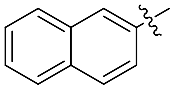
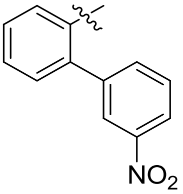
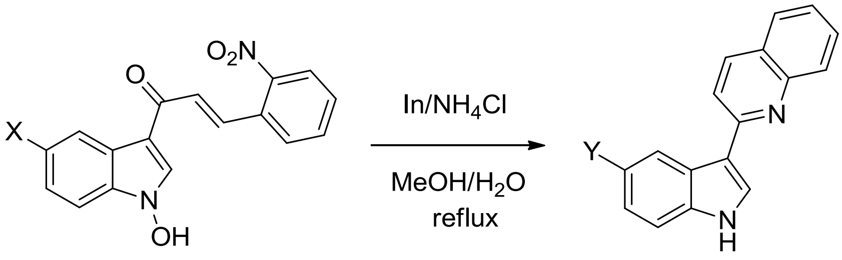
8	**18e**	2-CO_2Me	**27f**		**58**	OH	15
9	**18g**	H	**27f**		**59**	H	53
10	**18g**	H	**44**		**60**	H	32
11	**18a**	4-NO_2	**44**		**61**	H	30
12	**18d**	2-NO_2	**44**		**62**	H	45
13	**18g**	H	**27g**		**63**	OH	36
14	**18g**	H	**27g**		**64**	H	15
15	**18a**	4-NO_2	**27g**		**65**	OH	68
16	**18c**	4-CN	**27g**		**66**	OH	30
17	**18a**	4-NO_2	**36**		**67**	OH	32

Table 2.8

As previously observed, *N*-hydroxy-3-aroylindoles are usually isolated by filtration (**51, 52, 54-58, 65, 66**), sometimes they precipitate with the azoxy-derivatives and are purified with recrystallization from ethanol (**67**) or flash chromatography (**53**, **63**). 3-Aroylindoles are instead mostly gained after flash chromatography (**59-62**, **64**). Electron withdrawing substituents in position 5 usually afford *N*-hydroxy-3-aroylindoles, the only exception is **61**, while the reaction with nitrosobenzene (**18g**) mostly forms 3-aroylindoles. In one case was possible to isolate both the indoles derivatives (**63**) and (**64**). Substrate **54** has not been fully characterized because it gave degradation products.

2-Nitrochalcone derivatives (**56-59**) are highly functionalizable compounds. They undergo, for example, to indium-mediated reductive cyclizations to afford quinoline-type products (**68**,**69**) (Scheme 2.30).



56-57 **68-69**

Scheme 2.30

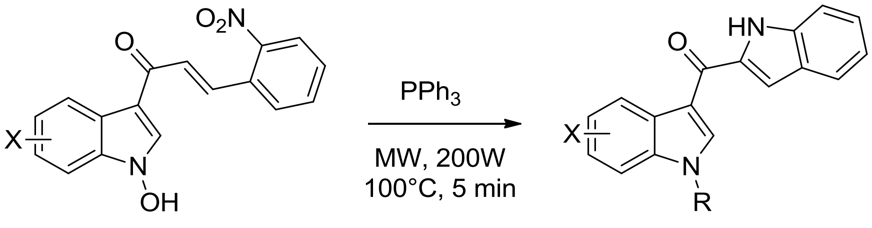
Entry	Reactant	X	Product	Y	Yield (%)
1	**56**	NO_2	**68**	NH_2	10
2	**57**	CN	**69**	CN	24

Table 2.9

The use of water as solvent makes the process particularly interesting from an environmental point of view. In literature this approach to indium-mediated reductive cyclization was studied from Banik and co-workers[39] and applied on 2-nitrochalcone derivatives from Kim and his collaborators[40]. The study has highlighted the importance of the solvent used and the molar ratio between the substrate and the In powder in order to improve the yield of the reaction. They obtained better yields with a 5 fold excess of In powder and a mixture 3:1 of MeOH and a saturated aqueous solution of NH_4Cl . The cyclization has been tried on two substrates, the first experiment was carried on substrate **56** using the same conditions described in the paper. The final product (**68**) showed the reduction of both the hydroxyl group and nitro group in position 5 and was obtained in low yield. On substrate **57** 1,4-dioxane was added as co-solvent to promote the solubility, the hydroxyl group has been reduced (**69**) and an improvement of the yield was observed. More experiments should be conducted testing how different solvents can improve the final result.

2-Nitrochalcone derivatives are also intensively employed in the synthesis of indole compounds by the Cadogan-Sundberg indole synthesis[41]. Modifications of the Cadogan-Sundberg process were introduced during the last decades, using microwave radiation as the source of heat instead of the conventional heating by reflux in a nitrogen atmosphere for several hours. Creencia and co-workers[42] succeeded in the synthesis of indazole, benzimidazole, carbonylindole, carbazole and phenazine derivatives. They found that, when the reaction with triethyl phospite produced only degradation products, triphenylphosphine was a good replacement to afford the desired products.

The reaction has been tried on different substrates. A successful experiment was carried out on substrates **56-58** . The reaction was initially run with triethyl phosphite, and gave only degradatation products, the phospithe was replaced with triphenylphosphine and this allowed us to isolate the bis-indolic compounds (**70-73**).



56-58 **70-73**

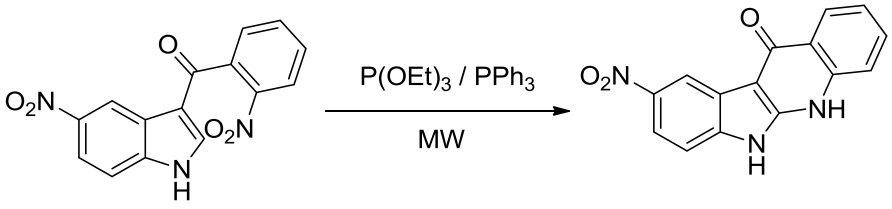
Scheme 2.31

Entry	Reactant	X	R	Product	Yield (%)
1	**56**	5-NO_2	OH	**70**	33
2	**57**	5-CN	OH	**71**	32
3	**57**	5-CN	H	**72**	25
4	**58**	7-CO_2Me	H	**73**	15

Table 2.10

Only with **57** was possible to isolate both the indole and the *N*-hydroxy-indole. At the moment there is not an explanation on why some substrates give indoles and others produce *N*-hydroxyindole compounds. Bis-indole products (**70-73**) were gained after flash chromatography using high polar eluting conditions. **70** and **72** needed methanol as final eluting solvent. Yields are modest and maybe a screening of different irradiating powers or time could help improving them.

The cyclization reaction was carried out on (5-nitro-1*H*-indol-3-yl)(2-nitrophenyl)methanone (**47c**) with triethyl phosphite and the supposed cyclizated product (**74**) was not observed. The procedure with triphenylphosphine is still under development (Scheme 2.32).



47c **74**

Scheme 2.32

2.4 *References*

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CHAPTER 3 : CONCLUSIONS

3 Conclusions

In this work the nitroso-alkyne cycloaddition reaction has been applied to the synthesis of 3-aryl- and 3-aroyl-indoles variously substituted.

- ✓ The synthesis of 3-arylindole derivatives needs a large excess of alkyne and the presence of an alkylating agent to minimize decomposition reaction to the corresponding azoxy compounds. The purification process consists always in flash chromatography.

  A serendipitous observation has allowed us to isolate policlyclic compounds and study a plausible mechanism for the process.

- ✓ 3-Aroylindoles are generally afforded by precipitation, only few compounds needed recrystallization or flash chromatography. Reactions are run with a nitrosoarene/alkyne ratio of 1:1, the 3-aroylindoles isolated are stable and do not require alkylating conditions. Electrochemical studies are under development to understand the mechanism leading to the formation of indoles in some cases or *N*-hydroxy derivatives.

  These syntheses tolerate a large number of functional groups. Yields used to be higher when electron poor nitrosoarenes were applied, but even if yields sometimes appeared to be low, the method can still be useful since allows the synthesis of an indole nucleus in a one-pot reaction, directly from *N*-aromatic precursors, as in the Fischer indole synthesis.

- ✓ Cyclizations of 2-nitro-chalcone derivatives to bis-indole (**70-73**) and quinoline (**68-69**) compounds were achieved, and optimizations of reaction conditions are under development.

  Cyclizations to bis-indole substrates appear to be particularly interesting because were run in few minutes and in solvent free conditions. In literature this cylization is usually run under pressure of carbon monoxide, metal-catalysts and long reaction times[1]. Applying a procedure similar to the one presented by Creencia and co-workers[2], microwave irradiation was used as heating source instead of the classical refluxing system.

- ✓ In collaboration with Prof. Cravotto and Dr. Barge from Università degli Studi di Torino, the cicloaddition reaction between nitrosobenzene (**18g**) and 1-phenylprop-2-yn-1-one (**27a**) was carried out with three different approaches: *a*) the classic refluxing conditions in toluene (25% yield), *b*) mill-balling technology (12% yield) and *c*) microwave irradiation (62% yield). The microwave experiment provides solvent free conditions, better yields and shorter reaction time. More experiments should be done in order to create a general protocol in solvent free conditions.

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[1] Some examples are : a) Davies, I. W.; Smitrovich, J. H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron* **2005**, *61*, 6425-6437; b) Okuro, K.; Gurnham, J.; Alper, H. *J. Org. Chem*. **2011**, *76*, 4715-4720; c) Akazome, M.; Kondo, T.; Watanabe, Y. *Chem. Lett*. **1992**, 5, 769-772

[2] a) Creencia, E. C.; Kosaka, M.; Muramatsu, T.; Kobayashi, M.; Iizuka, T.; Horaguchi, T. J. *Heterocyclic Chem*. **2009**, *46*, 1309-1317

CHAPTER 4 : EXPERIMENTAL SECTION

Experimental Details

NMR spectra were obtained using the Bruker Avance 400 MHz spectrometer. Unless differently stated, all the spectra were collected at 25°C using tetramethylsilane as standard.

Mass spectra were obtained by VG7070 EQ mass spectrometer with CI (Chemical Ionization).

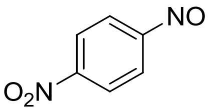
GC-MS spectra were recorded on Shimadzu GCMS-QP5000.

IR spectra were obtained using the Jasco FT-IR 5300.

Melting points were measured with BÜCHI 535 or GALLENKAMP melting point apparatus and are uncorrected.

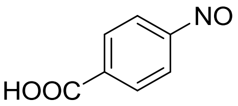
4.1 Synthesis of nitrosoarenes

4.1.1 Synthesis of 4-nitro-nitrosobenzene (18a)



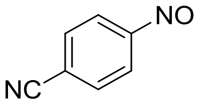
A solution of 4-nitroaniline (**17a**) (7.04 g, 51 mmol) and Oxone® (31.4 g, 51 mmol) in water (300 ml) was stirred at 0°C for 30 minutes and then at room temperature for 48 hours. The yellow solid was filtered and **18a** was obtained after crystallization in hot methanol.(95 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.53 (2H, d, *J* = 9 Hz); 8.05 (2H, d, *J* = 9 Hz). Spectroscopic data for this compound were in agreement with the literature[1].

4.1.2 Synthesis of 4-nitrosobenzoic acid (18b)



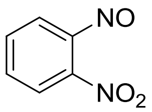
An aqueous solution of Oxone®(9 g, 14.6 mmol in 45 ml) was added to a solution of 4-aminobenzoic acid (**17b**) (1 g, 7.3 mmol) in CH_2Cl_2 (12 ml). The suspension was vigorously stirred at rt for 1 hour. Substrate **18b** was collected by filtration, washed with H_2O and dried (quant. yield). ^{1}H-NMR (DMSO-d_6) δ: 13.5 (br s, 1H); 8.27 (d, 2H, *J* = 8.8 Hz); 8.08 (d, 2H, *J* = 8.8 Hz). Spectroscopic data for this compound were in agreement with the literature[2].

4.1.3 Synthesis of 4-cyano-nitrosobenzene (18c)



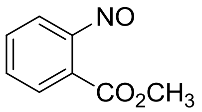
4-Aminobenzonitrile (**17c**) (2.4 g, 20 mmol) was dissolved in a mixture 1:1 of CH_2Cl_2 (50 ml) and *n*-pentane (50 ml). Sodium tungstate dihydrate (660 mg, 2 mmol), H_3PO_4 85% (1 ml, 15 mmol), H_2O_2 30% (20 ml, 196 mmol) and tetrabutylammonium bromide (200 mg, 0.62 mmol) were added to the solution and the mixture was stirred 2.5 hours at 35-40°C. The reaction mixture was washed with HCl 0.01 M (50 ml) and H_2O (50 ml), the organic layer dried over Na_2SO_4, filtered and rotary evaporated. Substrate **18c** was isolated as a yellow solid after recrystallization from hexane (65 % yield). ^{1}H-NMR ($CDCl_3$) δ: 7.98 (s, 4H). Spectroscopic data for this compound were in agreement with the literature[3].

4.1.4 Synthesis of 2-nitro-nitrosobenzene (18d)



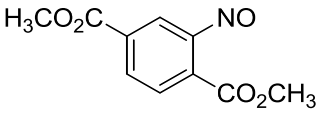
Sodium tungstate dihydrate (1 g, 3 mmol), H_3PO_4 85% (1 ml, 15 mmol), and H_2O_2 30% (10 ml, 98 mmol) were added to a solution of 2-nitroaniline (**17d**) (1.4 g, 10 mmol) in ethanol (20 ml). The mixture was stirred at 60°C until precipitation of a solid was observed. After complete conversion of the reactant, the solid was filtered and washed with H_2O to afford **18d** as a yellow solid (70 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.17 (d, 1H, J = 8.0 Hz); 7.96 (t, 1H, J = 8.0 Hz); 7.77 (t, 1H, J = 8.0 Hz); 6.63 (d, 1H, J = 8.0 Hz). Spectroscopic data for this compound were in agreement with the literature[4].

4.1.5 Synthesis of methyl 2-nitrosobenzoate (18e)



H_3PO_4 85% (2 ml, 29.7 mmol), sodium tungstate dihydrate (2 g, 6 mmol) and H_2O_2 30% (6 ml, 0.2 mmol) were added to a solution of methyl antranilate (**17e**) (2.6 ml, 19.8 mmol) in ethanol (200 ml). The mixture was stirred at 60°C for 2 hours, cooled to rt and filtrated. The obtained product was washed with H_2O to afford **18e** as a yellow solid (92 % yield). ^{1}H-NMR (DMSO-d_6) δ: 8.09 (dd, 1H, J = 7.8, 1.1 Hz); 7.97 (dt, 1H, J = 7.8, 1.4 Hz); 7.79 (dt, 1H, J = 7.7, 1.2 Hz); 7.72 (dd, 1H, J = 8, 0.9 Hz); 3.92 (s, 3H). Spectroscopic data for this compound were in agreement with the literature[3].

4.1.6 Synthesis of dimethyl 2-nitrosoterephthalate (18f)



An excess of H_2SO_4 96% (10 ml) was slowly added to a solution of 2-aminoterephthalic acid (5 g, 27.6 mmol) in methanol (50 ml), and the mixture was refluxed until the end of the reaction. An aqueous solution of NaOH 1M was added up to neutralization and the solution was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford (**17f**). The crude material (2.1 g) was dissolved in ethanol (20 ml) and H_3PO_4 85% (1 ml, 15 mmol), Na_2WO_4*$2H_2O$ (1 g, 3 mmol) and H_2O_2 30% (10 ml, 0.3 mmol) were added. The mixture was refluxed for 5 hours, cooled to rt and filtrated. The obtained product was washed with H_2O to afford **18f** as a yellow solid (79 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.42(dd, 1H, J = 7.9, 1.5 Hz); 7.99 (d, 1H, J = 7.9 Hz); 7.45 (d, 1H, J = 1.5 Hz); 4.08 (s, 1H); 3.99 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 167.1; 165.0; 161.7; 134.8; 134.0; 133.3; 130.0; 113.5; 53.4; 52.9. GC-MS (EI) : m/z = 223 $[M]^+$. IR (KBr): v (cm^{-1}) = 2959; 1722; 1435; 1288; 758. m.p. : 130°C.

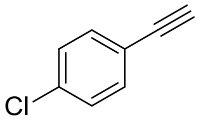
4.2 Synthesis of 3-arylindoles

4.2.1 Synthesis of alkynes

<u>General Procedure for the synthesis of arylalkynes</u> ***(GP1)***

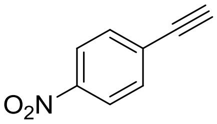
$PdCl_2(PPh_3)_2$ (0.01 mmol) and CuI (0.03 mmol) were added to a solution of the corresponding commercially available substituted haloarene (1 mmol) in Et_3N (10 ml). The mixture was cooled to 0°C and trimethylsilylacetylene (1.5 mmol) was added dropwise. The reaction was stirred for 1 hour at 0°C, then allowed to warm at rt and stirred for an additional 4 hours. The solution was then filtered over silica gel and the solvent removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The obtained product was dissolved in THF, cooled to 0°C and TBAF (0.003 mmol) was added to the solution. The reaction mixture was stirred for 2 hours, the solvent removed under reduced pressure and the crude material purified by flash chromatography over silica gel.

*4.2.1.1 Synthesis of 1-chloro-4-ethynylbenzene (**20a**)*



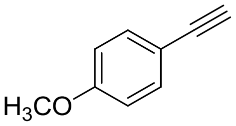
Substrate **20a** was synthesized from 1-chloro-4-iodobenze (**19a**) using *GP1* and isolated (Hexane-EtOAc 7:3, 69% yield) as a brown solid. ^{1}H-NMR ($CDCl_3$) δ: 7.43 (d, 2H, *J* = 8 Hz); 7.31 (d, 2H, *J* = 8 Hz); 3.11 (s, 1H). Spectroscopic data for this compound were in agreement with the literature[5].

*4.2.1.2 Synthesis of 1-ethynyl-4-nitrobenzene (**20b**)*



Substrate **20b** was synthesized from 1-iodo-4nitrobenzene (**19b**) using *GP1* and isolated (CH_2Cl_2, 95% yield) as a brown solid. ^{1}H-NMR ($CDCl_3$) δ: 8.21 (d, 2H, *J* = 8.9 Hz); 7.65 (d, 2H, *J* = 8.9 Hz); 3.37 (s, 1H). Spectroscopic data for this compound were in agreement with the literature[6].

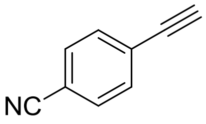
*4.2.1.3 Synthesis of 1-ethynyl-4-methoxybenzene (**20c**)*



Substrate **20c** was synthesized from 1-iodo-4methoxybenzene (**19c**) using *GP1* and isolated (Hexane-EtOAc 9:1, 70% yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 7.45 (d, 2H, *J* = 8.7 Hz); 6.86 (d, 2H, *J* = 8.7 Hz); 3.83 (s, 3H); 3.01

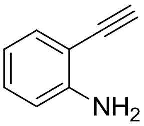
(s, 1H). Spectroscopic data for this compound were in agreement with the literature[7].

*4.2.1.4 Synthesis of 4-ethynylbenzonitrile (**20d**)*



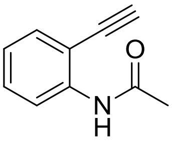
Substrate **20d** was synthesized from 4-bromobenzonitrile (**19d**) using *GP1* and isolated (CH_2Cl_2, 95 % yield) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.63 (d, 2H, *J* = 8.6 Hz); 7.58 (d, 2H, *J* = 8.6 Hz); 3.31 (s, 1H). Spectroscopic data for this compound were in agreement with the literature[8].

*4.2.1.5 Synthesis of 2-ethynylaniline (**20e**)*



Substrate **20e** was synthesized from 2-iodoaniline (**19e**) using *GP1* and isolated (hexane-EtOAc 7:3, 65 % yield) a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 7.35 (dd, 1H, J = 7.7, 1.5 Hz); 7.16 (td, 1H, *J* = 7.7, 1.5 Hz); 6.73-6.68 (m, 2H); 4.33 (s, 2H); 3.40 (s, 1H). Spectroscopic data for this compound were in agreement with the literature[9].

*4.2.1.6 Synthesis of N-(2-ethynylphenyl)acetamide (**20f**)*



Acetic anhydride (1.15 ml, 12 mmol) was added to a solution of **20e** (1.3 g, 11 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred at rt for 6 hours, the solvent removed under reduced pressure and the crude material purified by flash chromatography (hexane-EtOAc 6:4, 81 % yield) to afford **20f** as an orange solid. ^{1}H-NMR ($CDCl_3$) δ: 8.42 (d, 1H, *J* = 7.6 Hz); 7.92 (s, 1H); 7.48 (dd, 1H, *J* = 7.7, 1.3 Hz); 7.39 (td, 1H, *J* = 7.7, 1.3 Hz); 7.06 (t, 1H, *J* = 7.7 Hz); 3.52 (s, 1H); 2.25 (s, 3H). Spectroscopic data for this compound were in agreement with the literature[10].

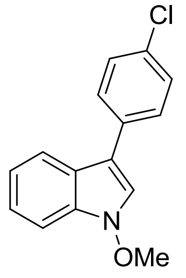
4.2.2 Synthesis of 3-arylindoles

General Procedure for the synthesis of 3aryl-indoles under alkylating conditions **(GP2)**

A mixture containing nitrosoarene (1.0 mmol), alkyne (12.0 mmol), K_2CO_3 (6.0 mmol), and the alkylating agent (6.0 mmol) in 80 mL of dry toluene was stirred at 80 °C for 3-8 h under nitrogen.

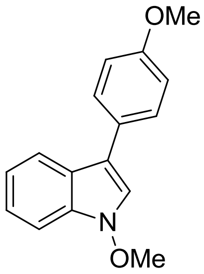
After cooling to r.t., the mixture was filtered and the filtrate was concentrated under reduced pressure. Flash chromatography of the residue over silica gel afforded the indole derivatives.

*4.2.2.1 Synthesis of 3-(4-Chlorophenyl)-1-methoxy-1H-indole (**21a**)*



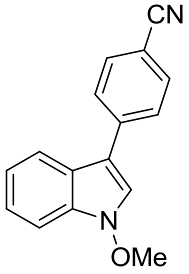
Substrate **21a** was synthesized from nitrosobenzene (**18g**), **20a** and Me_2SO_4 as alkylating agent using *GP2* and isolated (toluene/EDP 5:5, 29 % yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 8.04 (d, 1H, *J* = 7.8 Hz); 7.54 (d, 1H, *J* = 7.8 Hz); 7.46 (s, 1H), 7.50 (d, 2H, *J* = 8.5 Hz); 7.38 (d, 2H, *J* = 8.5 Hz); 7.09 (t, 1H, *J* = 7.8 Hz); 7.21 (t, 1H, *J* = 7.8 Hz); 3.81 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 135.6; 133.4; 128.9; 128.8; 125.8; 122.9; 121.6; 120.8; 120.6; 119.8; 112.7; 108.6; 68.1. MS (CI): *m/z* = 260 / 258 [M^{+1} ($^{37}Cl/^{35}Cl$)]. IR (film): ν (cm^{-1}) = 2933; 2836; 1609; 1549; 1503; 1454; 1244; 1178; 1033; 834; 741.

*4.2.2.2 Synthesis of 1-methoxy-3-(4-methoxyphenyl)-1H-indole (**21b**)*



Substrate **21b** was synthesized from nitrosobenzene (**18g**), compound **20c** and Me_2SO_4 as alkylating agent using *GP2* and isolated (toluene/EtOAc 6:4, 35% yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 7.90 (d, 1H, *J* = 7.8 Hz); 7.59 (d, 2H, *J* = 8.6 Hz); 7.51 (d, 1H, *J* = 7.8 Hz); 7.40 (s, 1H); 7.32 (t, 1H, *J* = 7.8 Hz); 7.21 (t, 1H, *J* = 7.8 Hz); 7.03 (d, 2H, *J* = 8.6 Hz); 4.13 (s, 3H); 3.89 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 158.2; 132.7; 128.7; 127.5; 122.7; 122.3; 120.4; 120.0; 119.9; 114.3; 113.7; 108.5; 65.9; 55.4. MS (CI): m/z = 254 $[M]^+$. IR (film): ν (cm^{-1}) = 3051; 2933; 2836; 1609; 1548; 1502; 1454; 1244; 1178; 1033; 834; 740.

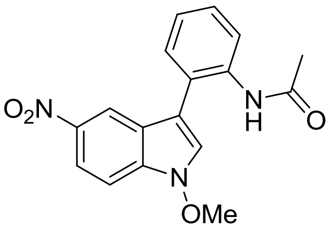
*4.2.2.3 Synthesis of 4-(1-Methoxy-1H-indol-3-yl)benzonitrile (**21c**)*



Substrate **21c** was synthesized from nitrosobenzene (**18g**), **20d** and Me_2SO_4 as alkylating agent using *GP2* and isolated (toluene/EtOAc 7:3, 30 % yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 7.91 (d, 1H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.72 (d, 2H, *J* = 8.5 Hz), 7.57 (s, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.36 (t, 1H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 8.0 Hz), 4.19 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 133.0; 132.7; 128.5; 127.4; 126.3; 123.3; 121.5; 121.4; 119.7; 119.3; 112.0; 110.4; 108.9; 66.3.

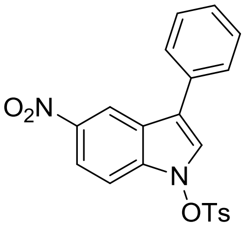
MS (CI): *m/z* = 249 [*M*]$^+$. IR (film): ν (cm^{-1}) = 2918; 2228; 1740; 1604; 1462; 1260; 1067; 909; 800; 732.

4.2.2.4 Synthesis of N-(2-(1-methoxy-5-nitro-1H-indol-3-yl)phenyl)acetamide (**21d**)



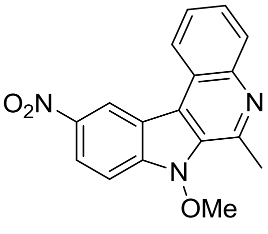
Substrate **21d** was synthesized from **18a**, **20f** and Me_2SO_4 as alkylating agent using *GP2* and isolated (EDP-EtOAc 4:6, 37 % yield) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 8.39 (d, 1H, *J* = 2.0 Hz); 8.24 (d, 1H, *J* = 8.0 Hz); 8.15 (dd, 1H, *J* = 9.0, 2.0 Hz); 7.56 (s, 1H); 7.55 (d, 1H, *J* = 9.0 Hz); 7.43-7.35 (m, 3H); 7.24 (t, 1H, *J* = 8.0 Hz); 4.24 (s, 3H); 1.99 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 169.0; 142.9; 136.1; 134.9; 131.4; 129.2; 125.2; 125.1; 123.6; 123.1; 122.4, 119.1; 117.8; 112.2; 109.2; 67.3; 24.9. MS (CI): *m/z* = 326 [M]$^+$. IR (film): ν (cm^{-1}) = 3283; 2924; 2853; 1669; 1582; 1516; 1447; 1372; 1331; 1301; 1064; 751. m.p.: 76-80 °C.

4.2.2.5 Synthesis of 5-nitro-3-phenyl-1H-indol-1-yl 4-methylbenzenesulfonate (**21e**)



Substrate **21e** was synthesized from **18a**, phenylacetilene (**20g**) and 4-toluenesulfonyl chloride as alkylating agent using *GP2* and isolated (EDP-EtOAc 8:2, 32 % yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 8.79 (d, 1H, *J* = 2.4 Hz); 8.41 (dd, 1H, *J* = 9.1, 2.4 Hz); 8.09 (d, 1H, *J* = 9.1 Hz); 7.72 (d, 2H, *J* = 9.1 Hz); 7.42 – 7.34 (m, 4H); 7.11 (d, 2H, *J* = 8.3 Hz); 7.03 (d, 2H, *J* = 8.5 Hz); 2.50 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 146.8; 146.2; 145.0; 144.7; 133.8; 130.9; 130.8; 130.1; 129.9; 128.9; 128.7; 128.5; 127.0; 124.1; 123.3; 114.0; 21.8. MS (CI): *m/z* = 409 [M]$^+$. IR (film): ν (cm^{-1}) = 3064; 2924; 2854; 1760; 1597; 1526; 1341; 1258; 1150; 1082; 750; 699.

4.2.2.6 Synthesis of 7-methoxy-6-methyl-10-nitro-7H-indolo[2,3-c]quinoline (**22**)



$POCl_3$ (30 µl, 0.32 mmol) was added to a solution of **21d** (70 mg, 0.22 mmol) in acetonitrile (15 ml), and the mixture was refluxed for 3 hours. The reaction mixture was cooled to 0°C and poured into water, then aqueous ammonia (28% solution) was added dropwise up to pH 8. The aqueous layer was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to afford **22** as an orange solid (86

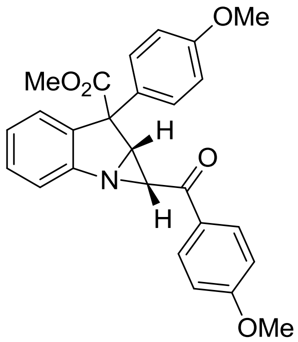
% yield). ^{1}H-NMR (DMSO-d$_6$) δ: 9.44 (d, 1H, *J* = 2.1 Hz); 8.75 (dd, 1H, *J* = 8.3, 1.2 Hz); 8.52 (dd, 1H, *J* = 9.1, 2.1 Hz); 8.13 (dd, 1H, *J* = 8.1, 1.2 Hz); 8.04 (d, 1H, *J* = 9.1 Hz); 7.77 (td, 1H, *J* = 8, 1.6 Hz); 7.73 (td, 1H, *J* = 7.6, 1.6 Hz); 4.33 (s, 3H); 3.20 (s, 3H). ^{13}C-NMR (DMSO-d$_6$) δ: 145.7; 143.2; 142.6; 138.6; 130.1; 129.8; 128.0; 127.4; 123.6; 122.9; 122.6; 120.3; 117.9; 117.1; 110.6; 67.2; 22.5. MS (CI): *m/z* = 308 [M]$^+$. IR (film): ν (cm^{-1}) = 2923; 2361; 1583; 1511; 1461; 1335; 1073; 755. m.p.: 214°C.

4.2.3 Synthesis of polycyclic compounds

General Procedure for the synthesis of indoline compounds ***(GP3)***

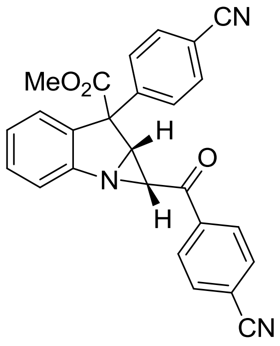
A mixture containing nitrosoarene (1.0 mmol), alkyne (12.0 mmol) in 80 mL of dry toluene was stirred at 80 °C for 3-8 h under nitrogen. After cooling to r.t., the mixture was filtered and the filtrate was concentrated by rotary evaporation. Flash chromatography of the residue over silica gel afforded the indole derivatives.

*4.2.3.1 Synthesis of methyl 1-(4-methoxybenzoyl)-7-(4-methoxyphenyl)-7,7a-dihydro-1H-azirino[1,2-a]indole-7-carboxylate (**24a**)*



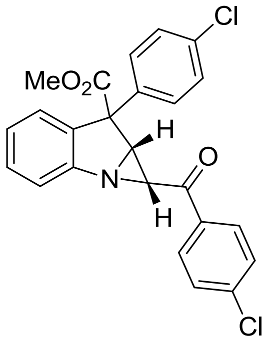
Substrate **24a** was synthesized from **18e** and **20c** using *GP3* and isolated (Hexane-EtOAc 7:3, 54 % yield) as a brown oil. ^{1}H-NMR (CDCl$_3$) δ: 7.56 (d, 1H, *J* = 7.6 Hz); 7.47 (d, 1H, *J* = 7.6 Hz); 7.42 (t, 1H, *J* = 7.6 Hz); 7.30 (d, 2H, *J* = 8.4 Hz); 7.23 (t, 1H, *J* = 7.6 Hz); 6.92 (d, 2H, *J* = 8.5 Hz); 6.59 (d, 2H, *J* = 8.4 Hz); 6.37 (d, 2H, *J* = 8.5 Hz); 4.55 (d, 1H, *J* = 6.8 Hz); 3.79 (s, 3H); 3.71 (s, 3H); 3.63 (d, 1H, *J* = 6.8 Hz); 3.51 (s, 3H). ^{13}C-NMR (100 MHz) δ: 190.9; 172.4; 168.2; 164.0; 158.9; 141.7; 141.7; 137.1; 131.4; 131.1; 130.9; 129.5; 128.9; 114.4; 113.6; 113.5; 65.9; 56.7; 55.5; 55.3; 55.0; 49.1. MS (CI): *m/z* = 430 [M]$^+$. IR (film): ν (cm^{-1}) = 3380; 2959; 2852; 1731; 1676; 1600; 1512; 1299; 1257; 1176; 1029; 801; 733.

*4.2.3.2 Synthesis of methyl 1-(4-cyanobenzoyl)-7-(4-cyanophenyl)-7,7a-dihydro-1H-azirino[1,2-a]indole-7-carboxylate (**24b**)*



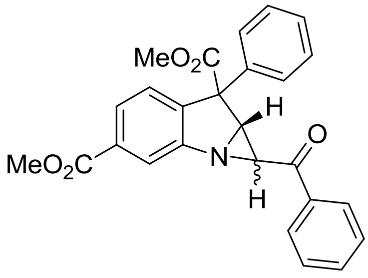
Substrate **24b** was synthesized from **18e** and **20d** using *GP3* and isolated (Hexane-EtOAc 8:2, 42 % yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 8.03 (d, 2H, *J* = 8.2 Hz), 7.76 (d, 2H, *J* = 7.8 Hz), 7.64 (d, 2H, *J* = 8.2 Hz); 7.60 (d, 1H, *J* = 7.5 Hz); 7.43 (d, 2H, *J* = 7.8 Hz); 7.35 (d, 1H, *J* = 7.5 Hz); 7.15 (t, 1H, *J* = 7.5 Hz); 7.07 (t, 1H, *J* = 7.5 Hz); 4.65 (d, 1H, *J* = 6.6 Hz); 3.73 (s, 3H), 3.68 (d, 1H, *J* = 6.6 Hz). ^{13}C-NMR (100 MHz) δ: 191.3; 171.2; 148.9; 147.5; 139.5; 137.8; 132.5; 132.2; 129.7; 128.8; 127.1; 127.0; 126.7; 125.6; 118.2; 117.7; 117.0; 116.5; 65.8; 54.3; 54.2; 49.5. MS (CI): *m/z* = 430 $[M]^+$. IR (film): v (cm^{-1}) = 3064; 2961; 2928; 2229; 1730; 1693; 1605; 1502; 1263; 1177; 1019; 840; 736.

*4.2.3.3 Synthesis of methyl 1-(4-chlorobenzoyl)-7-(4-chlorophenyl)-7,7a-dihydro-1H-azirino[1,2-a]indole-7-carboxylate (**24c**)*



Substrate **24c** was synthesized from **18e** and **20a** using *GP3* and isolated (Hexane-EtOAc 7:3, 25 % yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 7.56 (d, 1H, *J* = 7.8 Hz); 7.47-7.42 (m, 2H); 7.29 (m, 1H); 7.25 (d, 2H, *J* = 8.6 Hz); 7.14 (d, 2H, *J* = 8.6 Hz); 6.95 (d, 2H, *J* = 8.6 Hz); 6.85 (d, 2H, *J* = 8.6 Hz); 4.58 (d, 1H, *J* = 7.0 Hz); 3.71 (s, 3H); 3.65 (d, 1H, *J* = 7.0 Hz). ^{13}C-NMR (100 MHz) δ: 190.9; 172.5; 153.4; 139.6; 136.0; 134.1; 133.8; 133.5; 129.9; 129.3; 128.7; 128.6; 128.3; 128.2; 127.4; 122.4; 61.9; 54.4; 53.4; 49.6. MS (CI): *m/z* = 440 / 438 [*M*+1 ($^{37}Cl/^{35}Cl$)]. IR (film): v (cm^{-1}) = 2953; 2925; 2853; 1732; 1687; 1589; 1491; 1237; 1093; 1015; 959; 733.

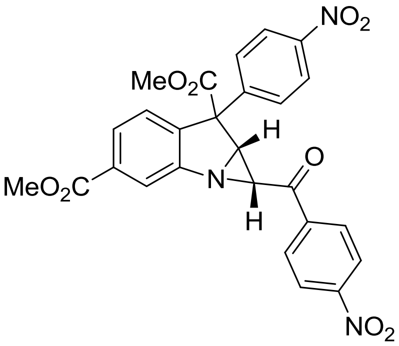
*4.2.3.4 Synthesis of dimethyl 1-benzoyl-7-phenyl-7,7a-dihydro-1H-azirino[1,2-a]indole-4,7-dicarboxylate (**24d+24e**) (cis- and trans-isomers)*



Substrates **24d** and **24e** were synthesized from **18f** and **20g** using *GP3* and isolated (Hexane-EtOAc 7:3, 32 % yield **24d**, 21 % yield **24e**) as colourless prism (cis) and brown oil (trans). **24d(*cis*-isomer)** ^{1}H-NMR ($CDCl_3$) δ: 8.20 (d, 1H, *J* = 1.2 Hz); 7.97 (dd, 1H, *J* = 8.0, 1.2 Hz); 7.58 (d, 1H, *J* = 8.0 Hz); 7.32 (m, 3H); 7.11 (t, 2H, *J* = 7.6 Hz); 7.03 (d, 1H, *J* = 7.6 Hz); 6.90 (t, 2H, *J* = 7.6 Hz); 6.77 (t, 1H, *J* = 7.6 Hz); 4.67 (d, 1H, *J* = 7.1 Hz); 3.97 (s, 3H); 3.72 (s, 3H); 3.71 (d, 1H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz) δ: 192.3; 172.4; 166.7; 154.1; 139.1; 136.8; 136.0; 132.7; 131.3; 128.5; 128.4; 127.8; 127.5; 127.3; 126.7; 126.4; 123.3; 62.3; 54.8; 53.4; 52.2; 49.8. MS (CI): *m/z* = 428 $[MH]^+$. IR (film):

ν (cm^{-1}) = 3419; 2951; 2928; 2856; 2257; 1722; 1689; 1596; 1580; 1435; 1289; 1250; 1222; 907; 733. **24e**(***trans*-isomer)** ^{1}H-NMR ($CDCl_3$) δ: 8.20 (d, 1H, *J* = 1.2 Hz); 7.97 (dd, 1H, *J* = 8.0, 1.2 Hz); 7.58 (d, 1H, *J* = 8.0 Hz); 7.32 (m, 3H); 7.11 (t, 2H, *J* = 7.6 Hz); 7.03 (d, 1H, *J* = 7.6 Hz); 6.90 (t, 2H, *J* = 7.6 Hz); 6.77 (t, 1H, *J* = 7.6 Hz); 4.67 (d, 1H, *J* = 7.1 Hz); 3.97 (s, 3H); 3.72 (s, 3H); 3.71 (d, 1H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz) δ: 192.5; 171.5; 166.4; 149.5; 144.8; 142.3; 137.1; 133.8; 130.4; 129.1; 128.7; 128.4; 127.9; 127.7; 126.7; 126.1; 122.1; 62.2; 55.3; 52.6; 52.2; 47.8. MS (CI): *m/z* = 428 [M]$^+$. IR (film): ν (cm^{-1}) = 3421; 2952; 2926; 2854; 2257; 1723; 1685; 1597; 1580; 1436; 1289; 1248; 1223; 909; 732.

*4.2.3.5 Synthesis of dimethyl 1-(4-nitrobenzoyl)-7-(4-nitrophenyl)-7,7a-dihydro-1H-azirino[1,2-a]indole-4,7-dicarboxylate (**24f**)*



Substrate **24f** was synthesized from **18f** and **20b** using *GP3* and isolated (Hexane-EtOAc 7:3, 37 % yield) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 8.14 (d, 1H, *J* = 1.5 Hz); 8.03 (d, 2H, *J* = 8.7 Hz); 8.02 (dd, 1H, *J* = 8.0, 1.5 Hz); 7.82 (d, 2H, *J* = 8.8 Hz); 7.60 (d, 1H, *J* = 8.0 Hz); 7.53 (d, 2H, *J* = 8.7 Hz); 7.31 (d, 2H, *J* = 8.8 Hz); 4.73 (d, 1H, *J* = 6.7 Hz); 3.97 (s, 3H); 3.82 (d, 1H, *J* = 6.7 Hz); 3.76 (s, 3H). ^{13}C-NMR (100 MHz) δ: 190.4; 171.0; 166.3; 153.1; 150.1; 146.9; 144.0; 139.8; 138.0; 132.0; 128.4; 128.0; 127.2; 127.1; 123.7; 123.5; 123.3; 59.5; 54.8; 53.9; 52.4; 49.1. MS (CI): *m/z* = 518 [M]$^+$. IR (film): ν (cm^{-1}) = 3419; 2924; 2854; 2360; 1723; 1600; 1524; 1494; 1437; 1349; 1291; 1248; 854; 756.

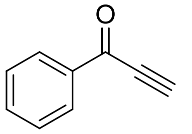
4.3 *Synthesis of 3-aroylindoles*

4.3.1 Synthesis of alkynones

*4.3.1.1 Synthesis of 1-phenylprop-2-yn-1-one (**27a**)*

Representative Procedure for the oxidation reaction using Jones Reagent ***(RP1)***

Jones reagent was added dropwise to a solution of **26a** (234 mg, 2 mmol) in acetone (30 ml) kept at 0°C, to the point of a persistent orange color. At the end of the reaction, the excess of Jones reagent was removed adding 2-propanol dropwise to the point of a persistent green color. The

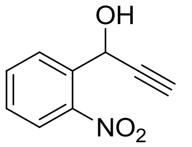


mixture was filtered through celite and the washings concentrated under reduced pressure to give an oil. The crude residue was dissolved in CH_2Cl_2 and washed with saturated Na_2HCO_3 and brine. The organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Substrate **27a** isolated (quant. yield) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 8.19 (d, 2H, *J* = 7.5 Hz); 7.66 (t, 1H, *J* = 7.5 Hz); 7.53 (t, 2H, *J* = 7.5 Hz); 3.45 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[11]

*4.3.1.2 1-(2-nitrophenyl)prop-2-yn-1-one (**27b**)*

Representative Procedure for the synthesis of arylynoles ***(RP2)***

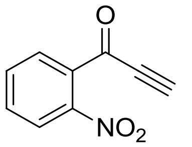
*Synthesis of 1-(2-nitrophenyl)prop-2-yn-1-ol (**26b**)*



A solution of ethynylmagnesium bromide 0.5 M in THF (39.6 ml, 19.8 mmol) was added dropwise to a solution of 2-nitro-benzaldehyde (**25b**) (2.5 g, 16.5 mmol) in THF (35 ml) cooled to 0°C. The mixture was allowed to warm to rt and stirred until the complete conversion of the aldehyde. A saturated aqueous solution of NH_4Cl (40 ml) was added to the reaction solution and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and the solvent removed under reduced pressure. **26b** was isolated (quant. yield) as a brown oil without any further purification.^{1}H-NMR ($CDCl_3$) δ: 8.00-7.97 (m, 2H); 7.69 (dt, 1H, *J* = 7.6, 1.1 Hz); 7.52 (dt, 1H, *J* = 7.6, 1.3 Hz); 6.06 (d, 1H, *J* = 2); 3.54 (br s, 1H); 2.66 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[12]

Representative Procedure for the oxidation reaction using Dess Martin Periodinane ***(RP3)***

*Synthesis of 1-(2-nitrophenyl)prop-2-yn-1-one (**27b**)*

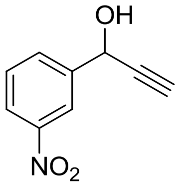


Dess-Martin periodinane (2.4 g, 5.6 mmol) was added to a solution of **26b** (1 g, 5.6 mmol) in CH_2Cl_2 (60 ml) and the mixture was stirred for 1 hour at rt. At the end of the reaction Et_2O (20 ml) and an aqueous solution of NaOH 1M (40 ml) were added and the mixture was stirred for 5 minutes. The aqueous phase was extracted with Et_2O (3x30 ml) and the combined organic layers were washed with H_2O, dried over Na_2SO_4 and the solvent removed under reduced pressure to afford **27b** as a brown solid (quant.

yield).^{1}H-NMR ($CDCl_3$) δ: 7.95 (dd, 1H, *J* = 7.6, 1.3 Hz); 7.84 (dd, 1H, *J* = 7.6, 1.8 Hz); 7.77-7.69 (m, 2H); 3.48 (s, 1H).^{13}C-NMR ($CDCl_3$) δ: 175.3; 147.9; 133.3; 133.2; 132.8; 130.1; 124.3; 82.1; 79.9. MS (CI): *m/z* = 176 $[M]^+$. IR (film): ν (cm^{-1}) = 3271; 2097; 1677; 1528; 1348; 1241; 855; 790; 702. m.p.: 94-96 °C.

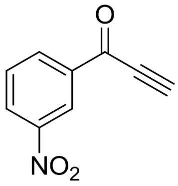
*4.3.1.3 1-(3-nitrophenyl)prop-2-yn-1-one (**27c**)*

*Synthesis of 1-(3-nitrophenyl)prop-2-yn-1-ol (**26c**)*



Substrate **26c** was synthesized from 3-nitrobenzaldehyde (**25c**) using *RP2* and isolated after flash chromatography over silica gel (hexane-EtOAc 8:2, 61 % yield) as a yellow oil . ^{1}H-NMR ($CDCl_3$) δ: 8.47 (s, 1H); 8.23 (dd, 1H, *J* = 8.0, 1.4 Hz); 7.92 (d, 1H, *J* = 8.0 Hz); 7.60 (t, 1H, *J* = 8.0 Hz); 5.60 (d, 1H, *J* = 2.2 Hz); 2.77 (d, 1H, *J* = 2.2 Hz). Spectroscopic data for this compound were in agreement with the literature.[13]

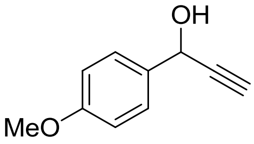
*Synthesis of 1-(3-nitrophenyl)prop-2-yn-1-one (**27c**)*



Substrate **27c** was synthesized from **26c** using *RP1* and isolated after flash chromatography over silica gel (EDP-EtOAc 8:2, 64 % yield) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 9.00 (s, 1H); 8.51 (dd, 1H, *J* = 7.8, 1.4 Hz); 8.50 (d, 1H, *J* = 7.8 Hz); 7.75 (t, 1H, *J* = 7.8 Hz); 3.62 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[13]

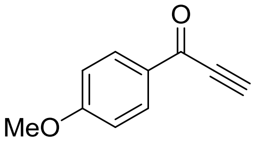
*4.3.1.4 1-(4-methoxyphenyl)prop-2-yn-1-one (**27d**)*

*Synthesis of 1-(4-methoxyphenyl)prop-2-yn-1-ol (**26d**)*



Substrate **26d** was synthesized from 4-methoxybenzaldehyde (**25d**) using *RP2* and isolated after flash chromatography over silica gel (hexane-EtOAc 8:2, 59 % yield) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.42 (d, 2H, *J* = 6.4 Hz); 6.88 (d, 2H, *J* = 6.4 Hz); 5.37 (s, 1H); 3.77 (s, 3H); 2.60 (s, 1H); 2.59 (br s, 1H). Spectroscopic data for this compound were in agreement with the literature.[14]

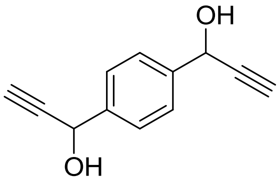
*Synthesis of 1-(4-methoxyphenyl)prop-2-yn-1-one (**27d**)*



Substrate **27d** was synthesized from **26d** using *RP1* and isolated as a white solid (77 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.16 (d, 2H, *J* = 8.8 Hz); 6.99 (d, 2H, *J* = 8.8 Hz); 3.92 (s, 3H); 3.39 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[15]

*4.3.1.5 1,1'-(1,4-phenylene)bis(prop-2-yn-1-one) (**27e**)*

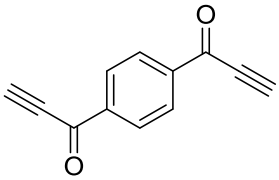
*Synthesis of 1,1'-(1,4-phenylene)bis(prop-2-yn-1-ol) (**26e**)*



Substrate **26e** was synthesized from terephthaldehyde (**25e**) using *RP2* and isolated after flash chromatography over silica gel (hexane-EtOAc 5:5, 38 % yield) as a brown solid. ^{1}H-NMR ($CDCl_3$) δ: 7.60 (s, 4H); 5.50 (d 2H, *J* = 2.2 Hz); 2.69 (d, 2H, *J* = 2.2 Hz); 1.65 (br s, 2H). Spectroscopic data for this compound were in agreement with the literature.[16]

<u>Representative Procedure for the oxidation reaction using MnO_2</u> ***(RP4)***

*Synthesis of 1,1'-(1,4-phenylene)bis(prop-2-yn-1-one) (**27e**)*

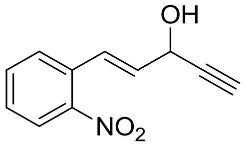


MnO_2 (6.2 g, 71 mmol) was added to a solution of **26e** (1.1 g, 5.9 mmol) in CH_2Cl_2 (200 ml) and the reaction was refluxed for 48 hours. The reaction mixture was cooled to rt and filtered through celite to afford substrate **27e** as a yellow oil (38 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.29 (s, 4H); 3.55 (s, 2H). Spectroscopic data for this compound were in agreement with the literature.[17]

*4.3.1.6 1 (E)-1-(2-nitrophenyl)pent-1-en-4-yn-3-one (**27f**)*

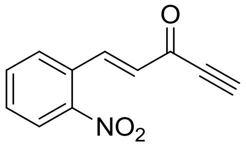
*Synthesis of (E)-1-(2-nitrophenyl)pent-1-en-4-yn-3-ol (**26f**)*

Synthesis of alkynones



Substrate **26f** was synthesized from (*E*)-3-(2-nitrophenyl)acrylaldehyde (**25f**) using *RP2* and isolated as a brown oil (quant. yield) without further purifications. ^{1}H-NMR (CDCl$_3$) δ: 7.96 (d, 1H, *J* = 7.9 Hz); 7.63-7.57 (m, 2H); 7.43 (m, 1H); 7.30 (dd, 1H, *J* = 15.6, 1.1 Hz); 6.27 (dd, 1H, *J* = 15.6, 5.6 Hz); 5.11 (m, 1H); 2.66 (d, 1H; *J* = 2.2 Hz); 2.67 (br s, 1H). Spectroscopic data for this compound were in agreement with the literature.[18]

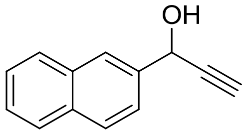
*Synthesis of 1 (E)-1-(2-nitrophenyl)pent-1-en-4-yn-3-one (**27f**)*



Substrate **27f** was synthesized from **26f** using *RP3* and isolated as a brown solid (75 % yield).^{1}H-NMR (DMSO-d$_6$) δ: 8.25 (d, 1H, *J* = 16 Hz); 8.13 (dd, 1H, *J* = 8.1, 1.2 Hz); 7.98 (dd, 1H, *J* = 7.8, 1.3 Hz); 7.81 (td, 1H, *J* = 7.4, 0.8 Hz); 7.73 (td, 1H, *J* = 7.8, 1.4 Hz); 6.96 (d, 1H, *J* = 16 Hz); 4.99 (s, 1H). ^{13}C-NMR (DMSO-d$_6$) δ: 177.7; 148.8; 144.9; 134.5; 132.2; 131.9; 130.0; 129.3; 125.4; 84.7; 80.3. MS (CI): *m/z* = 202 [M]$^{+}$. IR (film): v (cm^{-1}) = 3255; 3105; 2099; 1645; 1518; 1347; 1238; 970; 787; 741. m.p.: 102-104 °C.

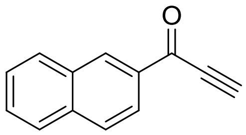
*4.3.1.7 1-(naphthalen-2-yl)prop-2-yn-1-one (**27g**)*

*Synthesis of 1-(naphthalen-2-yl)prop-2-yn-1-ol (**26g**)*



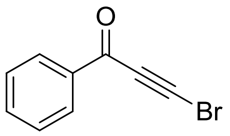
Substrate **26g** was synthesized from 2-naphthaldehyde (**25g**) using *RP2* and isolated after flash chromatography over silica gel (EDP-EtOAc 8:2, 83 % yield) as a yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 8.30 (d, 1H, *J* = 8.4 Hz); 7.89-7.80 (m, 3H); 7.59-7-49 (m, 3H); 6.11 (d, 1H, *J* = 2.0 Hz); 3.11 (br s, 1H); 2.73 (d, 1H, *J* = 2.0 Hz). Spectroscopic data for this compound were in agreement with the literature.[14]

*Synthesis of 1-(naphthalen-2-yl)prop-2-yn-1-one (**27g**)*



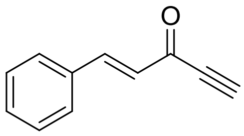
Substrate **27g** was synthesized from **26g** using *RP1* and isolated after flash chromatography over silica gel (EDP-EtOAc 9:1, 90 % yield) as a yellow solid. ^{1}H-NMR (CDCl$_3$) δ: 9.22 (d, 1H, *J* = 8.7 Hz); 8.63 (dd, 1H, J = 7.2, 0.8 Hz); 8.11 (d, 1H, J = 8.1 Hz); 7.92 (d, 1H, J = 8.1 Hz); 7.69 (td, 1H, J = 7.8, 1.2 Hz); 7.59 (t, 2H, J = 7.8 Hz); 3.45 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[15]

*4.3.1.8 Synthesis of 3-bromo-1-phenylprop-2-yn-1-one (**28**)*



Silver nitrate (85 mg, 0.5 mmol) was added to a solution of substrate **27a** (650 mg, 5 mmol) in acetone (10 ml). The mixture was stirred at rt for 5 minutes, then NBS (979 mg, 5.5 mmol) was added. The reaction mixture was stirred for 2 hours, the solids were then filtered off on a pad of Celite and washed several times with acetone. The solvent was removed under reduced pressure and **28** was isolated as a yellow solid after flash chromatography (Hexane-CH_2Cl_2 5:5, 75 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 2H, J = 7.9 Hz), 7.63 (t, 1H, J = 7.4 Hz), 7.49 (t, 2H, J = 8.0 Hz). Spectroscopic data for this compound were in agreement with the literature.[19]

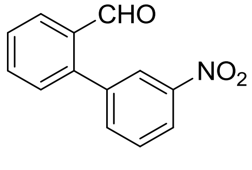
*4.3.1.9 (E)-1-phenylpent-1-en-4-yn-3-one (**30**)*



A mixture of cinnamoyl chloride (**29**) (333 mg, 2 mmol) and trimethylsilylacetilene (340 µl, 2.4 mmol) in CH_2Cl_2 (30 ml) was added dropwise to a solution of $AlCl_3$ (267 mg, 2 mmol) in CH_2Cl_2 (20 ml) cooled to -40°C under nitrogen atmosphere. The reaction mixture was stirred at -40°C for 1 hour, then the temperature was risen up to -10°C in about 3.5 hours. At the end of the reaction, ice was added and the mixture washed with HCl 1M (2 x 50 ml) and sat. $NaHCO_3$ (2 x 50 ml). The organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **30** was isolated after flash chromatography over silica gel (EDP-EtOAc 9:1, 52 % yield) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 7.91 (d, 1H, J = 16.1 Hz); 7.61 (d, 1H, J = 5.4 Hz); 7.47-7.44 (m, 3H); 6.83 (d, 1H, J = 16.1 Hz); 3.34 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[20]

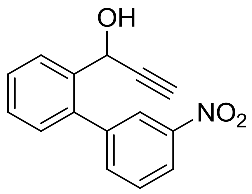
*4.3.1.10 1-(3'-nitro-[1,1'-biphenyl]-2-yl)prop-2-yn-1-one (**36**)*

*Synthesis of 3'-nitro-[1,1'-biphenyl]-2-carbaldehyde (**34**)*



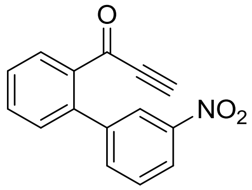
A round bottomed flask was charged with 1-iodo-3-nitrobenzene (**33**) (2 g, 8 mmol), 2-formylphenylboronic acid (**32**) (1.3 g, 8.9 mmol) and $Pd(PPh_3)_2Cl_2$ (281 mg, 0.4 mmol). The flask was purged with N_2 and deoxygenated DMSO (40 ml) was added. The reaction was further deoxygenated via N_2 bubbling for an additional 5 minutes before an aqueous solution of Na_2CO_3 deoxygenated 2M(8 ml, 16 mmol) was added. The mixture was heated to 80°C upon completion (20 hours), then cooled to rt and diluted with iced water. The resulting emulsion was extracted with EtOAc (3x40 ml), the combined organic layers washed with a saturated aqueous solution of NH_4Cl (30 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure to afford **34** as a brown solid (quant. yield).^{1}H-NMR ($CDCl_3$) δ: 9.99 (s, 1H); 8.34-8.31 (m, 1H); 8.30-8.29 (m, 1H); 8.08 (dd, 1H, *J* = 7.7, 1 Hz); 7.74-7.61 (m, 3H); 7.47-7.45 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ: 191.1; 148.2; 142.7; 139.8; 135.9; 134.0; 133.6; 130.9; 129.4; 129.0; 128.9; 124.4; 123.0. MS (CI): *m/z* = 229 $[M]^+$. IR (film): v (cm^{-1}) =2862; 1689; 1530; 1349. m.p. 113-115°C.

*Synthesis of 1-(3'-nitro-[1,1'-biphenyl]-2-yl)prop-2-yn-1-ol (**35**)*



Substrate **35** was synthesized from **34** using *RP2* and isolated after flash chromatography over silica gel (hexane-EtOAc 7:3, 89 % yield as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 8.35-8.34 (m, 1H); 8.28-8.25 (m, 1H); 7.93 (dd, 1H, *J* = 7.8, 0.8 Hz); 7.82-7.79 (m, 1H); 7.63 (t, 1H, *J* = 7.9 Hz); 7.53 (td, 1H, *J* = 7.7, 1.2 Hz); 7.48-7.44 (m, 1H); 7.31-7.27 (m, 1H); 5.35 (d, 1H, *J* = 1.6 Hz); 2.66 (d, 1H, *J* = 1.6 Hz); 2.29 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 148.1; 141.8; 138.5; 137.7; 135.6; 130.1; 129.2; 129.1; 128.8; 127.7; 124.4; 122.5; 83.7; 75.2; 61.4. MS (CI): *m/z* = 255 $[M]^+$. IR (film): v (cm^{-1}) = 3240; 2093; 1682; 1515; 1348; 1229; 1113; 980; 740.

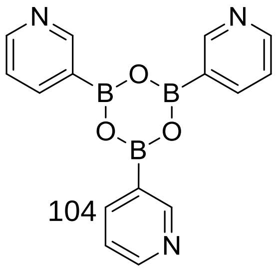
*Synthesis of 1-(3'-nitro-[1,1'-biphenyl]-2-yl)prop-2-yn-1-one (**36**)*



Substrate **36** was synthesized from **35** using *RP3* and isolated as a brown oil (quant. yield). ^{1}H-NMR ($CDCl_3$) δ: 8.26 (dt, 1H, *J* = 7.9, 1.8 Hz); 8.23-8.19 (m, 2H); 7.68 (td, 1H, *J* = 7.5, 1.3 Hz); 7.63-7.55 (m, 3H); 7.38 (d, 1H, *J* = 7.6 Hz); 3.28 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 178.1; 148.1; 142.3; 140.5; 135.6; 135.2; 133.2; 132.2; 131.4; 129.0; 128.6; 123.8; 122.5; 81.3. MS (CI): *m/z* = 253 $[M]^+$. IR (film): v (cm^{-1}) = 3256; 2089; 1645; 1520; 1345; 1229; 994; 725.

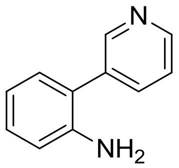
*4.3.1.11 (E)-1-(1-tosyl-1H-indol-3-yl)pent-1-en-4-yn-3-one (**44**)*

*Synthesis of 2,4,6-tri(pyridin-3-yl)-1,3,5,2,4,6-trioxatriborinane (**38**)*



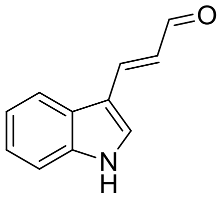
To a solution of toluene (320 ml), THF (80 ml), triisopropyl borate (55.4 ml, 240 mmol) and 3-bromopyridine (**37**) (19.3 ml, 200 mmol) cooled to -40°C under N_2 atmosphere, a solution 2.5M in hexane of *n*-BuLi (96 ml, 240 mmol) was added dropwise over 1 hour. The reaction mixture was stirred for an additional 30 minutes at -40°C, then warmed to -20°C and an aqueous solution 2N of HCl (200 ml, 400 mmol) was added. When the mixture reached rt the aqueous layer was separated and an aqueous solution 5N of NaOH was added up to pH 7.6-7.7 (a white solid precipitated at pH 7). The mixture was extracted with THF (3x250 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The solid residue was recrystallized from hot acetonitrile to afford **38** as a yellow solid (28 % yield). ^{1}H-NMR (CD_3OD) δ: 8.61 (s, 3H); 8.54 (dd, 3H, *J* = 5.4, 1.6 Hz); 8.33 (d, 3H, *J* = 7.5 Hz); 7.6 (t, 3H, *J* = 6 Hz). Spectroscopic data for this compound were in agreement with the literature.[21]

*Synthesis of 2-(pyridin-3-yl)aniline (**40**)*



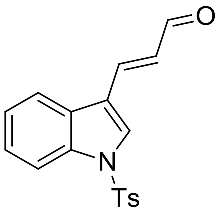
A solution of deoxygenated 1,4-dioxane (250 ml), **38** (9.6 g, 30.6 mmol), 2-bromoaniline (**39**) (10.3 ml, 90.7 mmol) and $PdCl_2(PPh_3)_3$ (2.7 g, 3.9 mmol) was stirred for 30 minutes at rt. An aqueous solution 1M of Na_2CO_3 (116 ml) was added and the reaction mixture was refluxed for 12 hours. At the end of the process, the reaction was concentrated in vacuo, the crude material dissolved in EtOAc (100 ml), washed with brine (3x 70 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and substrate **40** was isolated as a yellow oil after flash chromatography (EDP-EtOAc 6:4. 76 % yield). ^{1}H-NMR ($CDCl_3$) δ: 8.72 (d, 1H, *J* = 1.6 Hz); 8.60 (dd, 1H, *J* = 4.8, 1.5 Hz); 7.81 (dt, 1H, *J* = 7.8, 1.9 Hz); 7.40-7.37 (m, 1H); 7.21 (td, 1H, *J* = 7.7, 1.6 Hz); 7.11 (dd, 1H, *J* = 7.6, 1.5 Hz); 6.86 (td, 1H, *J* = 7.4, 1.0 Hz); 6.79 (dd, 1H, *J* = 8.0, 1.0 Hz); 3.49 (br s, 2H). Spectroscopic data for this compound were in agreement with the literature.[22]

*Synthesis of (E)-3-(1H-indol-3-yl)acrylaldehyde (**41**)*



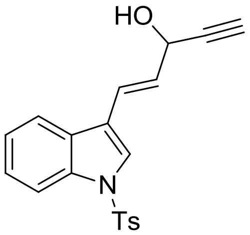
A solution of **40** (5 g, 29 mmol) and absolute ethanol (275 ml) was warmed to 40°C, then cyanogens bromide (6.2 g, 59 mmol) was added as a solution in ethanol (30 ml). After 20 minutes an aqueous solution 10% of NH_4Cl (100 ml) was added and the mixture stirred at 40°C for 3 hours. The reaction was concentrated in vacuo and the residue taken up in EtOAc (70 ml), washed with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4 and the solvent removed under reduced pressure. Substrate **41** was obtained as a brown oil after flash chromatography (EDP-EtOAc 6:4, 30 % yield). ^{1}H-NMR ($CDCl_3$) δ: 9.66 (d, 1H, *J* = 7.9 Hz); 8.89 (br s, 1H); 7.91 (d, 1H, *J* = 7.1 Hz); 7.72 (d, 1H, *J* = 15.8 Hz); 7.61 (d, 1H, *J* = 2.8 Hz); 7.47 (dd, 1H, *J* = 7.1, 1.6 Hz); 7.34-7.30 (m, 2H); 6.80 (dd, 1H, *J* = 15.8, 7.9 Hz). Spectroscopic data for this compound were in agreement with the literature.[22]

*Synthesis of (E)-3-(1-tosyl-1H-indol-3-yl)acrylaldehyde (**42**)*



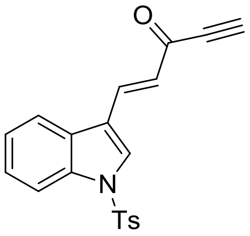
DMAP (105 mg, 0.86 mmol), Et_3N (1.9 ml, 13.8 mmol) and 4-toluenesulfonyl chloride (1.6 g, 8.6 mmol) were added to a solution of **41** (1.5 g, 8.6 mmol) in CH_2Cl_2 (80 ml), and the solution was stirred for 2 hours at rt. At the end of the reaction the solution was washed with water (2x70 ml) and brine (1x60 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure to afford substrate **42** as brown solid (91 % yield). ^{1}H-NMR ($CDCl_3$) δ: 9.68 (d, 1H, *J* = 7.6 Hz); 8.02 (d, 1H, *J* = 8.2 Hz); 7.95 (s, 1H); 7.84-7.80 (m, 3H); 7.59 (d, 1H, *J* = 16.1 Hz); 7.42 (td, 1H, *J* = 7.7, 1.2 Hz); 7.36 (td, 1H, *J* = 7.6, 1.2 Hz); 7.28 (d, 2H, *J* = 7.5 Hz); 6.81 (dd, 1H, *J* = 16.1, 7.6 Hz); 2.37 (s, 3H). Spectroscopic data for this compound were in agreement with the literature.[23]

*Synthesis of (E)-1-(1-tosyl-1H-indol-3-yl)pent-1-en-4-yn-3-ol (**43**)*



Substrate **43** was synthesized from **42** using *RP2* and isolated as a brown oil without further purifications (quant. yield). ^{1}H-NMR ($CDCl_3$) δ: 8.00 (d, 1H, *J* = 8.2 Hz); 7.78-7.74 (m, 3H); 7.65 (s, 1H); 7.36 (t, 1H, *J* = 7.6 Hz); 7.29 (t, 1H, *J* = 7.1 Hz); 7.23 (d, 2H, *J* = 8.4 Hz); 6.89 (dd, 1H, *J* = 16.0, 0.6 Hz); 6.40 (dd, 1H, *J* = 16.0, 5.9 Hz); 5.10 (d, 1H, *J* = 0.8 Hz); 2.67 (d, 1H, *J* = 2.2 Hz); 2.35 (s, 3H); 2.09 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 145.2; 135.5; 134.9; 129.9; 128.8; 128.7; 126.8; 125.1; 124.9; 123.6; 122.8; 120.4; 119.3; 113.8; 82.5; 74.7; 62.8; 21.5. MS (CI): *m/z* = 352 $[M]^+$. IR (film): ν (cm^{-1}) = 3291; 3056; 2924; 1598; 1447; 1368; 1265; 1173; 745; 665.

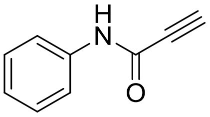
*Synthesis of (E)-1-(1-tosyl-1H-indol-3-yl)pent-1-en-4-yn-3-one (**44**)*



Substrate **44** was synthesized from **43** using *RP3* and isolated as a brown solid after recrystallization from Hexane/EtOAc. (75 % yield). ^{1}H-NMR (DMSO) δ: 8.67 (s, 1H); 8.08 (d, 1H, J = 16.3 Hz); 7.98 (d, 2H, J = 8.7 Hz); 7.94 (d, 2H, J = 8.7 Hz); 7.44 (dt, 1H, J = 7.3, 1.0 Hz); 7.42 (d, 2H, J = 8.7 Hz); 7.37 (dt, 1H, J = 7.3, 1.0 Hz); 7.01 (d, 1H, J = 16.3 Hz), 4.90 (s, 1H); 2.32 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 177.5; 145.8; 140.8; 135.7; 134.6; 130.2; 128.0; 127.6; 127.1; 125.9; 124.4; 120.8; 117.8; 113.9; 79.8; 79.5; 29.7; 21.6. MS (CI): *m/z* = 350 $[M]^+$. IR (film): ν (cm^{-1}) = 2098; 1625; 1172. m.p.: degradation > 170°C.

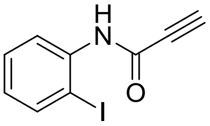
4.3.2 Synthesis of propargylamides

*4.3.2.1 Synthesis of N-phenyl-3-propiolamide (**46a**)*



A solution of *n*-BuLi 2.5 M in hexane (1.44 ml, 10.2 mmol) was added dropwise at 0°C to a solution of trimethylsilylacetylene (1.4 ml, 10.2 mmol)in THF (100 ml) under N_2. The reaction mixture was stirred at 0°C for 1 hour, then phenyl isocyanate (**45a**) (1.1 ml, 10.2 mmol) was added dropwise. When the reaction was complete, a saturated aqueous solution of NH_4Cl (50 ml) was added and the water phase extracted with CH_2Cl_2 (3x35 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was dissolved in THF (100 ml) at 0°C and was added tetrabutylammonium fluoride (3%) was added The reaction mixture was stirred at 0°C for 5 hours, then quenched with H_2O (50 ml). The water phase was extracted with Et_2O (3x35 ml), the combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification via flash chromatography (Hexane-EtOAc 7:3, 54 % yield) afforded **46a** as a brown oil. ^1H-NMR ($CDCl_3$) δ: 8.01 (br s, 1H); 7.54 (d, 2H, *J* = 8 Hz); 7.32 (2H, t, *J* = 8 Hz); 7.14 (1H, t, *J* = 8 Hz) ; 2.92 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[24]

*4.3.2.2 Synthesis of 1-hydroxy-N-(2-iodophenyl)-5-nitro-1H-indole-3-carboxamide (**46b**)*



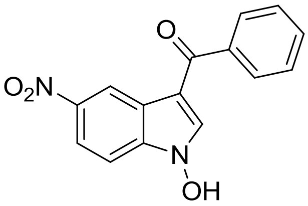
A solution of *n*-BuLi 2.5 M in hexane (1.6 ml, 4 mmol) was added dropwise at 0°C to a solution of trimethylsilylacetylene (575 μl, 4 mmol) in THF (40 ml), under N_2 atmosphere. The mixture was stirred at 0°C for 1h, then 2-iodo-phenylisocyanate (**45b**) (529 μl, 4 mmol) was added and the solution stirred at 0°C until the end of the reaction, then a saturated aqueous solution of NH_4Cl (30 ml) was added and the water phase extracted with CH_2Cl_2 (3x30 ml). The organic layers were combined, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was dissolved in THF, cooled at 0°C and a catalytic amount of TBAF was added (3%). The reaction was stirred for 2 h, the solvent removed under reduced pressure and substrate **46b** was obtained after flash chromatography (CH_2Cl_2, 60 % yield) as a yellow solid. ^1H-NMR ($CDCl_3$) δ: 8.19 (d, 1H, *J* = 8.1 Hz); 7.80 (d, 1H, *J* = 7.6 Hz); 7.27 (br s, 1H); 7.36 (td, 1H, *J* = 8.6, 1.1 Hz); 6.88 (t, 1H, *J* = 7.4 Hz); 3.01 (s, 1H). Spectroscopic data for this compound were in agreement with the literature.[25]

4.3.3 Synthesis of 3-aroylindoles

General Procedure for the synthesis of 3-aroyilindoles ***(GP4)***

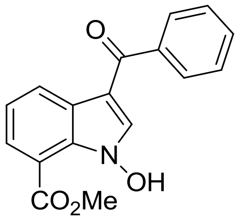
A mixture containing nitrosoarene (1.0 mmol), alkynole (1.0 mmol) in 10 ml of dry toluene was stirred at 80 °C for 5-12 h under nitrogen. The indole derivatives were obtained by filtration or flash chromatography over silica gel.

*4.3.3.1 Synthesis of (1-hydroxy-5-nitro-1H-indol-3-yl)(phenyl)methanone (**47a**)*



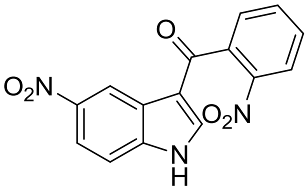
Substrate **47a** was synthesized from **18a** and **27a** using *GP4* and isolated by filtration (53 % yield) as a yellow solid. ^{1}H-NMR (DMSO-d$_6$) δ: 12.75 (s, 1H); 9.16 (d, 1H, *J* = 2.3 Hz); 8.39 (s, 1H); 8.22 (dd, 1H, *J* = 9.0, 2.3 Hz); 7.85 (dd, 1H, *J* = 7.5, 1.7 Hz); 7.75 (d, 2H, *J* = 9.0 Hz); 7.67 (td, 2H, *J* = 7.5, 1.7 Hz); 7.58 (td, 1H, *J* = 7.5, 1.7 Hz). ^{13}C-NMR (DMSO-d$_6$) δ: 189.0; 143.3; 139.4; 136.7; 136.5; 131.9; 128.7; 128.6; 122.1; 118.9; 118.3; 111.0; 110.4. MS (CI): *m/z* = 283[M]$^+$. IR (KBr): ν (cm^{-1}) = 1619; 1560; 1518; 1336; 850; 817; 740; 700. m.p.: 246-247°C.

*4.3.3.2 Synthesis of methyl 3-benzoyl-1-hydroxy-1H-indole-7-carboxylate (**47b**)*



Substrate **47b** was synthesized from **18e** and **27a** using *GP4* and isolated after flash chromatography over silica gel (EDP-EtOAc 8:2, 28 % yield) as an orange solid. ^{1}H-NMR (DMSO-d$_6$) δ: 12.94 (s, 1H); 8.85 (d, 1H, *J* = 7.8 Hz); 8.07 (d, 1H, *J* = 7.8 Hz); 7.85 (d, 2H, *J* = 7.0 Hz); 7.77 (s, 1H); 7.59 (t, 1H, *J* = 7.0 Hz); 7.52 (t, 2H, *J* = 7.0 Hz); 7.37 (t, 1H, J = 7.8 Hz); 4.10 (s, 3H). ^{13}C-NMR (DMSO-d$_6$) δ: 190.6; 170.7; 140.7; 135.2; 131.9; 131.8; 130.4; 129.1; 128.8; 128.5; 126.3; 122.3; 112.8; 111.2; 54.1. MS (CI): *m/z* = 296[M]$^+$. IR (KBr): ν (cm^{-1}) = 1666; 1631; 1601; 1520; 1440; 1385; 750; 700. m.p.: 99-100°C.

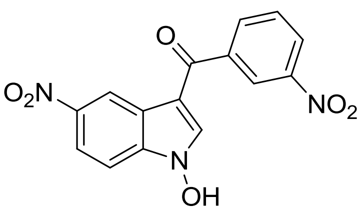
*4.3.3.3 Synthesis of (5-nitro-1H-indol-3-yl)(2-nitrophenyl)methanone (**47c**)*



Substrate **47c** was synthesized from **18a** and **27b** using *GP4* and isolated after flash chromatography (Toluene/EtOAc 5:5) and recrystallization from EtOAc/Hexane (33 % yield) as a brown solid. ^{1}H-

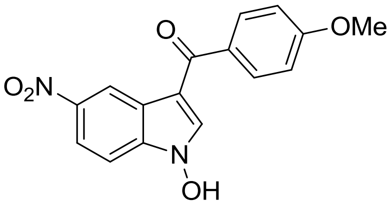
NMR (DMSO-d_6) δ: 9.02 (d, 1H, *J* = 2.3 Hz); 8.22 (dd, 1H, *J* = 8.2, 1.0 Hz); 8.18 (dd, 1H, *J* = 9.0; 2.3 Hz); 8.07 (s, 1H); 7.91 (td, 1H, *J* = 7.5, 1.2 Hz); 7.82 (td, 1H, *J* = 7.9, 1.5 Hz); 7.76 (dd, 1H, *J* = 7.4, 1.4 Hz); 7.72 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR (DMSO-d_6) δ: 187.6; 147.2; 143.5; 140.6; 140.0; 136.2; 134.8; 131.6; 129.7; 125.3; 125.2; 119.3; 117.9; 117.3; 113.9. MS (CI): *m/z* = 312 $[M]^+$. IR (film): ν (cm^{-1}) = 2725; 1616; 1526; 1461; 1377; 1112; 722. m.p.: 206°C.

4.3.3.4 Synthesis of (1-hydroxy-5-nitro-1H-indol-3-yl)(3-nitrophenyl)methanone (**47d**)



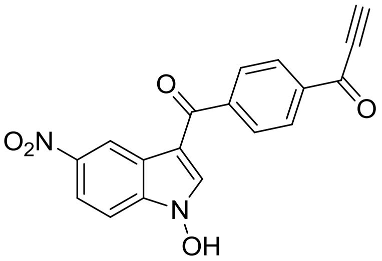
Substrate **47d** was synthesized from **18a** and **27c** using *GP4* and isolated by filtration (56 % yield) as a brown solid. ^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H); 9.14 (s, 1H); 8.62 (s, 1H); 8.54 (s, 1H); 8.47 (d, 1H, *J* = 8.1 Hz); 8.27-8.25 (m, 2H); 7.87 (t, 1H, *J* = 7.8 Hz); 7.78 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR (DMSO-d_6) δ: 187.5; 149.1; 145.5; 143.5; 137.4; 136.7; 129.8; 123.8; 122.0; 119.2; 118.1; 110.8; 110.5. MS (CI): *m/z* = 328 $[M]^+$. IR (KBr): ν (cm^{-1}) = 1620; 1589; 1568; 1533; 1338; 714. m.p.: 272-274°C.

4.3.3.5 Synthesis of (1-hydroxy-5-nitro-1H-indol-3-yl)(4-methoxyphenyl)methanone (**47e**)



Substrate **47e** was synthesized from **18a** and **27d** using *GP4* and isolated by filtration (37 % yield) as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ: 12.60 (s, 1H); 9.14 (s, 1H); 8.39 (s, 1H); 8.21 (d, 1H, *J* = 9.0 Hz); 7.87 (d, 2H, *J* = 8.4 Hz); 7.73 (d, 1H, *J* = 9.0 Hz); 7.11 (d, 2H, *J* = 8.4 Hz); 3.88 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ: 188.5; 163.2; 144.0; 137.2; 136.8; 132.5; 131.8; 123.1; 119.6; 119.2; 114.8; 112.0; 111.0; 56.4. MS (CI): *m/z* = 312 $[M]^+$. IR (KBr): ν (cm^{-1}) = 1604; 1572; 1521; 1473; 1367; 1331; 1176; 841. m.p.: 244-245°C.

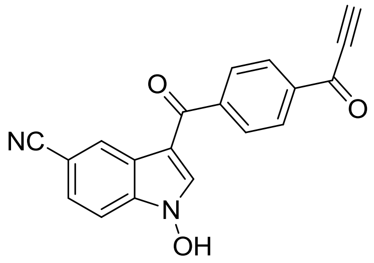
4.3.3.6 Synthesis of 1-(4-(1-hydroxy-5-nitro-1H-indole-3-carbonyl)phenyl)prop-2-yn-1-one (**47f**)



Substrate **47f** was synthesized from **18a** and **27e** using *GP4* and isolated by filtration as a yellow solid (40 % yield). ^{1}H-NMR (DMSO-d_6) δ: 12.69 (s, 1H); 9.17 (d, 1H, *J* = 2.2 Hz); 8.47 (s, 1H); 8.23-

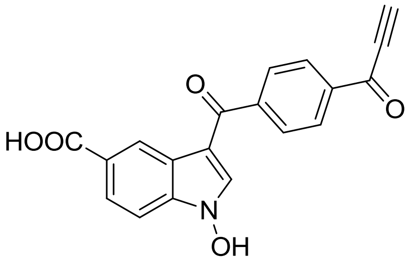
8.25 (m, 3H); 8.01 (d, 2H, *J* = 8.5 Hz); 7.77 (d, 1H, *J* = 9.0 Hz); 5.25 (s, 1H). ^{13}C-NMR (DMSO-d$_6$) δ: 167.3; 163.5; 143.9; 143.4; 140.4; 137.6; 130.0; 129.9; 129.2; 129.1;126.8; 119.5; 118.6; 112.3; 79.3; 73.5. MS (CI): *m/z* = 335 [M]$^+$. IR (film): ν (cm^{-1}) = 2096; 1583; 1520; 1340; 1244; 1217; 1180; 1112; 849; 739. m.p.: dec > 230°C.

*4.3.3.7 Synthesis of 1-hydroxy-3-(4-propioloylbenzoyl)-1H-indole-5-carbonitrile (**47g**)*



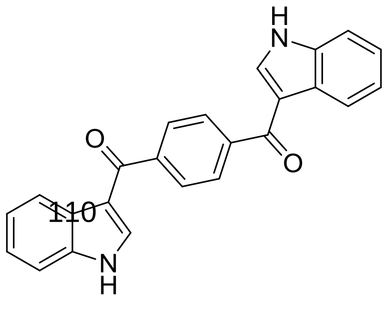
Substrate **47g** was synthesized from **18c** and **27e** using *GP4* and isolated by filtration as a yellow solid (63 % yield). ^{1}H-NMR (DMSO-d$_6$) δ: 12.57 (s, 1H); 8.67-8.66 (m, 1H); 8.41 (s, 1H); 8.26-8.24 (m, 1H); 8.24-8.22 (d, 2H, *J* = 8.6 Hz); 8.00-7.98 (d, 2H, *J* = 8.6 Hz); 7.75-7.74 (m, 1H); 5.25 (s, 1H). ^{13}C-NMR (DMSO-d$_6$) δ: 188.6; 177.1; 144.8; 137.9; 136.9; 136.0; 129.9; 129.5; 127.2; 127.1; 122.9; 120.3; 111.5; 110.1; 105.6; 87.3; 86.8. MS (CI): *m/z* = 315 [M]$^+$. IR (film): ν (cm^{-1}) = 3217; 2224; 2093; 1648; 1458; 1365; 1227; 832; 721. m.p.: carbon > 275C°.

*4.3.3.8 Synthesis of 1-hydroxy-3-(4-propioloylbenzoyl)-1H-indole-5-carboxylic acid (**47h**)*



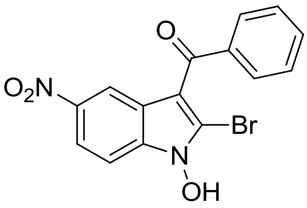
Substrate **47h** was synthesized from **18b** and **27e** (1,4-dioxane was used as solvent instead of toluene) using *GP4* and isolated by filtration as a yellow solid (43 % yield). ^{1}H-NMR (DMSO-d$_6$) δ: 12.50 (br s, 1H); 12.30 (br s, 1H); 9.00 (d, 1H, *J* = 0.9 Hz); 8.37 (d, 2H, *J* = 8.8 Hz); 8.32 (s, 1H);8.16 (d, 2H, *J* = 8.9 Hz); 7.96 (dd, 1H, *J* = 8.6, 0.9 Hz); 7.63 (d, 1H, *J* = 8.6 Hz); 5.23 (s, 1H). ^{13}C-NMR (DMSO-d$_6$) δ: 189.1; 168.3; 167.0; 146.9; 142.4; 137.0; 136.0; 134.7; 131.5; 125.7; 125.4; 124.6; 112.9; 110.8; 109.8; 78.9; 74.1. MS (CI): *m/z* = 334 [M]$^+$. IR (film): ν (cm^{-1}) = 2979; 2833; 2674; 1693; 1449; 1377; 1296; 722; 699. m.p.: deg > 250°C.

*4.3.3.9 Synthesis of 1,4-phenylenebis((1H-indol-3-yl)methanone)) (**48**)*



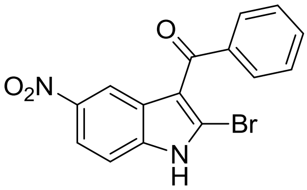
Substrate **48** was synthesized from nitrosobenzene **18g** and **27e** using *GP4* and isolated by flash chromatography (toluene-EtOAc 7:3) as a yellow solid (65 % yield). ^{1}H-NMR (DMSO-d$_6$) δ: 12.16 (br s, 2H); 8.33 (d, 2H, *J* = 8.2 Hz); 8.18 (s, 2H); 7.90 (s, 4H); 7.56(d, 2H, *J* = 8.2 Hz); 7.37-7.30 (m, 4H). ^{13}C-NMR (DMSO-d_6) δ: 189.1; 142.6; 137.2; 134.5; 134.3; 128.9; 124.2; 123.4; 123.3; 122.1; 109.9. MS (CI): *m/z* = 397 $[M]^+$. IR (film): ν (cm^{-1}) = 2982; 1599; 1461; 1377; 1219; 723. m.p.: deg > 194°C.

*4.3.3.10 Synthesis of (2-bromo-1-hydroxy-5-nitro-1H-indol-3-yl)(phenyl)methanone (**49**)*



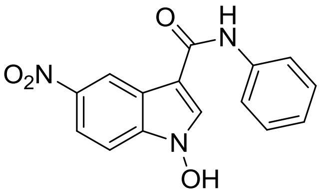
Substrate **49** was synthesized from **18a** and **28** using *GP4* and isolated by filtration (35 % yield) as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ: 7.79 (dd, 1H, *J* = 2.2, 0.4 Hz); 7.41 (dd, 1H, *J* = 9.0, 2.2 Hz); 6.95 (d, 2H, *J* = 7.6 Hz); 6.89-6.84 (m, 2H); 6.74 (t, 2H, *J* = 7.6 Hz). ^{13}C-NMR (DMSO-d_6) δ: 179.3; 142.7; 138.3; 135.5; 131.5; 128.1; 127.5; 121.7; 120.9; 120.6; 117.6; 116.0; 108.3. MS (CI): *m/z* = 362/360 [*M*+1 (^{81}Br/^{79}Br)]. IR (film): ν (cm^{-1}) = 3152; 1829; 1772; 1584; 1521; 1336; 1193; 1079; 848; 820; 736. m.p.: 157°C.

*4.3.3.1 Synthesis of (2-bromo-5-nitro-1H-indol-3-yl)(phenyl)methanone (**50**)*



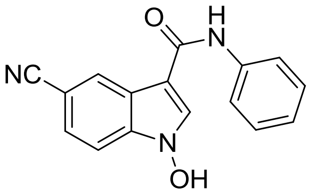
A solution of **49** (100 mg, 0.28 mmol) and 2-bromo-1-phenylethanone (**63**) (60 mg, 0.28 mmol) in MeOH (5 ml) was stirred at rt for 5 minutes. Et_3N (0.96 ml, 0.69 mmol) was added and the reaction mixture was stirred at 40 °C for 2 days. After 72 hours the starting materials were still present, the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (toluene-EtOAc 8:2, 15% yield) to afford **50** as a brown oil. ^{1}H-NMR (acetone-d_6) δ: 12.15 (br s, 1H); 8.63 (d, 1H, *J* = 2.3 Hz); 8.17 (dd, 1H, *J* = 9.0 Hz, 2.3 Hz); 7.84-7.82 (m, 2H); 7.71-7.66 (m, 2H); 7.56 (t, 2H, *J* = 7.5 Hz). ^{13}C-NMR (acetone-d_6) δ: 190.1; 143.2; 139.4; 139.2; 132.4; 129.2; 128.5; 126.9; 119.0; 118.5; 117.0; 116.7; 111.8. IR (film): ν (cm^{-1}) = 1775; 1571; 1521; 1357; 1198; 1088; 850.

*4.3.3.2 Synthesis of 1-hydroxy-5-nitro-N-phenyl-1H-indole-3-carboxamide (**51**)*



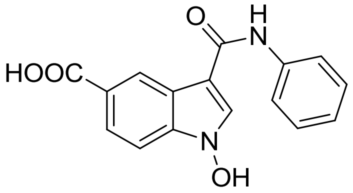
Substrate **51** was synthesized from **18a** and **46a** using *GP4* and isolated as a brown solid by filtration (14 % yield). ^{1}H-NMR (DMSO-d_6) δ: 9.87 (br s, 1H); 9.16 (dd, 1H, *J* = 2.0, 0.4 Hz); 8.67 (s, 1H); 8.13 (dd, 1H, *J* = 9.2, 2.4 Hz); 7.76 (dd, 2H, *J* = 8.4, 0.8 Hz); 7.67 (d, 1H, *J* = 8.8 Hz); 7.35 (t, 2H, *J* = 8.0 Hz); 7.08 (t, 1H, *J* = 7.4 Hz). ^{13}C-NMR (DMSO-d_6) δ : 162.0; 142.7; 139.6; 136.2; 131.4; 129.1; 123.7; 122.4; 120.4; 118.7; 118.4; 110.3; 107.7. MS (CI): *m/z* = 298 $[M]^+$. IR (KBr): v (cm^{-1}) = 2682, 1635, 1601, 1541, 1513, 1442, 1374, 1323, 1293, 746, 686. m.p.: 270-274 °C.

4.3.3.3 Synthesis of 5-cyano-1-hydroxy-N-phenyl-1H-indole-3-carboxamide (52)



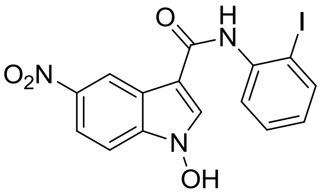
Substrate **52** was synthesized from **18c** and **46a** using *GP4* and isolated as a brown solid by filtration (11 % yield). ^{1}H-NMR (DMSO-d_6) δ: 12.36 (br s, 1H); 9.83 (s, 1H); 8.63 (s, 2H); 7.75 (d, 2H, *J* = 7.6 Hz); 7.67 (d, 1H, *J* = 8.5 Hz); 7.62 (dd, 1H, *J* = 8.5, 1.4 Hz); 7.35 (t, 2H, *J* = 7.9 Hz); 7.07 (t, 1H, *J* = 7.3 Hz).^{13}C-NMR (DMSO-d_6) δ: 162.3; 139.7; 135.1; 130.4; 129.1; 127.1; 125.8; 123.6; 122.9; 120.6; 120.4; 111.0; 106.3; 103.9. MS (CI): *m/z* = 278 $[M]^+$. IR (KBr): v (cm^{-1}) = 3340; 2217; 1629; 1538. m.p. : 278-280 °C.

4.3.3.4 Synthesis of 1-hydroxy-3-(phenylcarbamoyl)-1H-indole-5-carboxylic acid (53)



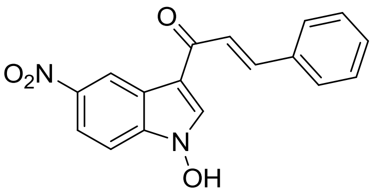
Substrate **53** was synthesized from **18b** and **46a** using *GP4* (1,4-dioxane was used as solvent instead of toluene) and isolated by flash chromatography (EDP/EtOAc 5:5, 15 % yield) as a brown oil. ^{1}H-NMR (DMSO-d_6) δ: 10.48 (br s, 1H); 9.76 (s, 1H); 8.93 (d, 1H, *J* = 0.4 Hz); 8.10 (s, 1H); 7.86 (dd, 1H, *J* = 8.5, 1.4 Hz); 7.75 (d, 2H, *J* = 8.2 Hz); 7.54 (d, 1H, *J* = 8.5 Hz); 7.34 (t, 2 H, *J* = 7.6 Hz); 7.05 (t, 1H, *J* = 7.5 Hz). ^{13}C-NMR (DMSO-d_6) δ: 168.5; 166.6; 146.9; 139.9; 131.8; 129.1; 125.4; 124.5; 124.2; 123.4; 122.1; 120.3; 109.3; 106.6. MS (CI): *m/z* = 297 $[M]^+$. IR (film): v (cm^{-1}) = 2553 ; 1700 ; 1603 ; 1564 ; 1312 ; 1295 ; 1267 ; 1121 ; 935 ; 871 ; 774, 690.

4.3.3.5 Synthesis of 1-hydroxy-N-(2-iodophenyl)-5-nitro-1H-indole-3-carboxamide (54)



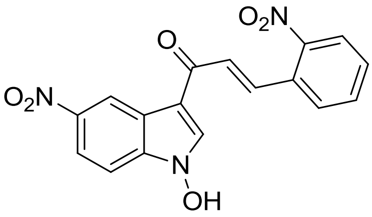
Substrate **57** was synthesized from **18a** and **46b** using *GP4* and isolated by filtration (22 % yield) as a brown solid. ^{1}H-NMR (DMSO-d_6) δ: 12.47 (bs, 1H); 9.71 (s, 1H); 9.11 (d, 1H, *J* = 2.3 Hz); 8.63 (s, 1H); 8.15 (dd, 1H, *J* = 9.1, 2.3 Hz); 7.94 (dd, 1H, *J* = 7.8, 1.1 Hz); 7.70 (d, 1H, *J* = 9.1 Hz); 7.51-7.43 (m, 2H); 7.06 (td, 1H, *J* = 7.6, 1.8 Hz. Degradation.

4.3.3.6 *Synthesis of (E)-1-(1-hydroxy-5-nitro-1H-indol-3-yl)-3-phenylprop-2-en-1-one (**55**)*



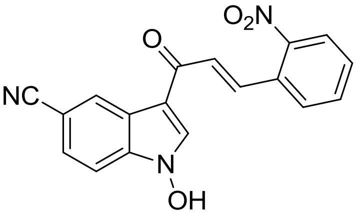
Substrate **55** was synthesized from **18a** and **30** using *GP4* and isolated by filtration (61 % yield) as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ: 12.67 (s, 1H); 9.24 (d, 1H, *J* = 2.2 Hz); 9.23 (s, 1H); 8.21 (dd, 1H, *J* = 9.0, 2.2 Hz); 7.90 (dd, 2H, *J* = 7.9, 1.6 Hz); 7.86 (d, 1H, *J* = 15.7 Hz); 7.75 (d, 1H, *J* = 9.0 Hz); 7.71 (d, 1H, *J* = 15.7 Hz); 7.51-7.45 (m, 3H). ^{13}C-NMR (DMSO-d_6) δ: 183.9; 144.1; 142.2; 137.2; 135.2; 134.0; 130.5; 129.2; 128.6; 123.5; 122.4; 120.0; 119.2; 114.5; 109.8. MS (CI): *m/z* = 309 $[M]^+$. IR (KBr): ν (cm^{-1}) = 1630; 1575; 1525; 1313; 974; 744; 680. m.p.: 282-283°C.

4.3.3.7 *Synthesis of (E)-1-(1-hydroxy-5-nitro-1H-indol-3-yl)-3-(2-nitrophenyl)prop-2-en-1-one (**59a**)*



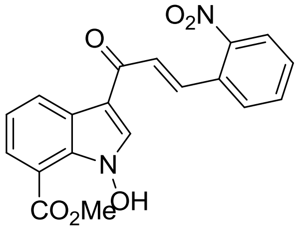
Substrate **56** was synthesized from **18a** and **27f** using *GP4* and isolated by filtration (50 % yield) as a brown solid. ^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H); 9.21-9.20 (m, 2H); 8.22-8.19 (m, 2H); 8.08 (dd, 1H, *J* = 8.1, 1 Hz); 7.95 (d, 1H, *J* = 15.4 Hz); 7.86-7.82 (m, 2H); 7.74 (d, 1H, *J* = 9 Hz); 7.70 (dt, 1H, *J* = 8.3, 1.3 Hz). ^{13}C-NMR (DMSO-d_6) δ: 182.9; 149.3; 143.9; 137.2; 137.1; 135.8; 134.0; 131.2; 130.2; 129.7; 128.6; 125.1; 122.1; 119.5; 118.8; 113.8; 110.8. MS (CI): *m/z* = 354 $[M]^+$. IR (film): ν (cm^{-1}) = 1580; 1568; 1510; 1342; 1314; 1153; 1055; 969; 784. m.p.: carbon. > 300°C.

4.3.3.8 *Synthesis of (E)-1-hydroxy-3-(3-(2-nitrophenyl)acryloyl)-1H-indole-5-carbonitrile (57)*



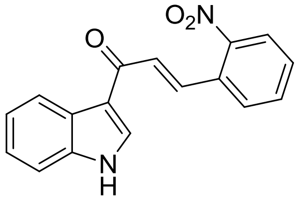
Substrate **57** was synthesized from **18c** and **27f** using *GP4* and isolated by filtration (33 % yield) as a yellow solid. ^{1}H-NMR (acetone-d$_6$) δ: 11.53 (bs, 1H); 8.89 (s, 1H); 8.83 (dd, 1H, *J* = 1.4, 0.7 Hz); 8.14-8.08 (m, 3H); 7.82 (td, 1H, *J* = 7.6, 0.8 Hz); 7.77-7.66 (m, 4H). ^{13}C-NMR (acetone-d$_6$) δ: 182.5; 149.3; 135.9; 135.7; 134.3; 133.4; 130.5; 130.4; 129.1; 128.1; 127.4; 126.6; 124.6; 122.7; 119.5; 112.8; 110.5; 105.9. MS (CI): *m/z* = 334 [M]$^+$. IR (film): ν (cm^{-1}) = 2924, 2854, 2225, 1643, 1603, 1514, 1452, 1345, 1205, 1069, 973, 740. m.p. : degradation from 270°C.

*4.3.3.9 Synthesis of (E)-methyl 1-hydroxy-3-(3-(2-nitrophenyl)acryloyl)-1H-indole-7-carboxylate (**58**)*



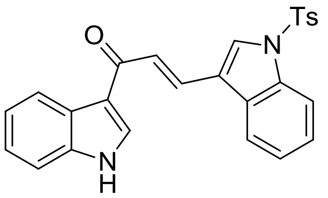
Substrate **58** was synthesized from **18e** and **27f** using *GP4* and isolated by filtration (15 % yield) as a brown solid. ^{1}H-NMR (acetone-d$_6$) δ: 12.66 (bs, 1H); 8.85 (d, 1H, *J* = 7.6 Hz); 8.74 (s, 1H); 8.17 (d, 1H, *J* = 7.6 Hz); 8.12-8.07 (m, 2H); 8.02 (d, 1H, *J* = 7.9 Hz); 7.84-7.77 (m, 2H); 7.70 (m, 1H); 7.42 (t, 1H, *J* = 7.9 Hz); 4.10 (s, 3H).^{13}C-NMR (acetone-d$_6$) δ: 182.3; 169.6; 166.0; 149.4; 139.6; 135.2; 133.3; 131.3; 130.3; 129.1; 128.9; 128.5; 127.6; 125.3; 124.6; 123.1; 122.0; 112.7; 53.2. MS (CI): *m/z* = 367 [M]$^+$. IR (film): ν (cm^{-1}) = 3447, 1684, 1654, 1559, 1521, 1507, 1437, 1340, 1266, 1199, 1143, 756. m.p.: 202-205°C.

*4.3.3.10 Synthesis of (E)-1-(1H-indol-3-yl)-3-(2-nitrophenyl)prop-2-en-1-one (**59**)*



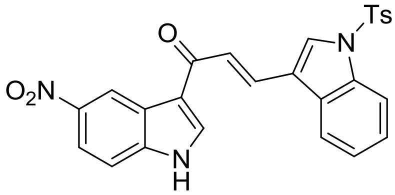
Substrate **59** was synthesized from **18g** and **27f** using *GP4* and isolated after filtration and flash chromatography (Hexane-EtOAc 7:3, 53% yield) as a brown solid. ^{1}H-NMR (acetone-d$_6$) δ: 11.20 (br s, 1H); 8.58 (d, 1H, *J* = 3.2 Hz); 8.49-8.46 (m, 1H); 8.13-8.06 (m, 3H); 7.80 (td, 1H, *J* = 7.3, 1.3 Hz); 7.75 (d, 1H, *J* = 15.4 Hz); 7.68 (td, 1H, *J* = 8.5, 1.4 Hz); 7.55-7.53 (m, 1H); 7.29-7.26 (m, 2H). ^{13}C-NMR (acetone-d$_6$) δ: 183.0; 149.3; 137.2; 134.4; 133.8; 133.3; 130.8; 130.1; 129.0; 128.9; 126.3; 126.5; 124.5; 122.3; 122.1; 118.3; 111.9. MS (CI): *m/z* = 293 [M]$^+$. IR (film): ν (cm^{-1}) = 3359; 2953; 2924; 2854; 1691; 1642; 1521; 1343; 1153; 972; 854; 747. m.p.: 194-196°C.

*4.3.3.11 Synthesis of (E)-1-(1H-indol-3-yl)-3-(1-tosyl-1H-indol-3-yl)prop-2-en-1-one (**60**)*



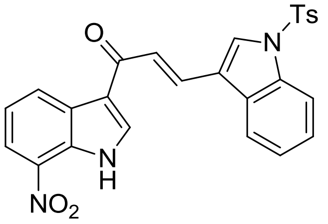
Substrate **60** was synthesized from **18g** and **44** using *GP4* and isolated after flash chromatography (Toluene/EtOAc 9:1, 32 % yield) as a brown solid. ^{1}H-NMR (DMSO-d$_6$) δ: 12.10 (br s, 1H); 8.74 (d, 1H, *J* = 2.8 Hz); 8.53 (s, 1H); 8.34 (dd, 1H, *J* = 7.2, 2.4 Hz); 8.14 (dd, 1H, *J* = 7.2, 1.2 Hz); 7.98 (dd, 1H, *J* = 7.6, 1.2 Hz); 7.92 (d, 2H, *J* = 8.4 Hz); 7.84 (d, 1H, *J* = 15.6 Hz); 7.79 (d, 1H, *J* = 15.6 Hz); 7.51 (dd, 1H, *J* = 6.8, 1.2 Hz); 7.48-7.33 (m, 4H); 7.29-7.17 (m, 2H); 2.32 (s, 3H). ^{13}C-NMR (DMSO-d$_6$) δ: 182.1; 137.3; 135.3; 135.2; 134.2; 130.9; 130.6; 129.3; 129.2; 127.5; 127.3; 127.2; 126.0; 125.0; 124.7; 123.6; 122.4; 122.3; 122.2; 121.6; 119.2; 113.8; 112.6; 21.5. MS (CI): *m/z* = 441 [M]$^{+}$. IR (film): ν (cm^{-1}) = 3360; 2918; 1642; 1527; 739. m.p.: 176°C.

*4.3.3.12 Synthesis of (E)-1-(5-nitro-1H-indol-3-yl)-3-(1-tosyl-1H-indol-3-yl)prop-2-en-1-one (**61**)*



Substrate **61** was synthesized from **18a** and **44** using *GP4* and isolated after flash chromatography (Toluene/EtOAc 8:2, 30 % yield) as a brown solid. ^{1}H-NMR (acetone-d$_6$) δ: 11.64 (br s, 1H); 9.43 (d, 1H, *J* = 2.4 Hz); 8.83 (d, 1H, *J* = 2.8 Hz); 8.36 (s, 1H); 8.20 (dd, 1H, *J* = 8.8, 2.0 Hz); 8.14 (d, 1H, *J* = 8.4 Hz); 8.09 (d, 1H, *J* = 84 Hz); 8.00 (d, 1H, *J* = 15.8 Hz); 7.97 (d, 2H, *J* = 8.8 Hz); 7.87 (d, 1H, *J* = 15.8 Hz); 7.76 (d, 2H, *J* = 9.2); 7.47 (td, 1H, *J* = 7.6, 1.2 Hz); 7.43-7.38 (m, 2H); 2.37 (s, 3H). ^{13}C-NMR (acetone-d$_6$) δ: 182.3; 146.0; 136.1; 134.7; 134.5; 131.9; 130.3; 130.2; 129.0; 127.2; 127.1; 125.4; 124.5; 124.2; 124.1; 123.8; 121.0; 119.1; 119.0; 118.8; 118.6; 113.7; 112.5; 20.5. MS (CI): *m/z* = 486 [M]$^{+}$. IR (film): ν (cm^{-1}) = 3583; 3184; 2921; 1721; 1640; 1525; 1376; 1337; 1261; 800, 634. m.p.: degradation from 128 °C.

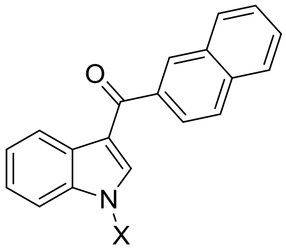
*4.3.3.13 Synthesis of (E)-1-(7-nitro-1H-indol-3-yl)-3-(1-tosyl-1H-indol-3-yl)prop-2-en-1-one (**62**)*



Substrate **62** was synthesized from **18d** and **44** using *GP4* and isolated after flash chromatography (Hexane/EtOAc 5:5, 45 % yield) as a brown oil. ^{1}H-NMR (DMSO-d$_6$) δ: 9.15 (s, 1H); 7.40 (d, 1H, *J* = 7.4 Hz); 8.57 (s, 1H); 8.19 (d, 1H, *J* = 7.6 Hz); 7.97 (d, 1H, *J* = 8.1 Hz); 7.92 (d, 2H, *J* = 8.4 Hz); 7.87 (d, 1H, *J* = 15.6 Hz); 7.85 (d, 1H, *J* = 7.9 Hz); 7.80 (d, 1H, *J* = 15.6 Hz); 7.42 (m, 5H); 2.32 (s, 3H). ^{13}C-NMR (DMSO-d$_6$) δ: 183.5; 146-5; 136.6; 136.0; 135.2; 134.2; 132.1; 130.9; 129.9; 128.5; 127.5; 127.3; 126.1; 126.7; 124.1; 122.4; 121.8; 120.2; 119.0;

113.8; 113.0; 21.5. MS (CI): *m/z* = 486 $[M]^+$. IR (film): ν (cm^{-1}) = 3579; 3190; 2903; 1719; 1640; 1527; 1374; 1335; 1261; 806.

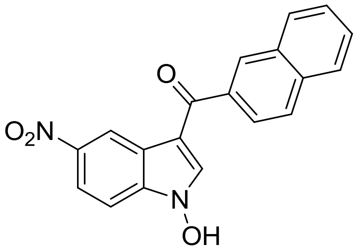
*4.3.3.14 Synthesis of (1-hydroxy-1H-indol-3-yl)(naphthalen-2-yl)methanone (**63**) and (1H-indol-3-yl)(naphthalen-2-yl)methanone (**64**)*



Substrates **63** and **64** were synthesized from **18g** and **27g** using *GP4* and isolated after flash chromatography over silica gel (Hexane-EtOAc 7:3) as orange solids (**63** 36 % yield, **64** 15 % yield).

63, X = OH ^{1}H-NMR (DMSO-d_6) δ: 12.17 (br s, 1H); 8.25 (dd, 1H, *J* = 7.3, 0.9 Hz); 8.08 (d, 1H, *J* = 8.1 Hz); 8.00 (td, 2H, *J* = 7.3, 0.9 Hz); 7.73 (s, 1H); 7.68 (dd, 1H, *J* = 7.0, 1.3 Hz); 7.61 (d, 1H, *J* = 8.1 Hz); 7.60 (t, 1H, *J* = 8.1 Hz); 7.57-7.49 (m, 2H); 7.35 (td, 1H, *J* = 8.0, 1.3 Hz); 7.30 (td, 1H, *J* = 8.0, 1.3 Hz). ^{13}C-NMR (DMSO-d_6) δ: 190.7; 138.4; 134.3; 134.0; 133.4; 130.1; 130.0; 128.5; 126.9; 126.4; 125.9; 125.3.; 125.1; 123.8; 123.1; 122.7; 121.6; 111.6; 109.6. MS (CI): *m/z* = 288 $[M]^+$.IR (KBr): ν (cm^{-1}) = 1594; 1503; 1364; 1318; 1224; 787; 746. m.p.: 182-184°C. **64, X = H** ^{1}H-NMR (DMSO-d_6) δ: 12.03 (s, 1H); 8.26 (d, 1H, *J* = 8.3 Hz); 8.07 (d, 1H, *J* = 8.1 Hz); 8.01 (d, 1H, *J* = 8.0 Hz); 7.98 (d, 1H, *J* = 8.3 Hz); 7.67 (dd, 1H, *J* = 8.1, 1.3 Hz); 7.65 (d, 1H, *J* = 3.2 Hz); 7.61 (t, 1H, *J* = 8.1 Hz); 7.56 (td, 1H, *J* = 8.0, 1.3 Hz); 7.52 (td, 1H, *J* = 8.0, 1.3 Hz); 7.50 (td, 1H, *J* = 8.3, 1.5 Hz); 7.30-7.24 (m, 2H). ^{13}C-NMR (DMSO-d_6) δ: 191.7; 138.7; 137.1; 136.9; 133.4; 130.2; 129.8; 128.4; 126.9; 126.4; 125.9; 125.8.; 125.4; 125.1; 123.5; 122.4; 121.5; 117.3; 112.6. MS (CI): *m/z* = 272 $[M]^+$. IR (KBr): ν (cm^{-1}) = 1597; 1513; 1430; 1383; 1097; 785; 746. m.p.: 273°C.

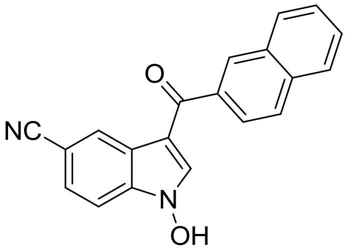
*4.3.3.15 Synthesis of (1-hydroxy-5-nitro-1H-indol-3-yl)(naphthalen-2-yl)methanone (**65**)*



Substrate **65** was synthesized from **18a** and **27g** using *GP4* and isolated by filtration as an orange solid (68 % yield). ^{1}H-NMR (DMSO-d_6) δ: 12.60 (br s, 1H); 9.19 (d, 1H, *J* = 2.3 Hz); 8.24 (dd, 1H, *J* = 9.0, 2.3 Hz); 8.13 (d, 1H, *J* = 7.0 Hz); 8.11 (s, 1H); 8.06 (dd, 1H, *J* = 7.9, 0.7 Hz); 8.04 (d, 1H, *J* = 7.9 Hz); 7.77 (dd, 1H, *J* = 7.0, 1.0 Hz); 7.74 (d, 1H, *J* = 9.0 Hz); 7.63 (td, 1H, *J* = 7.0, 1.0 Hz); 7.59 (td, 1H, *J* = 7.9, 1.3 Hz); 7.55 (td, 1H, *J* = 7.9, 1.3 Hz). ^{13}C-NMR (DMSO-d_6) δ: 190.6; 143.6; 137.5; 137.2; 136.8; 133.4; 130.6; 130.0;

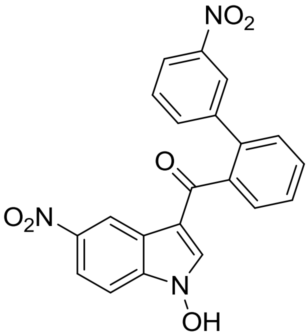
128.5; 127.1; 126.6; 126.5.; 125.2; 125.0; 121.8; 119.0; 118.2; 113.1; 110.5. MS (CI): *m/z* = 333 $[M]^+$. IR (KBr): ν (cm^{-1}) = 1602; 1578; 1517; 1334; 775. m.p.: 268-270°C.

*4.3.3.16 Synthesis of 3-(2-naphthoyl)-1-hydroxy-1H-indole-5-carbonitrile (**66**)*



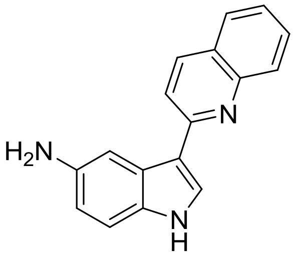
Substrate **66** was synthesized from **18c** and **27g** using *GP4* and isolated by filtration as an orange solid (30 % yield). ^{1}H-NMR (DMSO-d_6) δ: 12.54 (br s, 1H); 8.66 (d, 1H, *J* = 1.0 Hz); 8.12 (d, 1H, *J* = 8.2 Hz); 8.04 (s, 1H); 8.03 (d, 2H, *J* = 8.0 Hz); 7.74 (dd, 1H, *J* = 8.0, 1.0 Hz); 7.73-7.72 (m, 2H); 7.63 (dd, 1H, *J* = 8.2, 1.0 Hz); 7.58 (td, 1H, *J* = 8.0, 1.4 Hz); 7.53 (td, 1H, *J* = 8.0, 1.4 Hz). ^{13}C-NMR (DMSO-d_6) δ: 190.6; 137.4; 136.5; 135.7; 133.5; 130.5; 130.0; 128.5; 127.1; 126.8; 126.5.; 125.2; 125.1; 122.3; 120.0; 112.0; 111.2; 105.2. MS (CI): *m/z* = 313 $[M]^+$. IR (KBr): ν (cm^{-1}) = 2221; 1571; 1509; 1364; 1341; 1225; 775. m.p.: 272-274°C.

*4.3.3.17 Synthesis of (1-hydroxy-5-nitro-1H-indol-3-yl)(3'-nitro-[1,1'-biphenyl]-2-yl)methanone (**67**)*



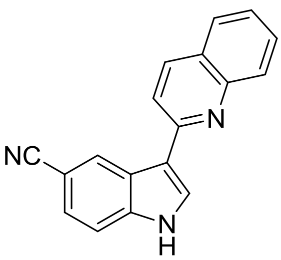
Substrate **67** was synthesized from **18a** and **36** using *GP4* and isolated by filtration and ricrystallization from hot ethanol as a brown solid (32% yield). ^{1}H-NMR (DMSO-d_6) δ: 14.78 (br s, 1H); 9.71 (s, 1H); 9.52 (d, 1H, J = 1.8 Hz); 8.94 (d, 1H, J = 8.3 Hz); 8.56 (d, 1H, J = 8.0 Hz); 8.49-8.36 (m, 5H); 8.35 (dd, 1H, J = 9, 1.8 Hz); 7.96 (t, 1H, J = 7.2 Hz); 7.83 (t, 1H, J = 7.4 Hz). ^{13}C-NMR (DMSO-d_6) δ: 166.2; 157.2; 148.7; 148.3; 145.3; 144.8; 136.5; 133.4; 132.8; 129.2; 128.4; 126.2; 125.6; 125.4; 125.2; 124.2; 123.9; 122.4; 121.9; 119.6; 112.8. MS (CI): *m/z* = 404 $[M]^+$. IR (film): ν (cm^{-1}) = 1663; 1568; 1532; 1342; 1338; 1125; 969; 800. Degradation.

*4.3.3.18 Synthesis of 3-(quinolin-2-yl)-1H-indol-5-amine (**68**)*



To a solution of **56** (100 mg, 0.28 mmol) in MeOH (6 ml) under nitrogen atmosphere, were added a saturated solution of NH_4Cl (12 ml) and In powder (163 mg, 1.42 mmol). The mixture was refluxed for 12 hours, cooled to rt and filtered over silica gel (EtOAc). To the aqueous layer was added an aqueous solution of NaOH 1M until pH 9, then was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography (Toluene/EtOAc 6:4, 10 % yield) to afford **68** as a brown solid. ^{1}H-NMR ($CDCl_3$) δ: 8.31 (br s, 1H); 8.18-8.10 (m, 3H); 7.83 (d, 1H, *J* = 1.8 Hz); 7.87 (d, 2H, *J* = 8.6 Hz); 7.70 (t, 1H, *J* = 7.5 Hz); 7.46 (t, 1H, *J* = 7.5 Hz); 7.25 (d, 1H, *J* = 8.6 Hz); 6.77 (dd, 1H, *J* = 8.6, 1.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 155.4; 148.5; 141.1; 135.9; 131.7; 129.3; 129.0; 127.4; 127.4; 126.8; 126.3; 125.7; 125.1; 119.3; 113.6; 111.7; 107.2. MS (CI): *m/z* = 260 $[M]^+$. IR (film): ν (cm^{-1}) = 3583; 3371; 1601; 1536; 1462; 1240; 1140; 801. m.p.: 178°C.

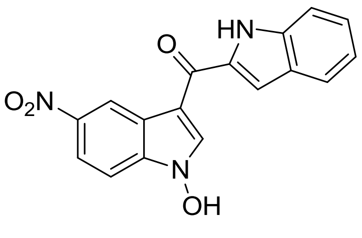
*4.3.3.19 Synthesis of 3-(quinolin-2-yl)-1H-indole-5-carbonitrile (**69**)*



Substrate **57** (102 mg, 0.31 mmol) was dissolved in a solution of MeOH (6 ml) and 1,4-dioxane (2 ml) under nitrogen atmosphere. A saturated solution of NH_4Cl (15 ml) and In powder (175 mg, 1.53 mmol) were added to the solution. The mixture was refluxed for 12 hours, cooled to rt and filtered over silica gel (MeOH). The crude residue was purified by flash chromatography (toluene-EtOAc 7:3) and **69** was obtained as a brown solid. (24 % yield). ^{1}H-NMR (acetone-d_6) δ: 11.28 (br s, 1H); 9.47 (dd, 1H, *J* = 1.6, 0.7 Hz); 8.45 (d, 1H, *J* = 2.8 Hz); 8.27 (dd, 1H, *J* = 8.7, 0.4 Hz); 8.18 (dd, 1H, *J* = 8.4, 1.0 Hz); 8.04 (d, 1H, *J* = 8.7 Hz); 7.89 (dd, 1H, *J* = 8.1, 1.4 Hz); 7.76 (td, 1H, *J* = 7.7, 1.4 Hz); 7.71 (dd, 1H, *J* = 8.4, 0.7 Hz); 7.56-7.51 (m, 2H).^{13}C-NMR (acetone-d_6) δ: 154.7; 148.3; 139.3; 136.0; 129.5; 129.0; 128.9; 128.6; 127.6; 126.5; 126.0; 125.4; 125.1; 120.4; 118.9; 117.1; 112.9; 103.6. MS (CI): *m/z* = 270 $[M]^+$. IR (film): ν (cm^{-1}) = 3386; 2923; 2854; 2224; 1600; 1524; 1440; 1261; 1093; 803. m.p.: 250°C.

*4.3.3.1 Synthesis of (1-hydroxy-5-nitro-1H-indol-3-yl)(1H-indol-2-yl)methanone (**70**)*

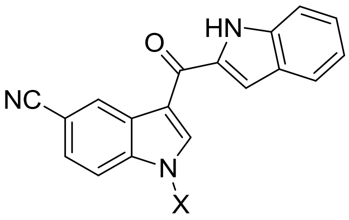
Representative Procedure for the synthesis of bis-indole compounds using PPh_3 ***(RP5)***



Substrate **56** (50 mg, 0.16 mmol) and PPh_3 (168 mg, 0.64 mmol) were stirred under microwaves irradiation for 5 minutes at 200 W and 100°C. The reaction mixture was then diluted with acetone, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography (first eluting with EDP/EtOAc 5:5 to eliminate side products, then with MeOH, 33 % yield) and **70** was isolated as a brown solid. ^{1}H-NMR (DMSO-d_6) δ: 9.12 (d, 1H, *J* = 2.2 Hz); 8.60 (s, 1H); 8.24 (dd, 1H, *J* =

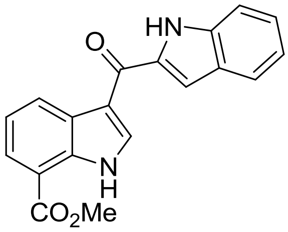
8.2, 1.2 Hz); 8.01 (dd, 1H, *J* = 8.2, 1.1 Hz); 7.89 (dd, 1H, *J* = 9, 2.4 Hz); 7.78 (td, 1H, *J* = 7.6, 1.2 Hz); 7.75 (s, 1H); 7.62 (td, 1H, *J* = 7, 1.3 Hz); 7.57 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR (DMSO-d_6) δ: 178.7; 175.3; 149.3; 142.5; 139.7; 136.3; 133.8; 132.5; 132.0; 130.6; 129.4; 124.8; 123.0; 118.6; 116.0; 112.2; 110.5. MS (CI): *m/z* = 322 $[M]^+$. IR (film): ν (cm^{-1}) = 3419; 1641; 1557; 1416; 1374; 1336; 1199; 1113; 1023; 869; 800. m.p. : 298-300°C.

4.3.3.2 Synthesis of 1-hydroxy-3-(1H-indole-2-carbonyl)-1H-indole-5-carbonitrile (**71**) and 3-(1H-indole-2-carbonyl)-1H-indole-5-carbonitrile (**72**)



Substrates **71** and **72** were synthesized from **57** and PPh$_3$ using *RP5* and isolated after flash chromatography over silica gel, elution with Hexane/EtOAc (5:5) afforded **72** (25 % yield), then elution with MeOH gained **71** (32 % yield), both as brown solids. **71, X = OH** : ^{1}H-NMR (DMSO-d_6) δ: 8.56 (d, 1H, *J* = 1.1 Hz); 8.51 (s, 1H); 8.22 (dd, 1H, *J* = 7.8, 0.3 Hz); 8.00 (dd, 1H, *J* = 8.1; 1.2 Hz); 7.77 (td, 1H, *J* = 7.6, 1.3 Hz); 7.72 (s, 1H); 7.63-7.58 (m, 2H); 7.34 (dd, 1H, *J* =8.4, 1.6 Hz). ^{13}C-NMR (DMSO-d_6) δ: 178.5; 174.8; 149.3; 138.7; 133.8; 131.6; 130.7; 130.6; 130.3; 129.4; 126.6; 124.8; 123.8; 123.5; 121.5; 113.1; 108.8;103.2. MS (CI): *m/z* = 302 $[M]^+$. IR (film): ν (cm^{-1}) = 3388; 2924; 2221; 1564; 1414; 1344; 1098; 870; 801. m.p.: deg > 274°C. **72, X = H** : ^{1}H-NMR (acetone-d_6) δ: 11.61 (br s, 1H); 10.99 (br s, 1H); 8.77 (dd, 1H, *J* = 1.6, 0.7 Hz); 8.68 (s, 1H); 7.77 (dd, 1H, *J* = 8.5, 0.7 Hz); 7.72 (dd, 1H, *J* = 9.0, 0.9 Hz); 7.63-7.60 (m, 2H); 7.43 (dd, 1H, *J* = 2.2, 0.9 Hz); 7.32 (td, 1H, *J* = 7.6, 1.1 Hz); 7.12 (td, 1H, *J* = 7.5, 1.0 Hz). ^{13}C-NMR (acetone-d_6) δ: 180.2; 138.6; 137.6; 135.9; 134.8; 127.9; 127.1; 126.7; 126.0; 125.0; 122.5; 120.3; 119.8; 116.1; 113.4; 112.4; 107.9; 105.0. MS (CI): *m/z* = 286 $[M]^+$. IR (film): ν (cm^{-1}) = 3314; 2922; 2226; 1718; 1602; 1521; 1438; 1343; 1225; 1129; 874; 804. m.p.: deg > 265°C.

4.3.3.3 Synthesis of methyl 3-(1H-indole-2-carbonyl)-1H-indole-7-carboxylate (**73**)



Substrate **73** was synthesized from **58** and PPh$_3$ using *RP5* and isolated after flash chromatography over silica gel, (hexane/EtOAc 5:5, 15 % yield) as a brown oil. ^{1}H-NMR (acetone-d_6) δ: 11.40 (br s, 1H); 10.95 (br s); 8.66 (dd, 1H, J = 7.4, 1.0 Hz); 8.49 (d, 1H, J = 3.0 Hz); 7.99 (dd, 1H, J = 7.6, 1.0 Hz); 7.74 (dd, 1H, J = 8.0, 0.9 Hz); 7.62 (dd, 1H, J = 8.3, 0.9 Hz); 7.41-7.37 (m, 2H); 7.31 (td, 1H, J = 7.6, 1.1 Hz); 7.13 (td, 1H, J = 7.5, 1.0 Hz); 4.01 (s, 3H). ^{13}C-NMR (acetone-d_6) δ: 180.5; 166.6; 137.5; 136.3; 135.6; 133.7; 128.2; 127.9; 127.6; 125.6; 124.8; 122.5;

121.4; 120.2; 116.0; 113.7; 112.4; 107.7; 51.5. MS (CI): *m/z* = 319 $[M]^+$. IR (film): ν (cm^{-1}) = 3326; 3294; 1692; 1591; 1524; 1278; 1094; 801.

4.4 *References*

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