UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI SCIENZE DEL FARMACO

Doctorate Course in Pharmaceutical Sciences - XXXIII Cycle

Metal-catalyzed synthesis of polycyclic indoles
CHIM/06

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Abbreviations

Ac	Acetyl
Alk	Alkyl
Ar	Aryl
Å	Ångström
BAr^F_4	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
Bs	Broad signal
Bs	Besyl
Bu	Butyl
Bz	Benzoyl
°C	Celsius degree
cat.	Catalytic
Cbz	Carboxybenzyl
COSY	Correlation spectrometry
Cy	Cyclohexyl
δ	Chemical shift
d	Doublet
dd	Double doublet
ddd	Double double doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPA	Diisopropylamide
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	1,2-Dimethoxyethan
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	Dimethylformamide
dt	Double triplet
ED	Electron-donating

EDA	Ethyl-diazoacetate
EI	Electron collision ionization
Equiv.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
EW	Electron-withdrawing
g	Gram
h	Hours
Hal	Halogen
HetAr	Heteroaryl
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear Correlation
Hz	Hertz
i-Pr	*iso*-Propyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	Coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L	Ligand
m	Multiplet
M	Molar
[M+]	Molecular ion peak
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minutes
mL	Millilitre
mmol	Millimol
m.p.	melting point
MS	Mass spectrometry
ms	Molecular sieves
m/z	Mass/Load
NaHMDS	Sodium bis(trimethylsilyl)amide

NBS	N-bromosuccinimide
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect
n-Pr	normal-Propyl
Np	Naphtyl
Ns	Nosyl
NTf	Bis(trifluoromethanesulfonyl)imide
Oct	Octanoate
OTf	Triflate
p-	para
Pc-L	Pyridine-containing macrocyclic ligand
Ph	Phenyl
$PicAuCl_2$	Dichloro(2-pyridinecarboxylato)gold
Piv	Pivaloyl
ppm	Parts per million
Py	Pyridine
p-Tol	*p*-Tolyl
q	Quartet
rt	Room temperature
s	Singlet
SbF_6	Hexafluoroantimoniate
sex	Sextet
Styr	Styryl
T	Temperature
t	Triplet
t	Time
TMEDA	Tetramethylethylenediamine
td	Triplet doublet
tert	Tertiary
t-Bu	*tert*-Butyl
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl

Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFE	1,1,1-trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Transition metal
Ts	Tosyl

Index

Chapter 1. The chemistry of 2-vinylindoles and 4*H*-furo[3,2-*b*]indoles

1.1 Indole core in pharmaceutical field

The indole core is ubiquitous in bioactive natural products and pharmaceutical compounds and the chemistry of the indole nucleus is the subject of intense investigations both for the synthesis of the indole core and the functionalization at both pyrrole and benzene moieties.[1–3]

Simple natural indole derivatives include, for example, tryptophan, one of the naturally occurring essential amino acids, and its decarboxylated analogous tryptamine. Furthermore, indole compounds bearing substituents on the benzene ring, especially hydroxyl groups, include serotonin, melatonin, bufotenine, psilocybin that was found in the skins of toads, toxic mushrooms, and West Indian snuff. Some of these compounds present well-known psychotropic effects (figure 1.1).

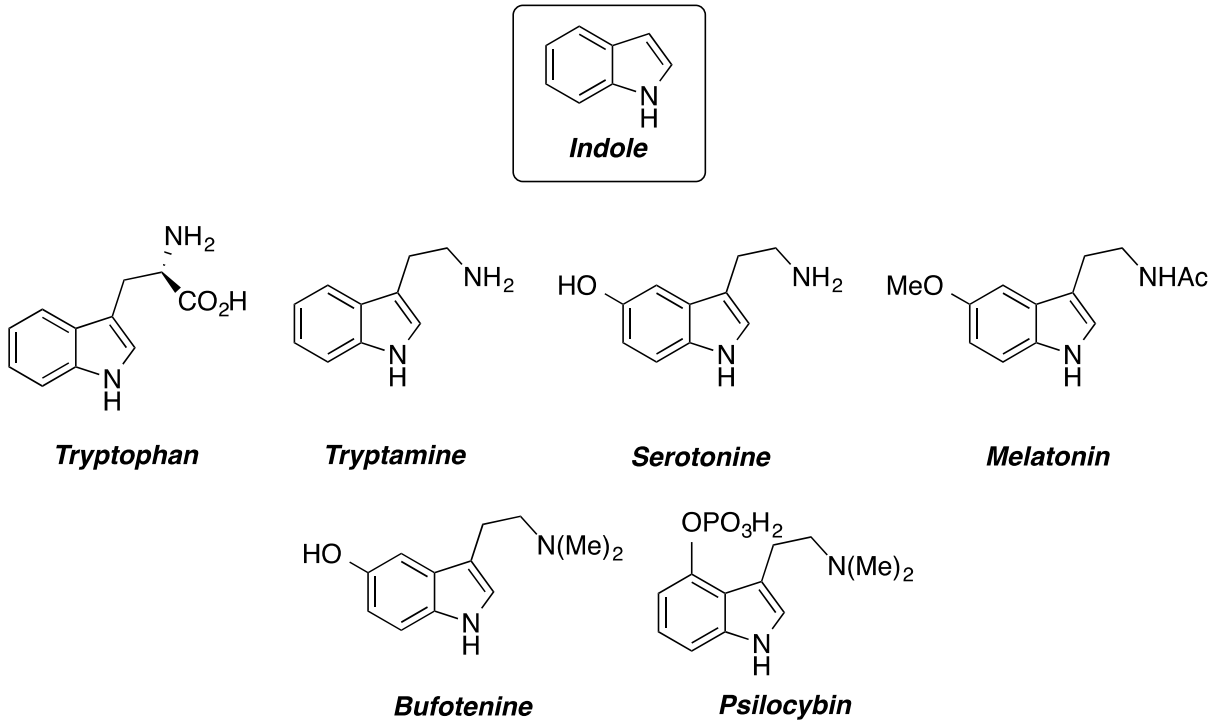


Figure 1.1

Moreover, indole provides the skeleton of several alkaloids exerting considerable pharmacological activities (figure 1.2).

- *Strychnos* alkaloid strychnine, a powerful muscle contractor.
- *Ergot* alkaloids, such as ergometrine with its direct action on the contraction of uterine muscle, ergotamine for migraine relief and the modified alkaloid, bromocriptine, which suppresses lactation and has some applications for the treatment of mammary carcinoma.
- *Rauvolfia* alkaloids, and specifically reserpine, which was the forerunner of the tranquillizers.

- The dimeric alkaloids of *Catharanthus*, vinblastine and vincristine extremely important in the treatment of leukemia.

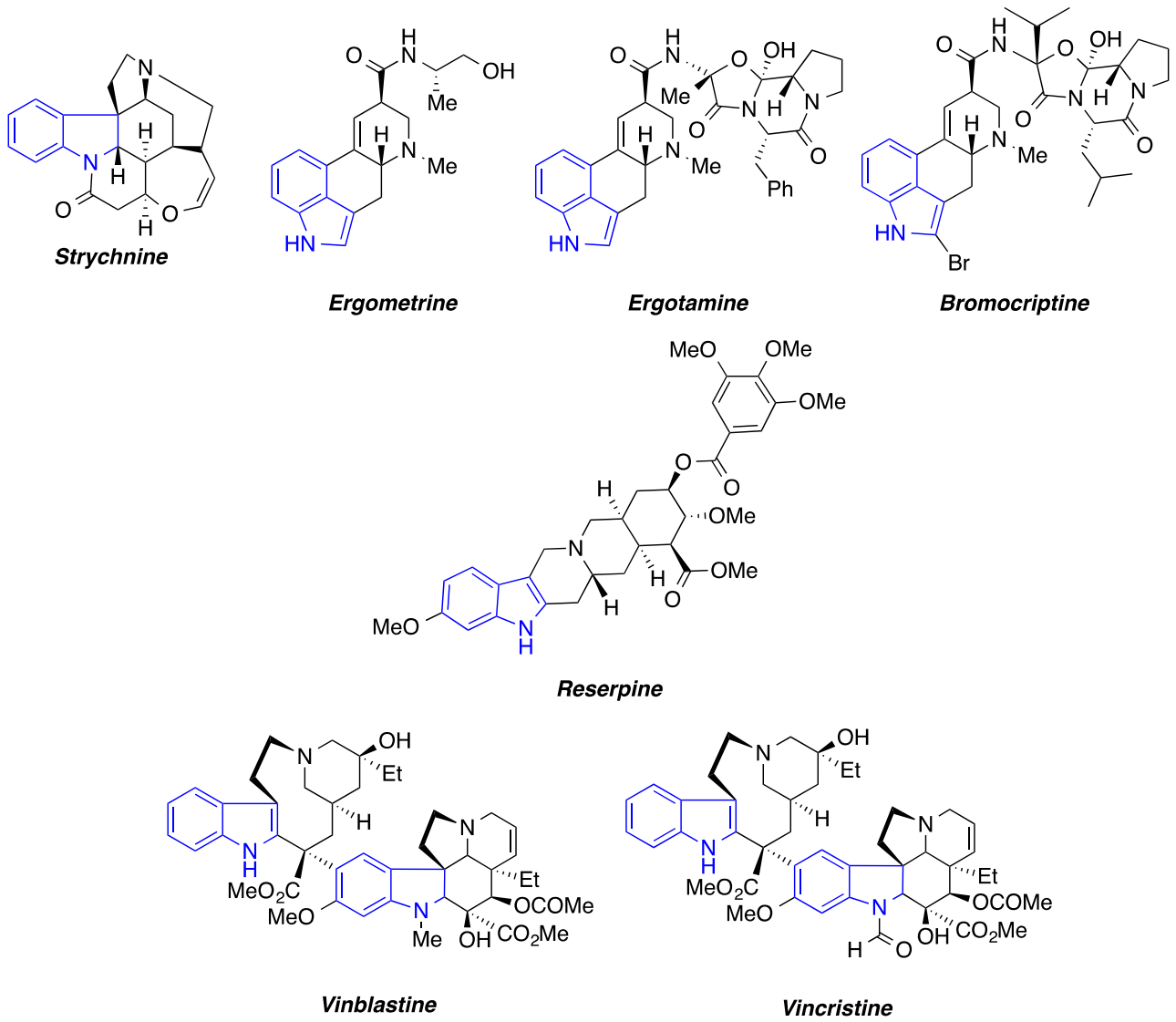


Figure 1.2

Other indole-containing therapeutics, natural or from synthesis, are summarized in table 1.1

Table 1.1

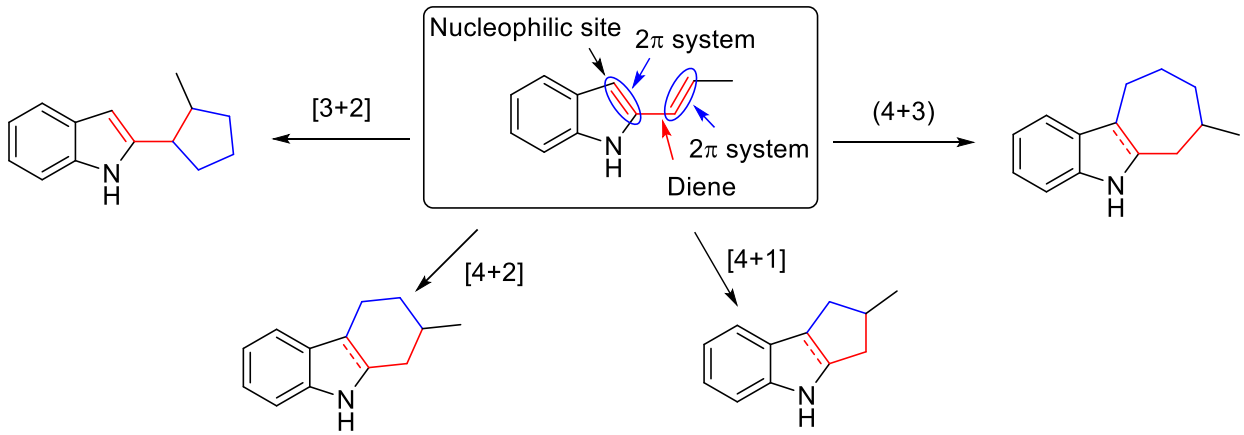
Drug	Application	Drug	Application	Drug	Application
Vinorelbina	Anticancer	Vincamine	Vasodilator	Roxindole	Schizophrenia
Vindestine	Anticancer	Peridopril	Antihypertensive	Delavirdine	Anti-HIV
Mitraphylline	Anticancer	Peridopril	Antihypertensive	Atevirdine	Anti-HIV
Cediramib	Anticancer	Pindolol	Antihypertensive	Arbinol	Antiviral
Panobinostat	Anti-leukemic	Binedaline	Antidepressant	Zafirlukast	Anti-asthmatc
Apaziquone	Anticancer	Amedalin	Antidepressant	Bucindolol	*beta-Blockers*
Tropisetron	Antiemetic	Oxypertine	Antipsyichotic	Pericine	Oppioid agonist
Doleasetron	Antiemetic	Siramesine	Antidepressant	Mitragynine	Oppioid agonist
Oglufanide	Immunomodulatory	Indalpine	Antidepressant	Pravadoline	Analgesic
Indomethacin	Anti-inflammatory	Yohimbine	Sexual disorder	Proamanullin	Toxin

Considering the importance of the indole nucleus and of more complex indole derivatives, the proposal of new methodologies for their synthesis and functionalization is still of great interest in synthetic organic chemistry. For this reason, many papers have been published in the last 15 years, using innovative and selective methods.[4–13] Some selected recent results reached on this topic and in particular on the synthesis of (poly)cyclic complex indoles from 2-vinylindoles and 4*H*-furo[3,2-*b*]indoles will be resumed in the next paragraphs. The reported results are only general and recent results in this field. A more detailed discussion on this and related topics can be found at the beginning of the following chapters.

1.2 General reactivity of 2-vinylindoles

Heterocyclic internal-external ring dienes represent a particular and useful class of molecules and their cycloadditions with various dienophiles provide an easy access to poly(hetero)cycles. Among these building blocks, 2-vinylindoles play a privileged role since they represent synthetically attractive starting materials for the regio- and stereocontrolled construction of [*b*]annelated indoles,[13–15] which in turn serve as lead substances for pharmaceutical applications and as building blocks for the synthesis of several alkaloid families.[16]

The most relevant feature of 2-vinylindoles is the presence of a 4π system that can take part in [4+*n*] cyclization reactions with a series of different reaction partners. In addition, the two double bonds can be involved separately in cyclization reactions as 2π components with appropriate reagents. Moreover, 2-vinylindoles present a nucleophilic site at the C3 position that could influence the behavior of these compounds in cyclization reactions. Thus, thanks to this particular structure the employment of 2-vinylindoles leads to the synthesis of a huge number of complex indole-based derivatives (scheme 1.1).

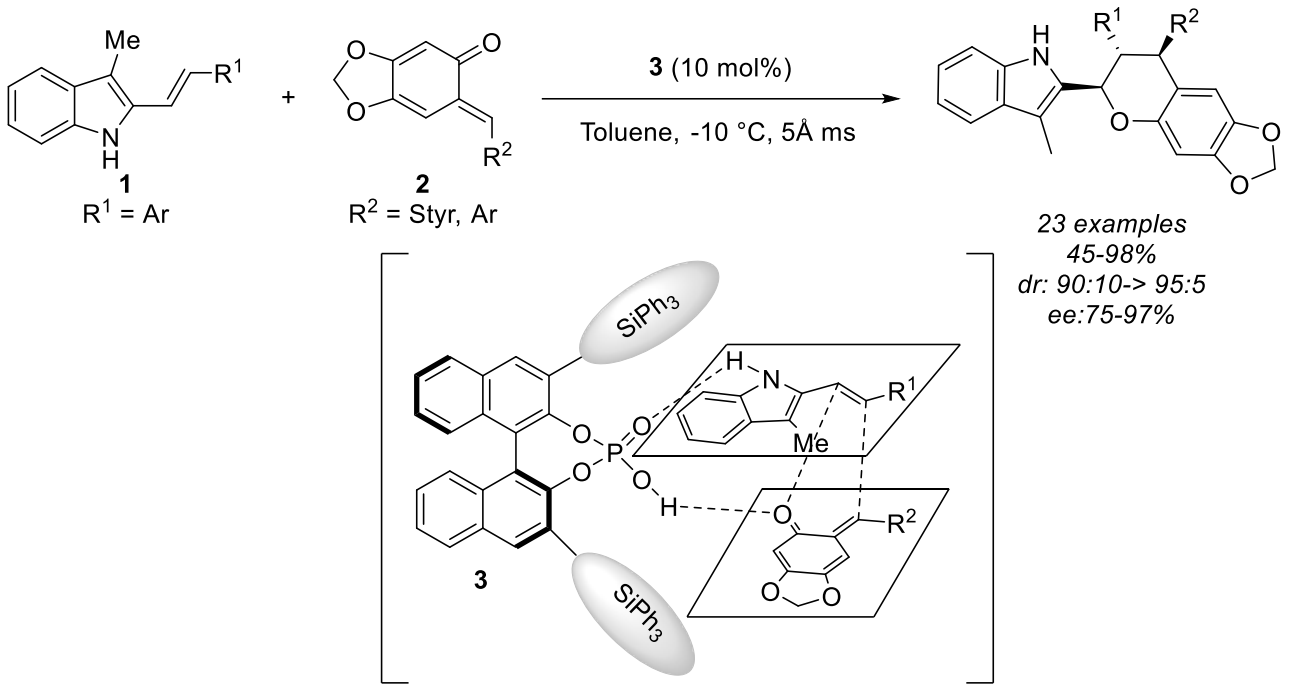


Scheme 1.1

Below are reported some recent examples involving 2-vinylindoles in [4+2], [4+1] and (4+3) cyclization reactions as well as examples that involve the exocyclic double bond of the diene as two carbons partner for the synthesis of complex (poly)cyclic derivatives. The notation [4+n] refers to the number of electrons involved in the cyclization whereas (4+3) refers to the number of atoms involved. Thus, formally a (4+3) cyclization is [4+2] process in terms of electrons count.

One of the most recent examples of the involvement of the external double bond in cyclization reactions was reported by Shi and co-workers. They investigated the possibility of involving the olefinic moiety of 2-vinylinodoles in a [4+2] cyclization reaction. In fact, in 2020, they proposed the

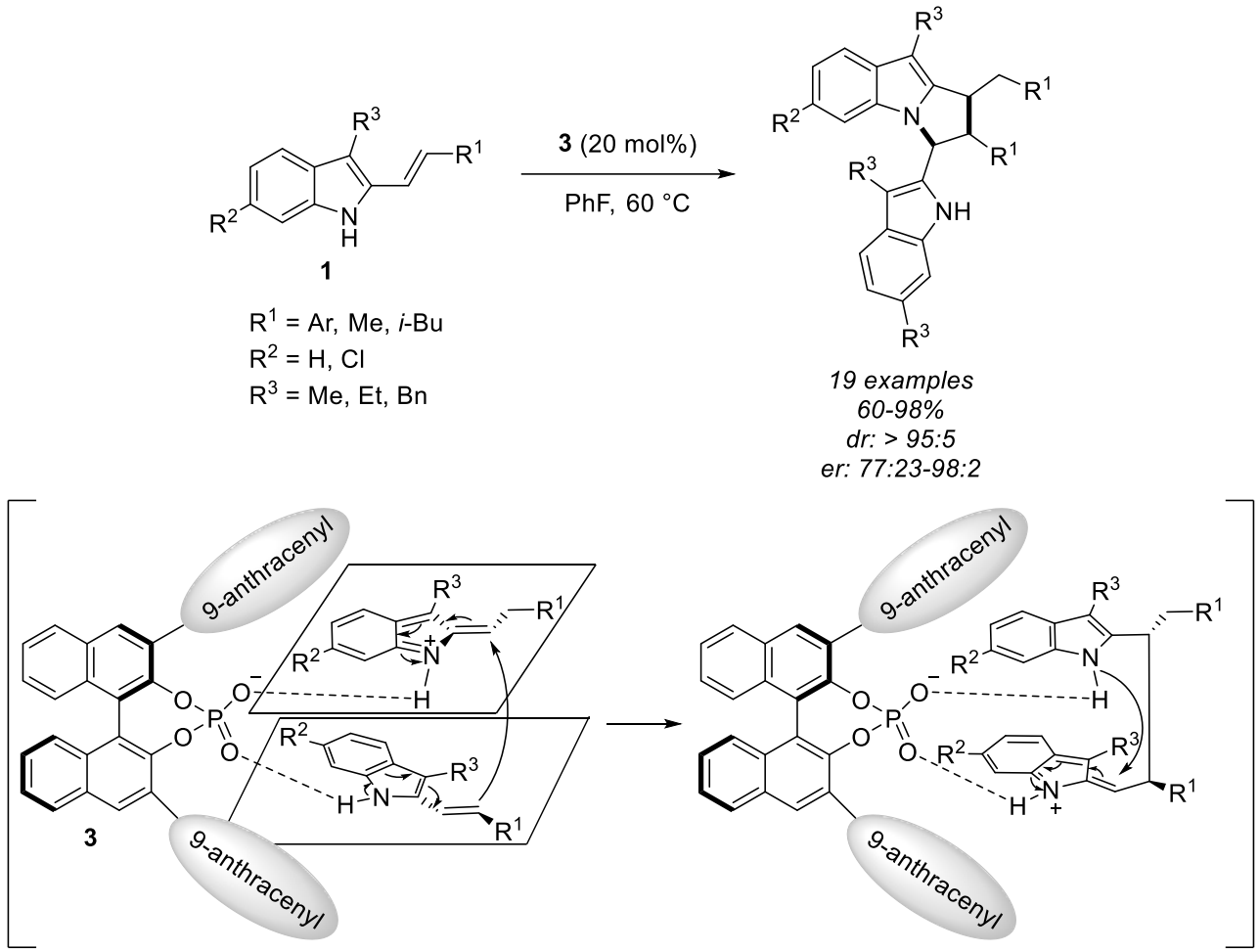
synthesis of biologically relevant 1,3-dioxolochroman derivatives in a diastereo- and enantioselective fashion.[17] The transformation took place employing 3-methyl-2-vinylindoles **1** as alkene partners and sesamol-derived ortho-quinone methides **2** as diene systems, using as chiral catalyst phosphoric acid **3** (scheme 1.2). The phosphoric acid **3** was able to interact with the two reagents through two hydrogen bonds with the carboxyl moiety of the diene and the NH hydrogen of indole, inducing diastereo and enantioselection during the addiction. The reaction presented a good tolerance of different functional groups on both vinylindoles **1** and sesamol-derived ortho-quinone methides **2** resulting in the isolation of the desired compounds in good yields, excellent diastereoselectivity and high enantioselectivity.



Scheme 1.2

Moreover, the external double bond of 2-vinylinodoles can participate in [3+2] cyclization reactions and one of the most recent example involves the [3+2] cyclodimerization of 3-alkyl-2-vinylindoles **1** and was reported by Shi and coworkers in 2017.[18] They developed a powerful method for the construction of diastereo- and enantioenriched pyrrolo[1,2-*a*]indole derivatives though an asymmetric [3+2] cycloaddition under chiral phosphoric acids catalysis. The transformation showed high tolerance for different functional groups on the indole nucleus giving rise to pyrroloindoles in high yields, excellent diastereoselectivity and good enantioselectivity (scheme 1.3). The selectivity of the reaction was promoted by the formation of two hydrogen bonds between the highly hindered chiral phosphoric anion **3** and two molecules of 3-alkyl-2-vinylindole **1**. Thus, the first step of the

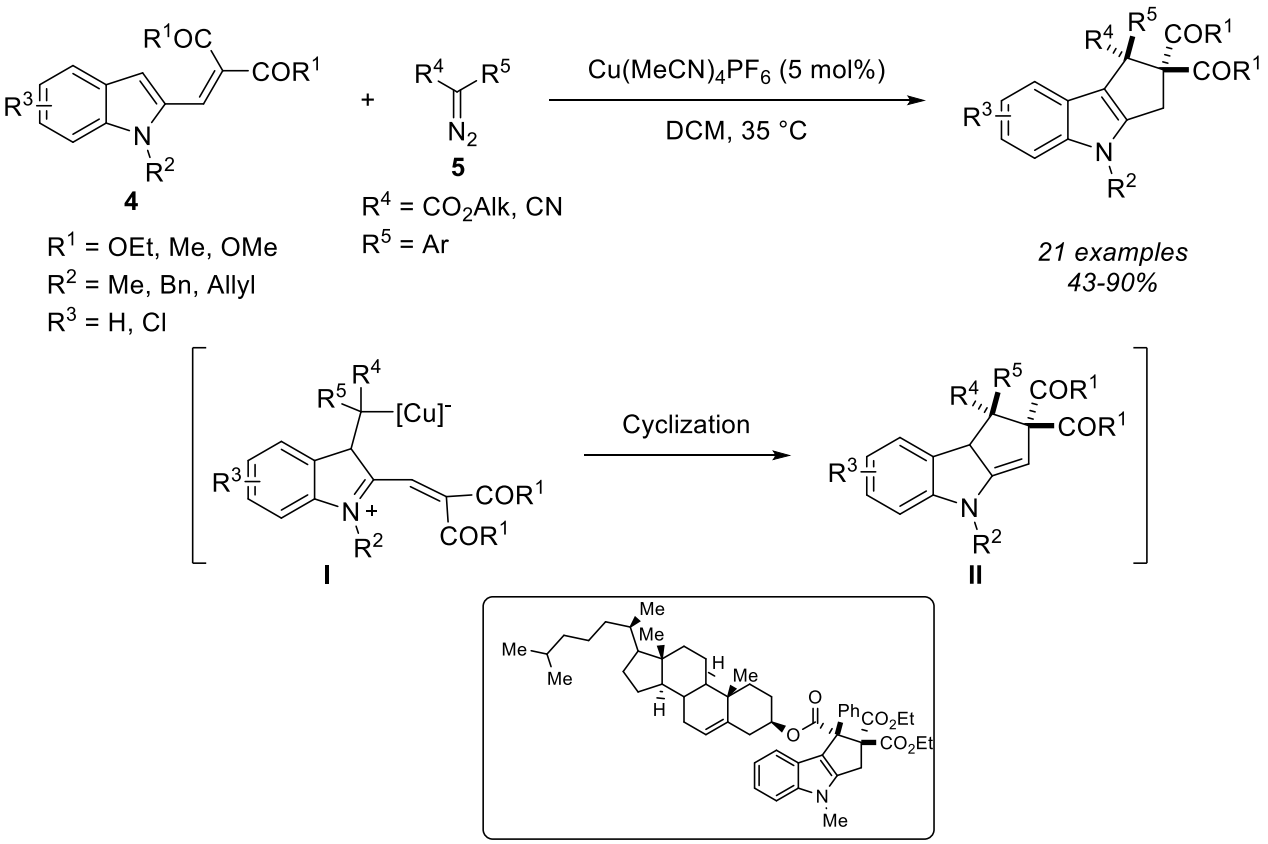
reaction was the conversion of one molecule of 3-alkyl-2-vinylindole **1** into the vinyliminium intermediate **I**, then intermediate **I** and another molecule of 3-alkyl-2-vinylindole **1** formed simultaneously a hydrogen bond and an ion pair interaction with the phosphoric anion **3**. Successively, a vinylogous Michael addition/intramolecular aza-Michael addition cascade reaction occurred in order to obtain the diastereo- and enantioselective [3+2] cycloadduct. Enantioselection is favored by the presence of the bulky 3,3'-(9-anthracenyl) substituents on the rigid (R)-BINOL backbone.



Scheme 1.3

As reported before, 2-vinylindoles can participate in cycloaddition as 4π system. In 2020, Xu and co-workers developed the synthesis of dihydrocyclopenta[*b*]indoles from 2-vinylindoles **4**.[19] They proposed a [4+1] annulation between 2-vinylindoles **4** and aryldiazoacetatates **5** under copper catalysis (scheme 1.4). The reaction proceeded with the formation of a copper-carbene *via* copper catalyzed decomposition of the corresponding diazo compound and it is followed by a concerted and asynchronous annulation process involving the C3 position of 2-vinylindole **4**. The cyclization step

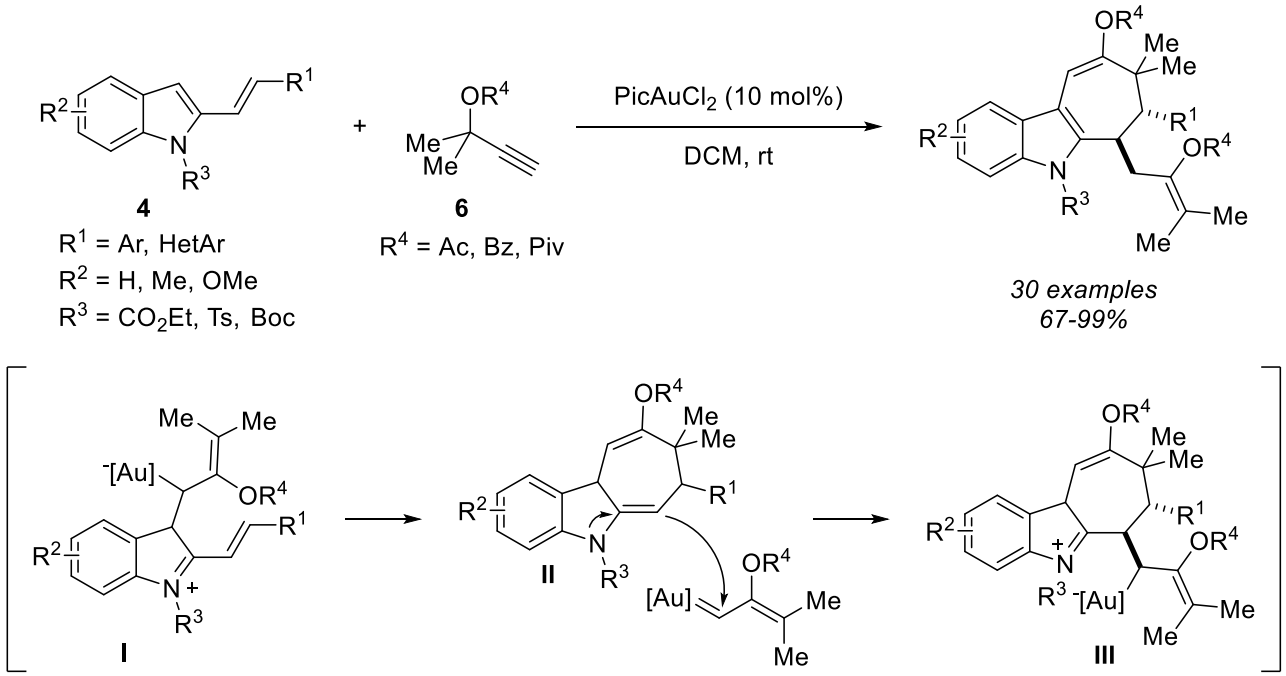
led to the dearomatized cyclic intermediate **II** that underwent re-aromatization to give the final dihydrocyclopenta[*b*]indole derivative. The peculiarity of the transformation resides in the possibility to employ also a complex aryldiazoacetate bearing tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene derivative as ester moiety (see box in scheme 1.4).



Scheme 1.4

Moreover, there are only few examples of reactions involving 2-vinylindoles as 4π system in (4+3) cyclizations for the synthesis of seven-member rings. In particular, in 2017 the research group of Zhang proposed the synthesis of cyclohepta[*b*]indoles through a gold-catalyzed (4+3) cycloaddition/C-H functionalization cascade reaction (scheme 1.5).[20] The reaction involved the annulation between 2-vinylindoles **4** and two units of propargyl esters **6**. In fact, the cyclohepta[*b*]indole derivative arising from the initial (4+3) cyclization reacts with a second molecule of propargyl ester *via* a C-H insertion reaction. This method allowed for the obtainment of a series of highly functionalized indole derivatives in high yield and with excellent diastereoselectivity and atom economy under mild reaction conditions. The reaction proceeded *via* the gold activation of propargyl ester **6** generating the corresponding gold-carbene that underwent nucleophilic attack from the C3 carbon of the indole, forming the iminium intermediate **I**. After a ring closure event the first

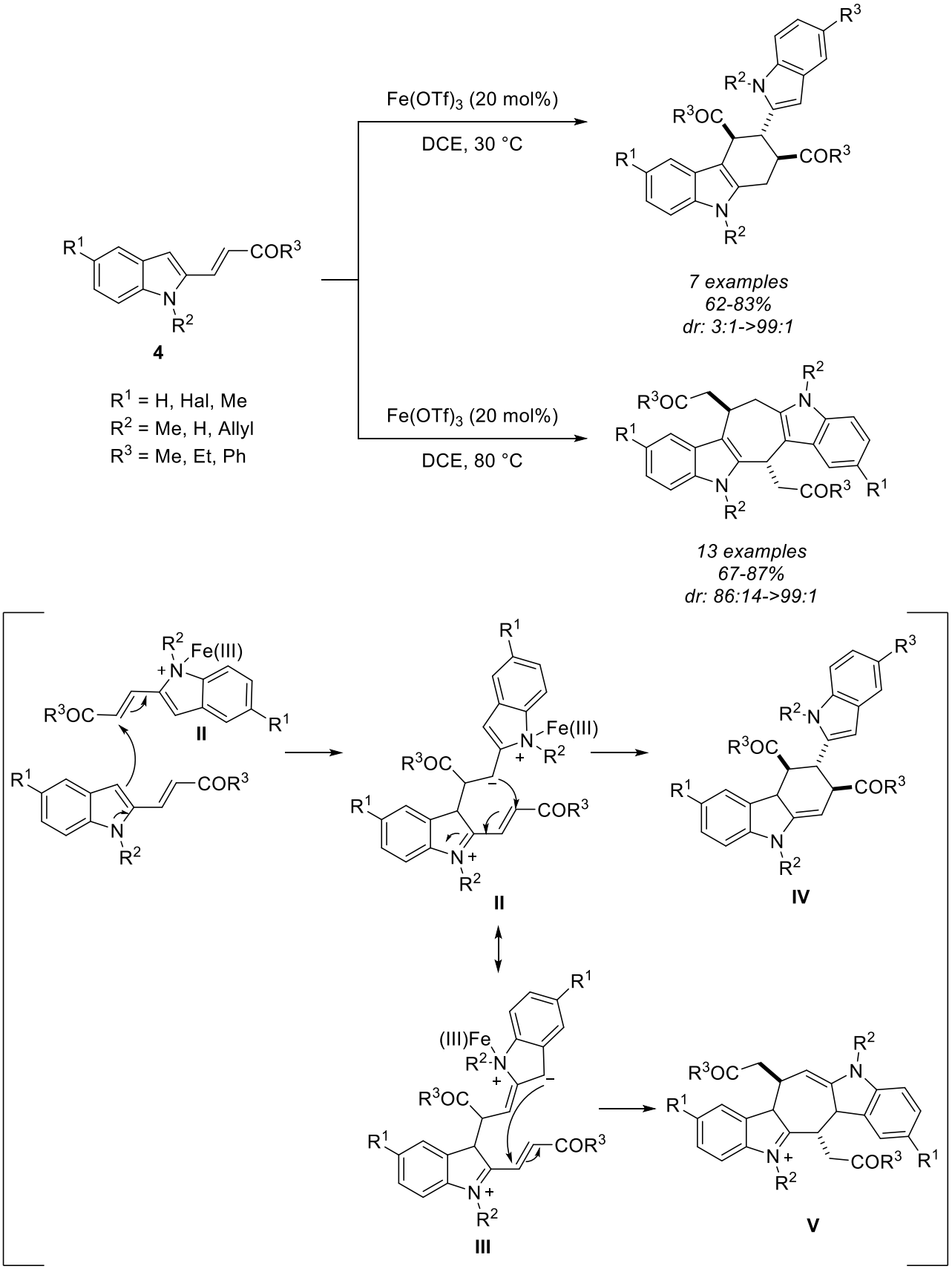
dearomatized (4+3) cycloadduct (intermediate **II**) was obtained and successively a second gold activated propargyl ester was involved in a nucleophilic attack generating a second iminium intermediate **III**. The final product was obtained *via* a protodeauration mechanism regenerating the gold catalyst.



Scheme 1.5

Finally, 2-vinylindoles have been often used in [4+2] cyclization reactions for the synthesis of carbazole derivatives[8,14]. In 2018, the research group of Ghorai and co-workers reported divergent syntheses of tetrahydrocarbazoles and tetrahydrocycloheptadiindoles from the dimerization of 2-vinylindoles **4** under Lewis acid catalysis (scheme 1.6).[21] In fact, they demonstrated the ability of 2-vinylindoles **4** bearing an electron deficient external double bond to take part into [4+2] cyclization reactions. In addition, the same building block could undergo (4+3) cyclization by performing the reaction at higher temperature with the same Lewis acid catalyst with complete stereoselection. Both transformations start with the nucleophilic attack of the C3 position of one molecule of 2-vinylindoles on the external double bond of a second molecule of 2-vinylindole activated by $Fe(OTf)_3$. Coordination of nitrogen atom reverts the polarity of the external double bond (intermediate **I**). The obtained intermediate **II** presents a negative charge on C1' of the indole and it undergoes [4+2] ring closure and rearomatization leading to the formation of the tetrahydrocarbazole derivative. However, intermediate **II** is in equilibrium with intermediate **III** bearing the negative charge on the C3 carbon, thus nucleophilic attack on the C1' position and the subsequent rearomoatization leads to the

synthesis of tetrahydrocycloheptadiindole derivative. Additional computational studies confirmed the proposed mechanism underling the energetically more favorable formation of seven-member product at high temperature. Both the transformations allowed for the isolation in high yields and with excellent diastereoselection of two different products in a selective temperature-controlled fashion.


Fe(OTf)3 (20 mol%)
DCE, 30 °C
7 examples
62-83%
dr: 3:1->99:1
Fe(OTf)3 (20 mol%)
DCE, 80 °C
13 examples
67-87%
dr: 86:14->99:1
4
R1 = H, Hal, Me
R2 = Me, H, Allyl
R3 = Me, Et, Ph
II
III
IV
V

Scheme 1.6

1.3 Reactivity of 4*H*-furo[3,2-*b*]indoles

4*H*-furo[3,2-*b*]indoles are a class of compounds firstly reported in literature for their anti-allergic,[22] analgesic, anti-inflammatory, anti-pyretic[23–25] and anti-cancer[26] activities (figure 1.3).

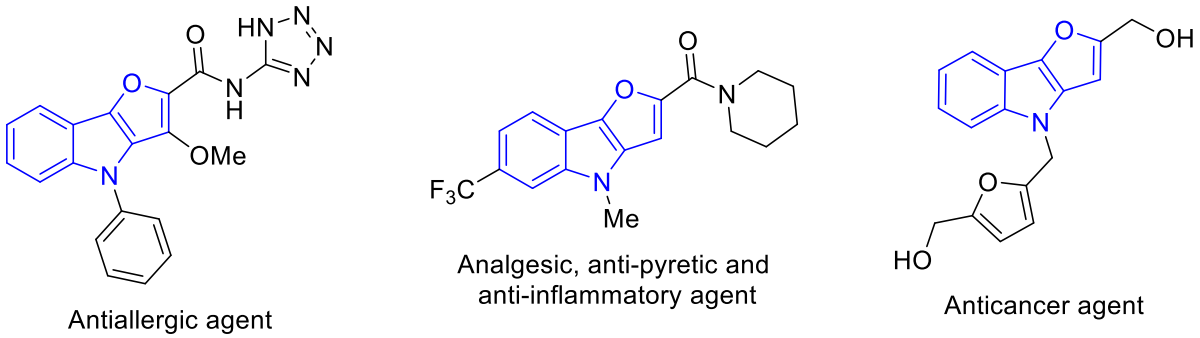


Figure 1.3

This class of compounds contains a 4π-system embedded in the rigid framework of a furan ring. Thus, 4*H*-furo[3,2-*b*]indoles can take part in different cycloaddition reactions as 4π components or as dienophile partners. Furthermore, the C2 carbon of furan shows nucleophilic properties and can participate in reactions with different electrophiles, like the parent furan derivatives (figure 1.4).[27]

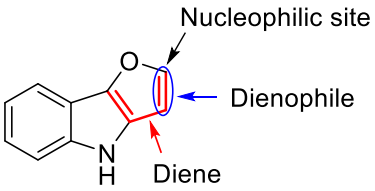
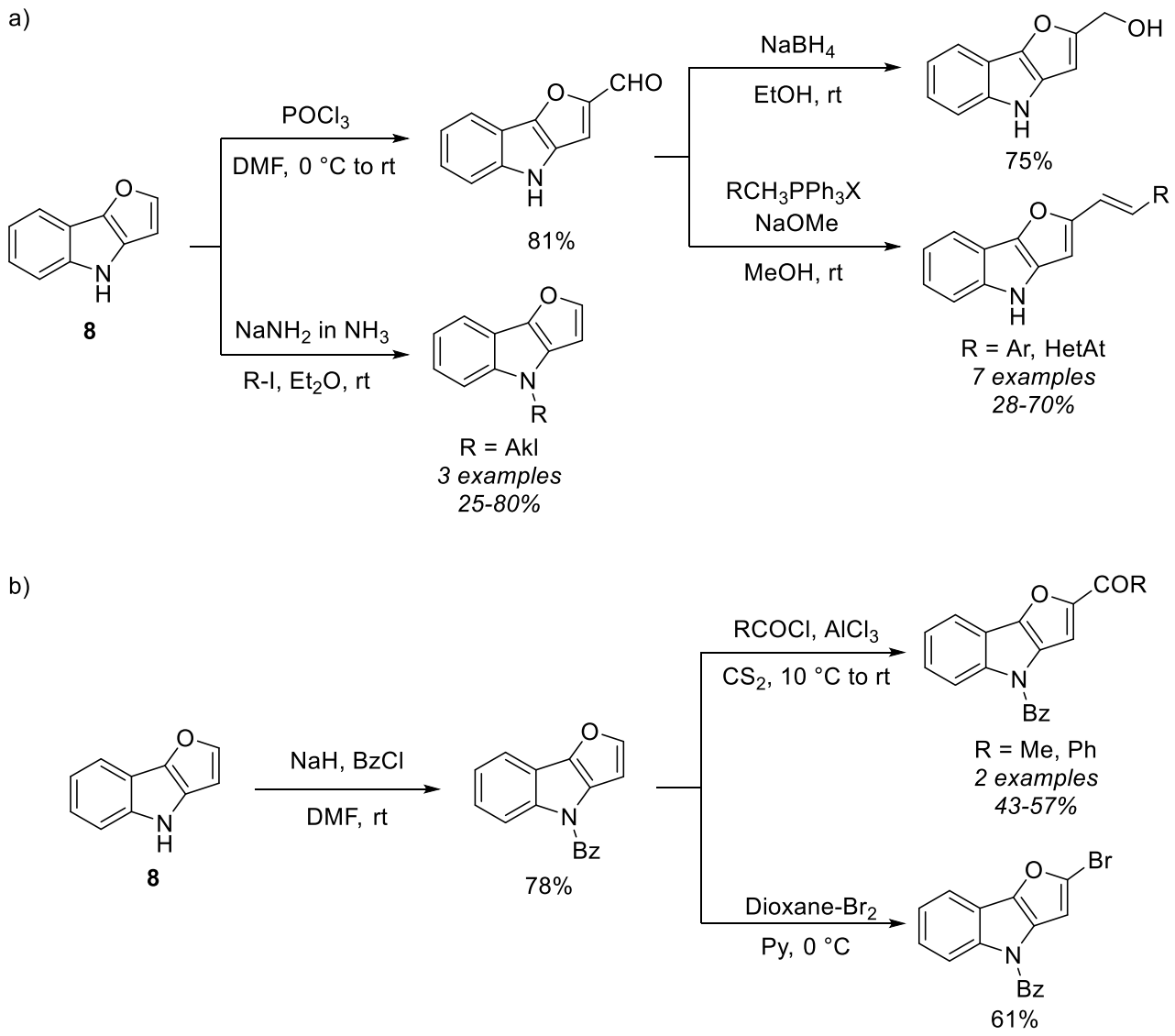


Figure 1.4

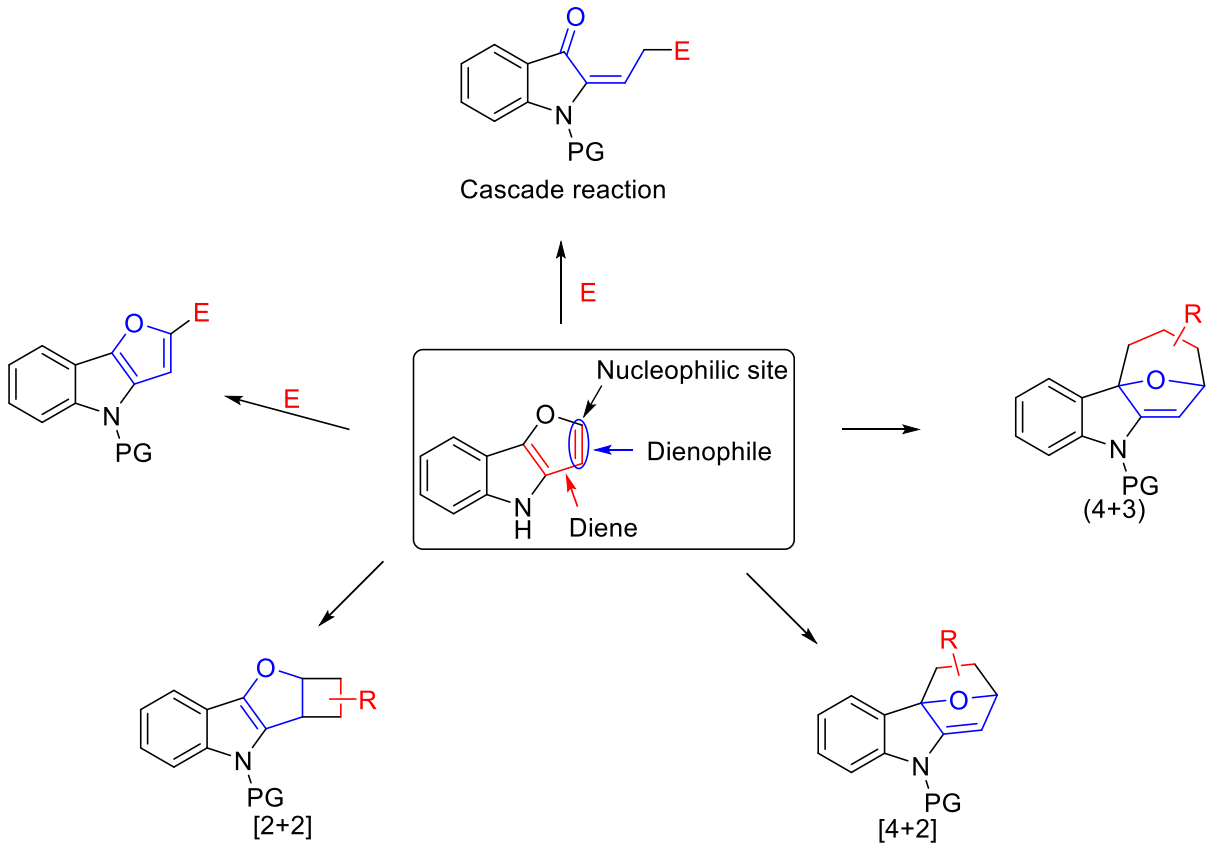
However, in literature only few examples of functionalization of this nucleus are reported. In particular, these transformations concern only the functionalization at the C2 carbon and at the nitrogen atom. In 1977, Tanaka and co-workers reported the formylation at C2 of 4*H*-furo[3,2-*b*]indole **8** and the subsequent transformation of the new aldehyde into the corresponding alcohol by chemical reduction or into a double bond *via* Wittig reaction. In addition, he reported the alkylation of the nitrogen atom (scheme a) 1.7).[28] The next year, Yoshina and co-worker proposed the bromination and the acylation at C2 using a nitrogen protected furoindole (scheme b) 1.7).[29]


a)
8
POCl3
DMF, 0 °C to rt
81%
NaNH2 in NH3
R-I, Et2O, rt
R = AkI
3 examples
25-80%
NaBH4
EtOH, rt
75%
RCH3PPh3X
NaOMe
MeOH, rt
R = Ar, HetAt
7 examples
28-70%
b)
8
NaH, BzCl
DMF, rt
78%
RCOCl, AlCl3
CS2, 10 °C to rt
R = Me, Ph
2 examples
43-57%
Dioxane-Br2
Py, 0 °C
61%

Scheme 1.7

1.4 Aim of the research

Over the years, we investigated in deep the chemistry of vinylindoles especially in their cyclization and cycloaddition reactions. [6,14,27,30] Starting from the obtained results and owing to the unique structural features of the 4*H*-furo[3,2-*b*]indole nucleus we decided to investigate both the synthesis and the reactivity of this class of compounds. The peculiar structure of this 4π-system embedded in the furan ring could lead to an increase of reactivity in comparison to 2-vinylindole congeners. Thus, potentially, 4*H*-furo[3,2-*b*]indoles could take part in different cycloaddition reactions as dienes when employed in [4+2] or (4+3) cyclizations or as dienophilic partners in [2+2] reactions with the C1-C2 double bond of the furan moiety. Furthermore, the C2 carbon of furan shows nucleophilic properties and can participate in simple functionalization reactions with different electrophiles. Moreover, as reported for simple furan derivatives, the addition of an electrophile at C2 can be followed by rearrangement processes that include a ring opening step (cascade reactions, scheme 1.8).

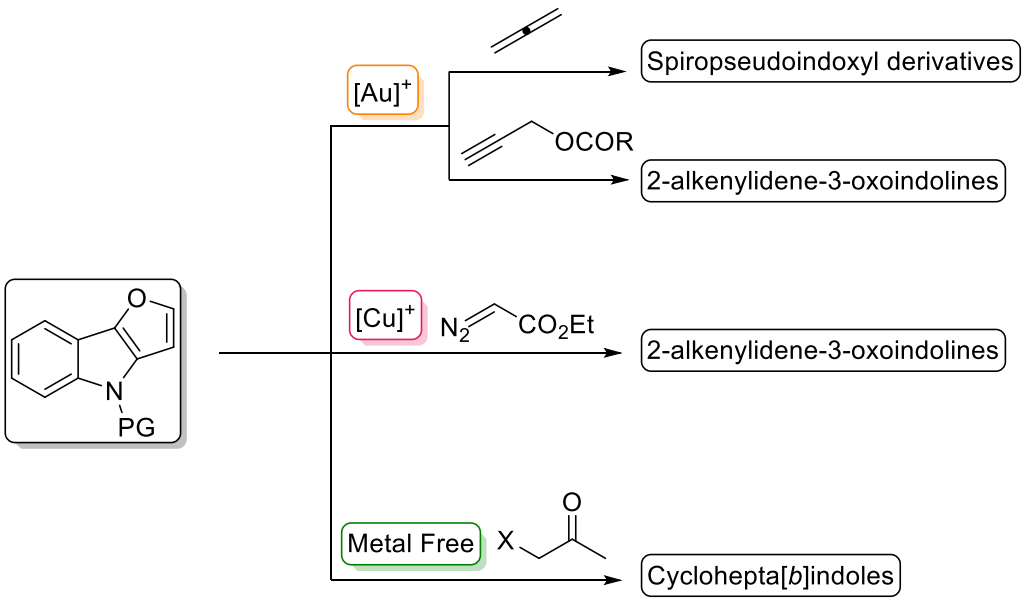


Scheme 1.8

1.5 Summary of the research results

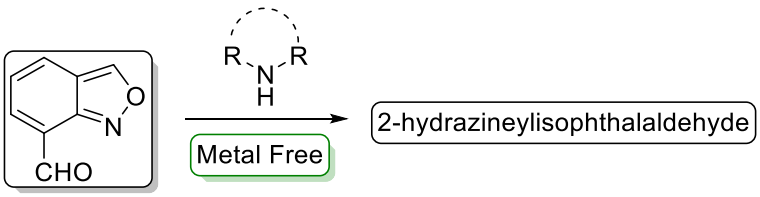
Starting from these premises, this thesis focuses on the synthesis of different functionalized 4*H*-furo[3,2-*b*]indoles and on the study of their reactivity in the presence of different electrophilic partners (scheme 1.9). In detail, the obtained results belong to three main research topics:

1. The first part was focused on the gold activation of different π systems for the synthesis of indole derivatives from 4*H*-furo[3,2-*b*]indoles. In particular, I reported the cationic gold(I) catalyzed cascade reactions of 4*H*-furo[3,2-*b*]indoles with allenamides for the synthesis of spiropseudo-indoxyls (*J. Org. Chem*., **2019**, *84*, 5150). Successively, the activation of propargyl esters by gold(I) catalysts led to the synthesis of 2-alkenylidene-3-oxoindoles in a process that included a furan ring rearrangement. (*Org. Chem. Front*., **2019**, *6*, 3078).
2. The second part reported the behavior of 4*H*-furo[3,2-*b*]indoles in the presence of a different electrophile, a copper(I) carbene, obtained from the *in situ* decomposition of a diazo compound under copper catalysis. The reaction allowed for the formation of a homologous series of the previously cited 2-alkenylidene-3-oxoindoles presenting a less extended conjugate system (*ChemCatChem*, **2020**, *12*, 5250).
3. Finally, I investigated the *in situ* generation of an oxyallyl cation in order to study the performance of 4*H*-furo[3,2-*b*]indoles in (4+3) cycloaddition reactions. In this case, the electrophile was obtained from a α-haloketone under basic condition and then reacted with both 2-vinylindoles and 4*H*-furo[3,2-*b*]indoles giving rise to complex cyclohepta[*b*]indoles (*J. Org. Chem*., **2020**, *85*, 3265).



Scheme 1.9

In addition, during my PhD, I spent six months as visiting student at the Organisch-Chemisches Institut, Ruprecht-Karls-Universität of Heidelberg in the research group of Professor A. Stephen K. Hashmi. During this period, I studied the reactivity of benzo[*c*]isoxazoles (anthranils) under basic condition for the synthesis of 2-hydrazineylisophthalaldehydes (scheme 1.10). However, the results reported in my PhD thesis represent the outcomes of preliminary investigations and additional researches are currently ongoing in Hashmi's laboratories.



Scheme 1.10

Chapter 2. Gold catalyzed synthesis of indole derivatives from 4*H*-furo[3,2-*b*]indoles

The works described in this chapter have been published in *J. Org. Chem*. **2019**, *84*, 5150-5167 as "Gold-Catalyzed Cascade Reactions of 4*H*-Furo[3,2-*b*]indoles with Allenamides: Synthesis of Indolin-3-one Derivatives" and in *Org. Chem. Front.,* **2019***, 6,* 3078-3084 as "Gold-Catalyzed Cascade Reactions of 4*H*-Furo[3,2-*b*]indoles with Propargyl Esters: Synthesis of 2-Alkenylidene-3-oxoindolines"

A mini-review related to this project was also published: "Vinyl-/Furoindoles and Gold Catalysis: New Achievements and Future Perspectives for the Synthesis of Complex Indole Derivatives", *Eur. J. Inorg. Chem.* **2020**, 962-977.

2.1 Homogeneous gold(I) catalysis for the activation of π systems

Homogeneous cationic gold(I) catalysts attracted the attention of the chemist's community at the beginning of the 2000s when their properties as powerful π-activating systems were recognized and applied in synthetic organic chemistry to efficiently generate molecular complexity.[31,32]

Due to the intrinsic properties of the parent gold atom, cationic gold(I) complexes are excellent Lewis acids, preferring orbital interactions over lone pair or charge interactions and forming stable and highly reactive intermediates with unsaturated systems. Gold(I) complexes may therefore be considered 'soft' Lewis acids, preferring 'soft' electrophiles such as C-C π systems. In short, cationic gold(I) complexes are more π-philics than σ-philics and this property gives to these catalysts unique advantages with respect to other transition metals of the same or different groups. The features of both gold atom and gold(I) complexes will be discussed in the following paragraphs.

The electronic properties of gold atom and gold(I) catalysts

Gold atom pertains to group 11 and period 6 of the periodical table of elements (figure 2.1). It has a valence configuration of $5d^{10}6s^{1}$ with a filled 5d shell and 6s shell similar to alkali atoms.

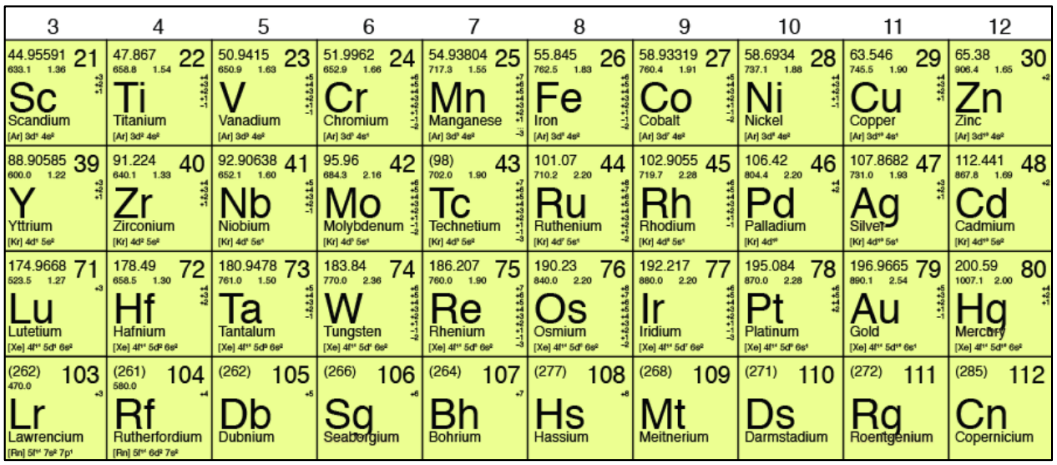


Figure 2.1

The ionization potential, i.e. the amount of energy required to remove the most loosely bound electron, to form a cation is unusually high (890 kJ/mol) for gold with respect to his congeners (figure 2.2). Moreover, on the Pauling scale, the electronegativity of gold, the highest among the metallic elements, is 2.5, which is close for example to that of S, C and I (2.5). In parallel, gold atom has an extremely high electron affinity (222 kJ/mol).

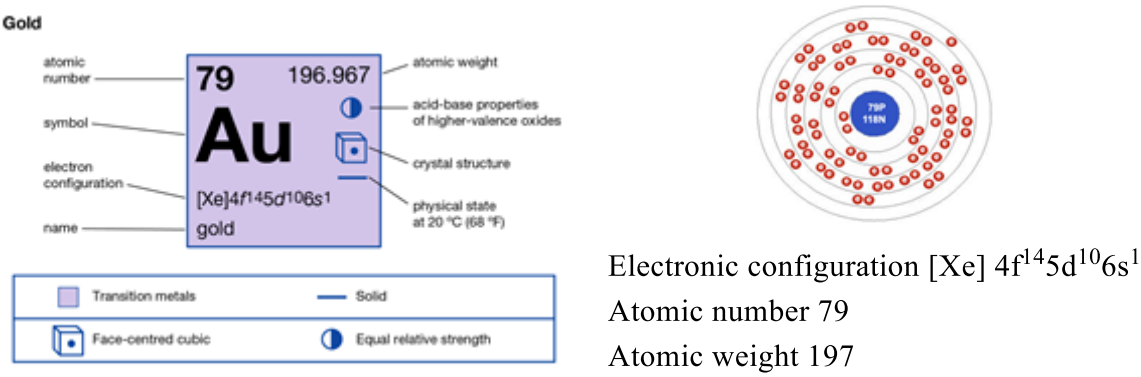


Figure 2.2

The unique characteristics of gold are the consequence of strong relativistic effects and the features of elemental gold influence the behaviour of both gold compounds and gold complexes. [33–37] "Relativistic effects" serve to justify and explain the variation of some properties of matter with respect to the predictable and expected properties deducted applying the laws of classical physics. In particular, relativistic effects are important to explain several properties for those elements possessing high atomic number (Z for gold = 79). Thus, when the mass of the atoms rises, the radial velocity of the electrons travelling around the nucleus increases as well and reaches the speed of light (c). The main consequence is that the mass of the electrons and in general of atoms increases towards infinity as the electron speed approaches to c. This mass enhancement is expressed with a mathematical equation:

$$m = m_o / \sqrt{\left[1 - \left(\frac{v}{c}\right)^2\right]}$$

where m is the corrected mass, m_o is the non-relativistic mass and v the velocity. These heavy electrons are now orbiting the nucleus with a smaller Bohr radius in effect contracting the s, and to a lesser extent, the p orbitals. The contraction of the s orbitals and partially of p orbitals and thus the enhancement of the ionization energy is one of the major consequences of the relativistic effects (figure 2.3).

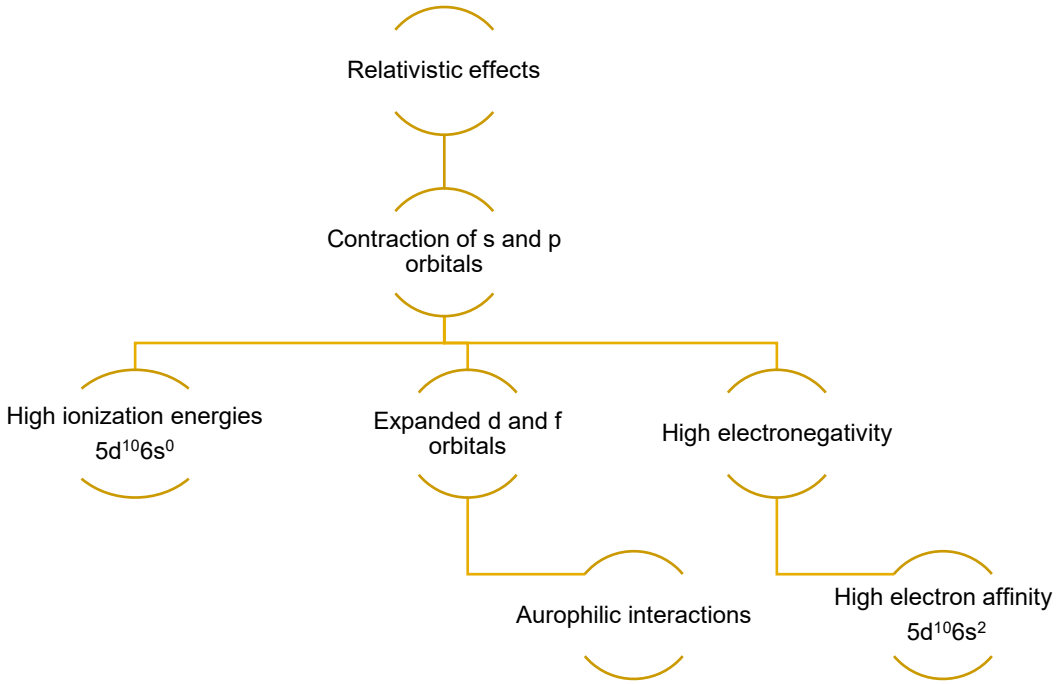


Figure 2.3

The valence contraction of gold orbitals results in the highest electronegativity among the metal elements of group 11. The second major manifestation of relativistic effects is indirect, the electrons occupying the d and f orbitals are shielded by the electrons in the contracted s and p orbitals and therefore experiment a weaker nuclear attraction. This induces expansion and destabilization of d and f orbitals that are responsible of the tendency of gold atom to form aggregates. The interactions between gold atoms are called aurophilic bonds with a strength of about 7–12 kcal/mol, comparable to a hydrogen bond. For the same reasons, gold(I) is a large and diffuse cation sharing the positive charge with the substrate preferring orbital interaction than charge or lone pair interaction. As a consequence, gold(I) is considered a soft Lewis acid that prefers soft electrophiles (C-C π systems). Another indirect consequence of these expanded and destabilized orbitals is the high strength of the bond between gold(I) and ligand and the tendency also for gold salts to form Au-Au aggregates, the phenomenon already described as aurophilicity. Furthermore, theoretical studies indicate that the gold 5d electrons are held with greater energy than in others transition metals due to the reduction of electron/electron repulsion in the expanded 5d orbitals. Thus, the result is a less nucleophilic metal species and high oxidative potential, reducing the tendency to undergo the oxidative addition. This characteristic is reflected in the gold(I) complexes generally less prone to undergo oxidative addition reaction pathways and very easy to handle with a good tolerance for the presence of oxygen, air, water, or alcohols during the assessment of the reactions.

The structure and the reactivity of gold(I) complexes

Gold(I) complexes, arising from the interaction of gold chloride and a ligand, show a strong preference for a linear bicoordinate geometry, with the gold atom in the middle between the chloride and the ligand, in contrast with Cu(I) and Ag(I) complexes which form tri or tetracoordinated complexes (figure 2.4).[38]

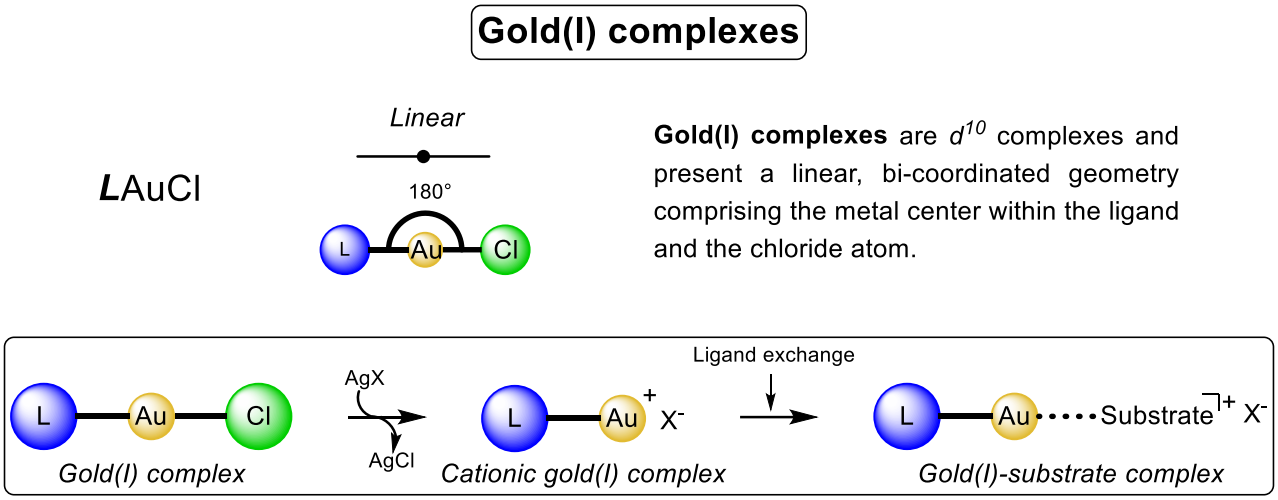


Figure 2.4

With a coordination number of two, to achieve the substrate bonding and the consequent substrate activation, an active catalyst must be generated by abstraction of the chloride ion and formation of the cationic gold(I) complex allowing the bonding of the substrate. In most cases, the generation of these active species occurs *in situ* by chloride abstraction upon treatment with a silver salt bearing a weakly coordinating anion. The corresponding cationic gold(I) complexes possess enhanced electrophilic properties and can enter the catalytic cycle by ligand exchange with the substrate.

The main counterions employed in Au-complexes are reported in figure 2.5 and roughly classified in less or more coordinating anions.[39]

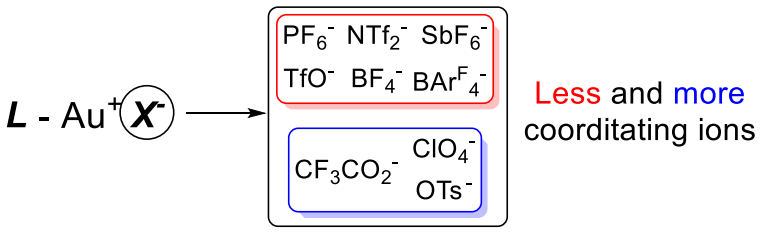


Figure 2.5

The use of different counterions influences the kinetic of the reactions by modulation of the coordinating properties of the resulting active catalyst. The influence of the counterion type on the reaction outcome is often difficult to predict depending not only on the effectively employed anion but also on other reaction parameters, like the type of solvent, reactants and catalyst concentrations, solubility and reaction temperature. This often results in the need of the evaluation of different anions during the catalyst screening of a reaction. Moreover, the structure of the catalytically active site in solution affects the chemo-, regio- and stereoselective outcome of the process. On this context, it is important to underline that the modulation of steric and electronic properties of the gold(I) catalysts strictly depends on the coordination strength and on the chemical structure of the adopted ligands.[40] The most common ligands in gold catalysis are phosphoroamidites, phosphites, phosphines or carbenes, with different variety of arrangements. In figure 2.6 the general structures of these ligands are reported besides some real examples.

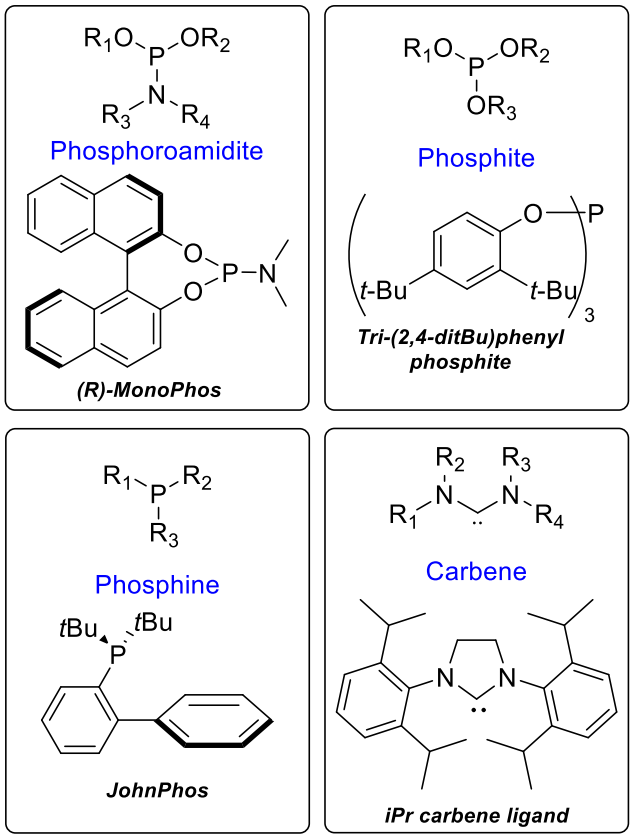


Figure 2.6

In general, complexes with donating N-heterocyclic carbenes present lower electrophilic character than complexes bearing phosphites and related ligands, while phosphine complexes show an intermediate electrophilicity. It is worth to underline that, over the years, a plethora of new ligands and chiral ligands has been reported in the literature offering unique chance of applications in synthetic organic chemistry.[41–45]

Activation of unsaturated systems

The π systems normally involved in cationic gold(I) catalyzed reactions are alkenes, alkynes and allenes. The activation mode of alkynes and alkenes is reported in this paragraph, whereas allenes are discussed in the following section. In gold(I) catalyzed reactions involving alkynes and alkenes, the first step is the activation of the π-system by the gold(I) catalyst followed by the anti-attack of a nucleophile (figure 2.7).[46–48]

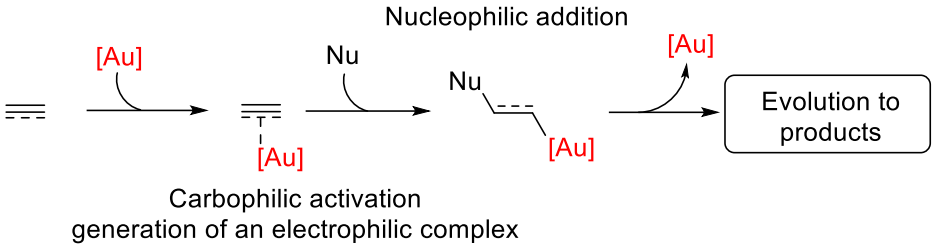


Figure 2.7

Nucleophiles can be simple hetero or carbon compounds and, in this case, the reaction ends with the formation of simple addition products across the π-system. However, more sophisticated reaction pathways comprise after the addition of a generic nucleophile, evolution toward the formation of more challenging compounds *via* enyne cycloisomerization, C-H functionalization, cycloaddition, rearrangement, cascade and multicomponent reactions.

The bond nature in the gold(I) complexes with alkynes and alkenes can be discussed considering the bond as a donor-acceptor interaction between two closed-shell fragments, the gold(I) d^{10} filled orbital and the π-unsaturated system. Thus, the theoretical model assumes that the formation of a σ-bond is due to the overlapping of the π-systems of the ligand with an empty metal orbital with suitable symmetry. Beside the σ-bond, a π interaction takes place through back-donation of electron density from a filled metal d orbital into an antibonding p^* orbital of the alkene or alkyne. These bond interactions are active in both alkynes and alkenes. Moreover, when alkynes are involved there are in principle four main components that can contribute to the bonding of these molecules to the catalyst. The already discussed σ-symmetric M←L donation and the π-symmetric M→L back-donation with the in-plane $\pi_{\parallel}$ orbitals are accompanied by the M←L π donation with out-of-plane $\pi_{\perp}$ orbitals and by an additional component of M→L backdonation with an occupied d orbital of the metal with an empty π^* orbital of the alkyne (figure 2.8).[35]

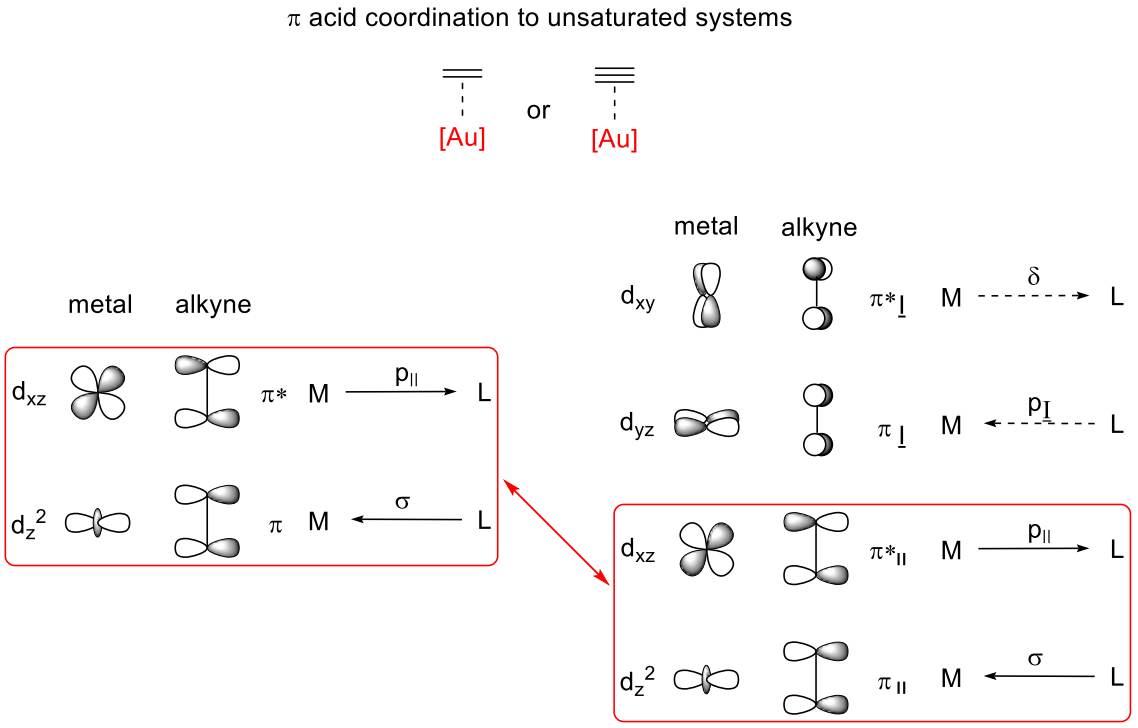


Figure 2.8

The contributions of the individual terms have been analyzed in a quantitative fashion by using high level computational methods. The relative contributions of the four proposed interactions for Au^{+}-acetylene complex are reported hereafter. The σ interaction accounts for the largest contribution to the orbital term (ca. 65%), followed by the in-plane back-donation (ca. 27%), whereas the effect of the orthogonal term is small (ca. 7%) and that of the last interaction can be ignored (ca. 1%). Thus, one may conclude that alkynes (as well as alkenes) are strong two-electron σ donors but fairly weak π acceptors toward Au(I), although some back-donation does occur and cannot be neglected. This dominance of σ-donation versus π-back bonding in these systems has been interpreted as resulting from the alkene and alkyne antibonding orbitals being too high in energy with respect to the interacting 5d orbitals. This effect is more dominant in gold than the other coinage metals due to the relativistic effects lowering the energy of the diffused 5d orbitals.

2.2 Synthesis of spiropseudo-indoxyl derivatives through a cascade reaction between allenamides and 4*H*-furo[3,2-*b*]indoles

2.2.1 Gold activation of allenes in intra and intermolecular reactions

Allenes represent interesting substrates widely employed in applied organic chemistry for the synthesis of complex compounds *via* enyne cycloisomerization, C-H functionalization, cycloaddition, rearrangement, cascade and multicomponent reactions.[49–51] As reported before, this particular π-system can be activated by gold catalysts. To describe the activation of the π-system of allenes it should be mentioned that allenes are characterized by a central *sp*-hybridized carbon linked with double bonds to other two sp^2-hybridized carbon atoms.

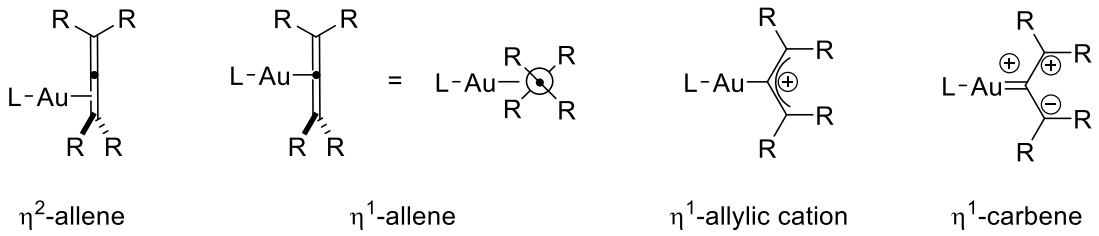
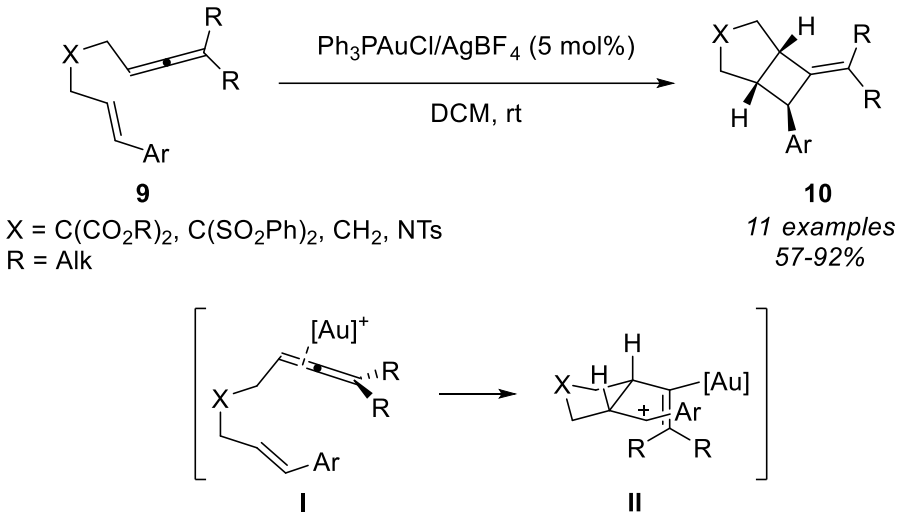


Figure 2.9

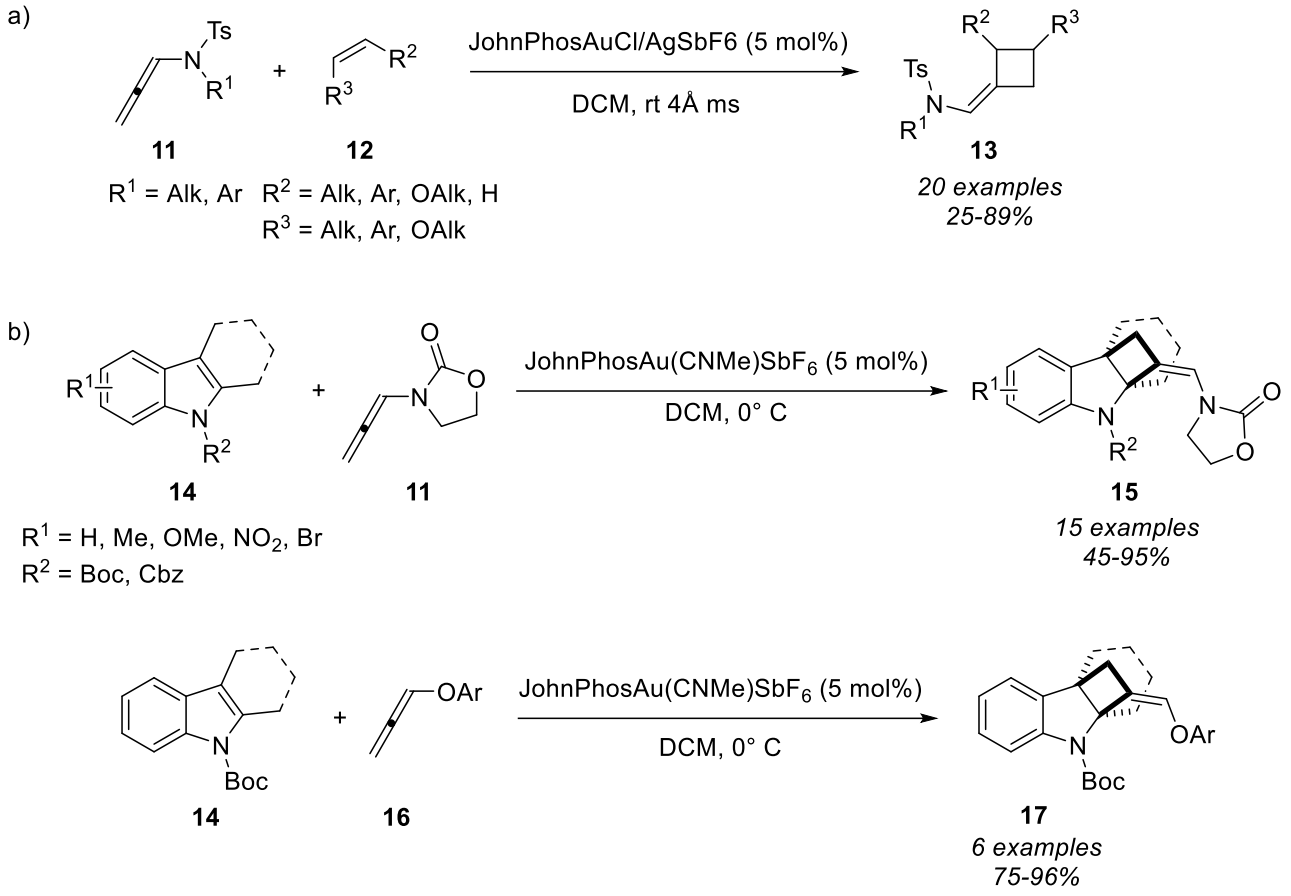
One of the most important complexes is the η^2-allene complex in which gold presents a symmetric or "slipped" interaction with the π-system of the substrate. The particular two orthogonal π-systems allow for the potential formation of four isomeric gold complexes depending on the coordination mode of the gold(I) atom, (figure 2.9).[52,53] Another type of complex is a η^1-species in which gold is bonded to the central *sp*-allenyl carbon atom. In this form, the gold is positioned 45° relative to the orthogonal allene π faces allowing the formation of a planar η^1-cationic complex (η^1-allylic cation). The zwitterionic η^1-carbene intermediate is another extreme representation of η^1-species underlining the possible reactivity of these species as 1,3-dipolar reactants in cycloaddition reactions. Computational study, X-ray crystallography as well as variable temperature NMR spectroscopy of isolated gold(I)-allene complexes established the preferential binding of the metal to the less substituted C-C double bond in the formation of η^2-allene. Gold activated allenes participate in a huge number of reactions from simple hydroarylation to cyclization/cycloaddition reactions. In this latter case, depending on the nature of the predominant gold-intermediate, the features of the catalyst, the type of nucleophile and electrophile, the gold-activated allene can be trapped in (n+2) and (n+3) cyclization/cycloaddition reactions. The first example of the use of allenes as two carbons partner in a gold(I)-catalyzed intramolecular [2+2] annulation was reported by Toste and co-workers in 2007.[54]

They described the synthesis of cyclobutane-containing bicycles **10** starting from allenes tethered vinyl arenes **9** under $Ph_3PAuCl/AgBF_4$ catalysis (scheme 2.1). The proposed mechanism involves addition of the nucleophilic alkene to η^2-gold activated allene to form a carbocationic intermediate **I**, which evolves to the final cyclobutane derivatives by reaction of the vinyl-gold intermediate **II** with the benzylic carbocation.



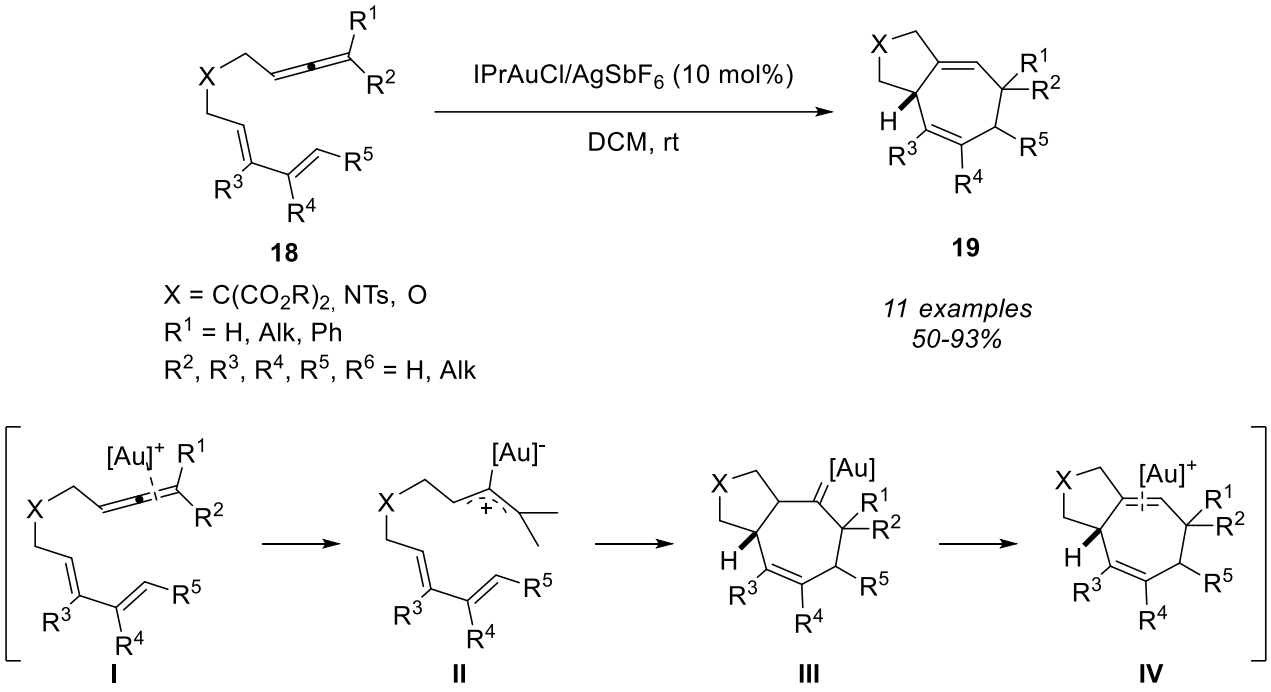
Scheme 2.1

Successively, different research groups proposed the intermolecular version of these [2+2] cyclization reactions. In particular, in 2012 Chen and co-workers reported the synthesis of poly-functionalized cyclobutane derivatives **13** from allenamides **11** and electron-rich olefins **12** under gold catalysis (scheme a) 2.2).[55] Moreover, in 2015, Bandini and co-workers demonstrated that indoles **14** can participate in these reactions with gold activated allenamides **11** and allenylethers **16** for the synthesis of 2,3-cyclobutane fused indolyl derivatives **15** and **17** (scheme b) 2.2).[56]



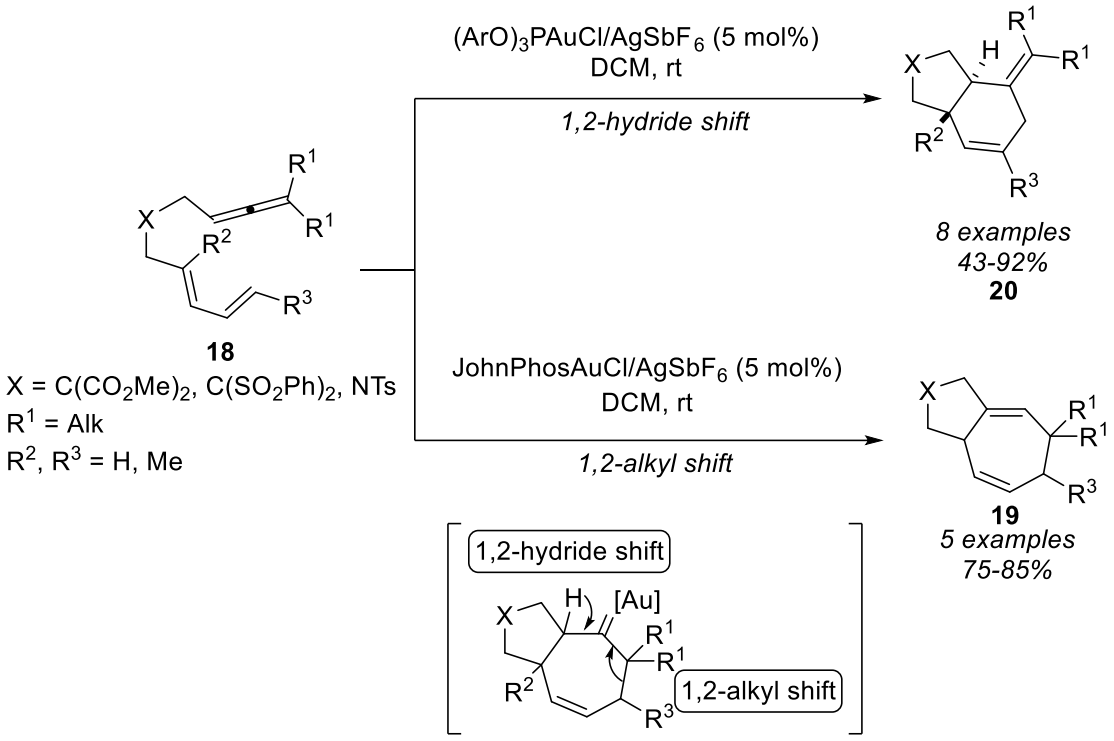
Scheme 2.2

As reported above, allenes can participate as three carbon atoms unit in (n+3) cyclization reactions as gold activated allyl cations. In this direction, in 2009 Mascareñas and co-workers proposed one of the first intramolecular (4+3) gold catalyzed cyclization of allenedienes **18** (scheme 2.3)[57] (Notation in round brackets refers to the number of atoms involved in the cyclization reactions, notation in square brackets refers to a cycloaddition reaction and in particular to the number of electrons involved). They showed the ability of allenes to take part in (4+3) cyclizations with good results in term of regioselectivity. The initial step involves coordination of gold(I) to the allene (intermediate **I**). Then, the first intermediate is the metal-allyl cation **II** and the following cyclization step affords carbene/carbocation seven-member ring **III** in a concerted process. The last step involves a 1,2-H-shift with simultaneous coordination of the newly formed C=C double bond to the metal (intermediate **IV**). In addition, after two years the same research group proposed the enantioselective version of the same (4+3) intramolecular cyclization, using a chiral gold(I) phosphoroamidite catalyst.[58]



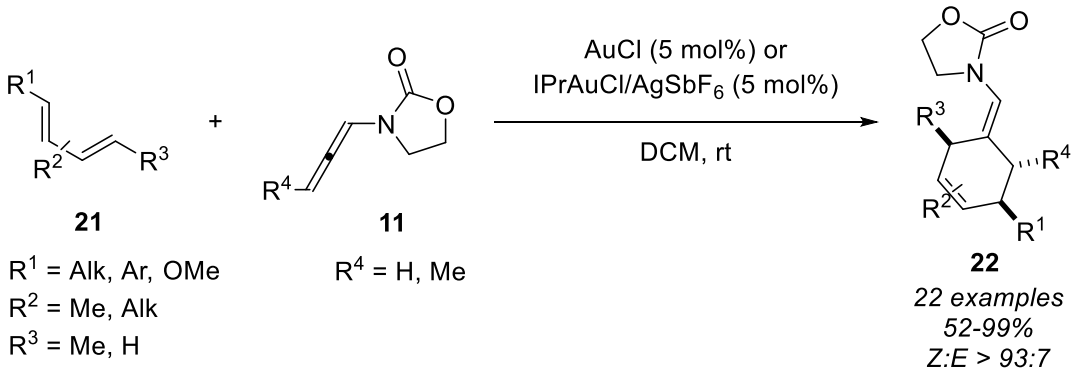
Scheme 2.3

Toste and co-workers made an important advance in these investigations in 2009. They demonstrated the possible reactivity modulation of the allene-diene **18** in order to obtain (4+3) or [4+2] cyclization reaction products **19** and **20**, respectively (scheme 2.4).[59] They demonstrated that the electronic properties of the gold ligand could influence the outcome of the reaction. In particular, employing electron-rich σ-donor ligands, the seven-membered intermediate evolves towards (4+3) cyclization products **19** following the mechanism of hydride shift shown in scheme 2.3. While π-acceptor-containing ligands enhance the [4+2] cyclization rate favoring a mechanism that involves 1,2-alkyl shift. These differences are related to the ability of different gold ligands to influence both steric and electronic chemical environment of the gold carbene intermediate.[60]



Scheme 2.4

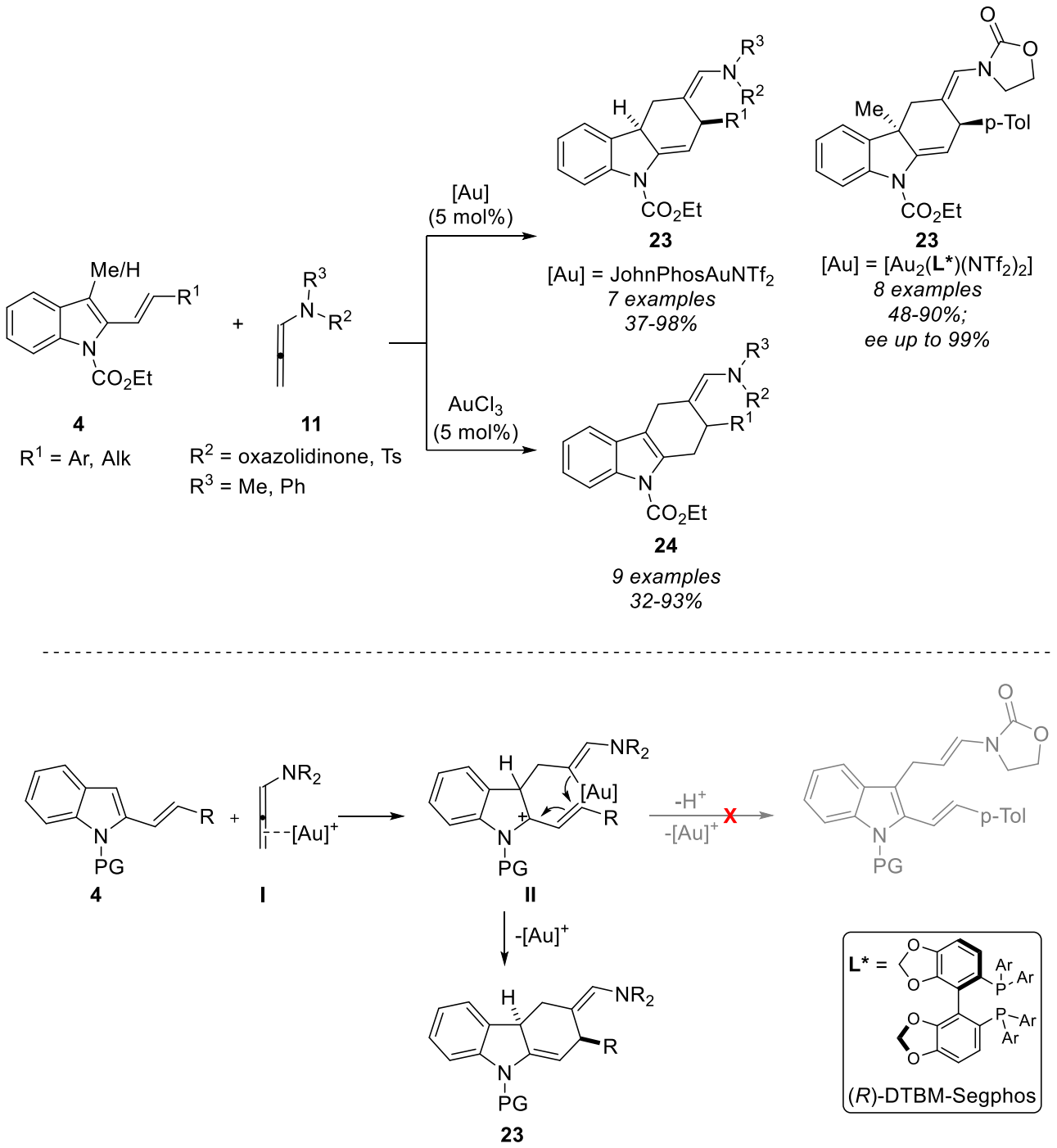
Further steps in this field involve the development of the intermolecular [4+2] cycloadditions forming poly-functionalized six-member rings. Mascareñas and co-workers reported one of the first examples in 2011. They developed the synthesis of cyclohexene derivatives **22** in a highly selective manner employing allenamides **11** and acyclic dienes **21** under gold catalysis (scheme 2.5).[61] The transformation presented a wide scope, allowing for the use of both electron-poor and electron-rich dienes.



Scheme 2.5

An interesting application of this methodology was reported by our research group in 2013[62] and later on in 2017[63] for the [4+2] cycloaddition reactions of vinylindoles **4** with allenes **11**. In

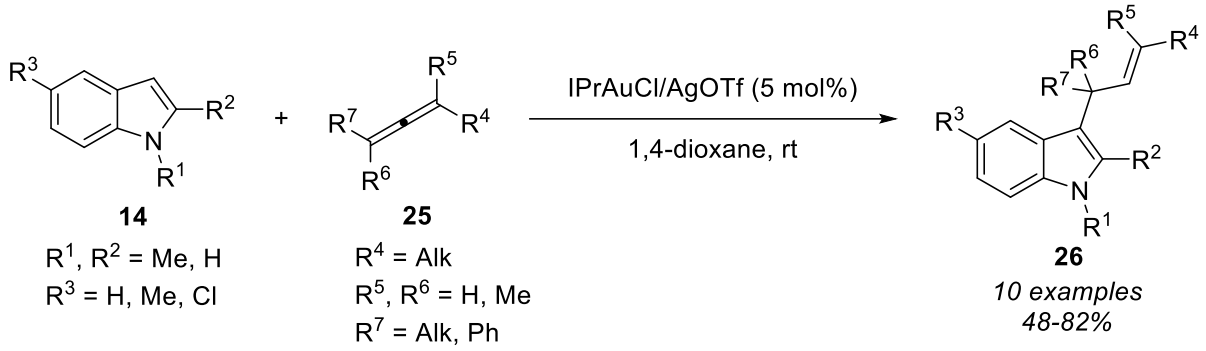
particular, in the first work we realized the synthesis of both aromatic and non-aromatic carbazole derivatives (**23** and **24**, respectively) starting from 2-vinylindoles **4** and allenamides **11** by modulation of the electrophilicity of the gold catalyst employed (scheme 2.6). Instead, in 2017 we reported the enantioselective version of dearomative [4+2] cycloadditions of 3-substituted 2-vinylindoles **4** with allenamides **11** (scheme 2.6). All these reactions involve a mechanism dictated by the polar nature of the involved reactants and intermediates. Thus, a plausible mechanistic rationale for these transformations comprises a gold-promoted activation of the allene followed by the nucleophilic attack of the indole through position C-3 to afford a cationic intermediate **II**. Then cyclization occurs, in a process that is faster than protodemetallation (hydroarylation path). This cyclization leads to the formation of desired carbazole nucleus.



Scheme 2.6

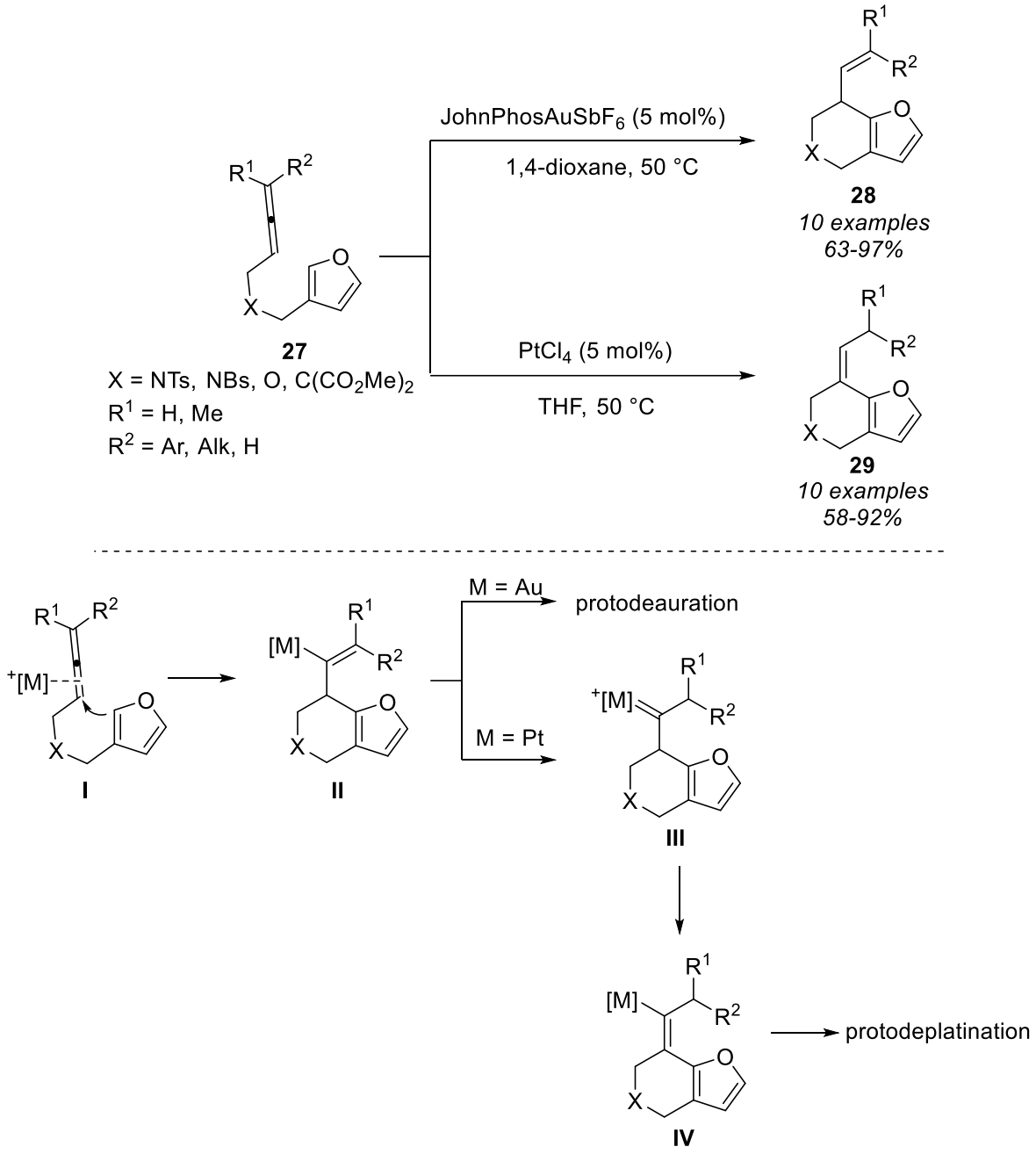
Another interesting aspect of the use of allenes in gold catalyzed processes is the possibility to use gold activated electrophilic gold-allene complexes in hydroarylation reactions with different nucleophiles.[64] As reported in the literature, the transformation requires the presence of electron-rich arenes or heteroarenes. In particular, the most employed are indoles and other heteroaromatics containing oxygen and nitrogen atoms. In literature there are many examples of intramolecular hydroarylation of indole derivatives leading to the formation of polycyclic compounds.[65–68]

However, Widenhoefer and co-workers reported one of the first example of intermolecular hydroarylation of indoles **14** in 2009. A series of substituted allenes **25** were reacted with various indole derivatives under IPrAuCl/AgOTf catalysis for the synthesis of 3-allyl-indoles **26** (scheme 2.7).[69]



Scheme 2.7

Moreover, also furan ring has been involved in hydroarylation reactions with allenes. The first example was reported by Hashmi and co-workers in 2000 for the intermolecular hydroarylation of furans catalyzed by gold(III) chloride.[70] More recently in 2014, Yu and co-workers described the intramolecular 6-*exo*-hydroarylation of 3-(penta-3,4-dien-1-yl)furans **27** for the synthesis of six-membered ring fused furans **28** under JohnPhosAuSbF$_6$ catalysis (scheme 2.8).[71] In addiction, they reported the same reaction catalyzed by another transition metal, platinum, able to activate allenes. In this case, the outcome of the reaction was different, underling the different reaction mechanisms and intermediates involved, leading to the formation of furan derivatives **29**. In gold catalyzed reactions, protodeauration is the final step of the catalytic cycle whereas with platinum a water-assisted proton transfer process *via* a platinum carbene intermediate (**III**) was proposed.


JohnPhosAuSbF6 (5 mol%)
1,4-dioxane, 50 °C
28
10 examples
63-97%
27
X = NTs, NBs, O, C(CO2Me)2
R1 = H, Me
R2 = Ar, Alk, H
PtCl4 (5 mol%)
THF, 50 °C
29
10 examples
58-92%
M = Au
protodeauration
M = Pt
I
II
III
IV
protodeplatination

Scheme 2.8

2.2.2 Synthesis of spiropseudo-indoxyl derivatives

2-spirocyclopentane-1,2-dihydro-3*H*-indol-3-one, commonly known as spiropseudo-indoxyl, is an important nucleus reported in literature as the main skeleton of several alkaloids, such as aristotelone,[72] brevianamide A, paraherquamide A[73,74] (figure a) 2.10). *Aristotelia chilensis* is a branched evergreen tree growing in the humid areas of Chile that contains different indole-based alkaloids of the family of aristotelone. These indole alkaloids seem to be responsible of muscle fibers relaxation, possess antiviral effects against the herpes virus and antitumoral activity in cultural cell of human epidermoid carcinoma of the nasopharynx. The family of brevianamides was originally discovered as metabolites in *Penicillium brevicompactum* and successively some members were found in fungus *Aspergillus fumigatus* or in bacterium *Streptomyces.* This class of compounds shows different biological activities and efficacies, from the treatment of cardiovascular dysfunction to antibacterial or antitumor activity. More complex natural spiropseudo-indoxyl derivatives pertain to the family of paraherquamides discovered from various *Penicillium* and *Aspergillus* species. Several components of the class possess potent anthelmintic and antinematodal activities interesting in veterinary medicine for the treatment of intestinal parasites.

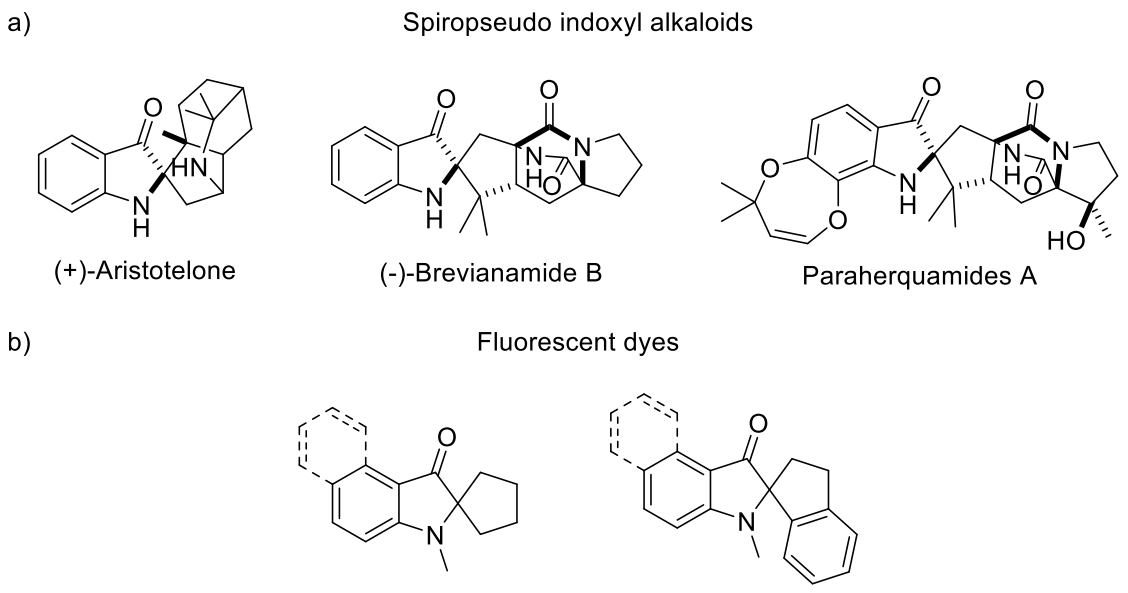
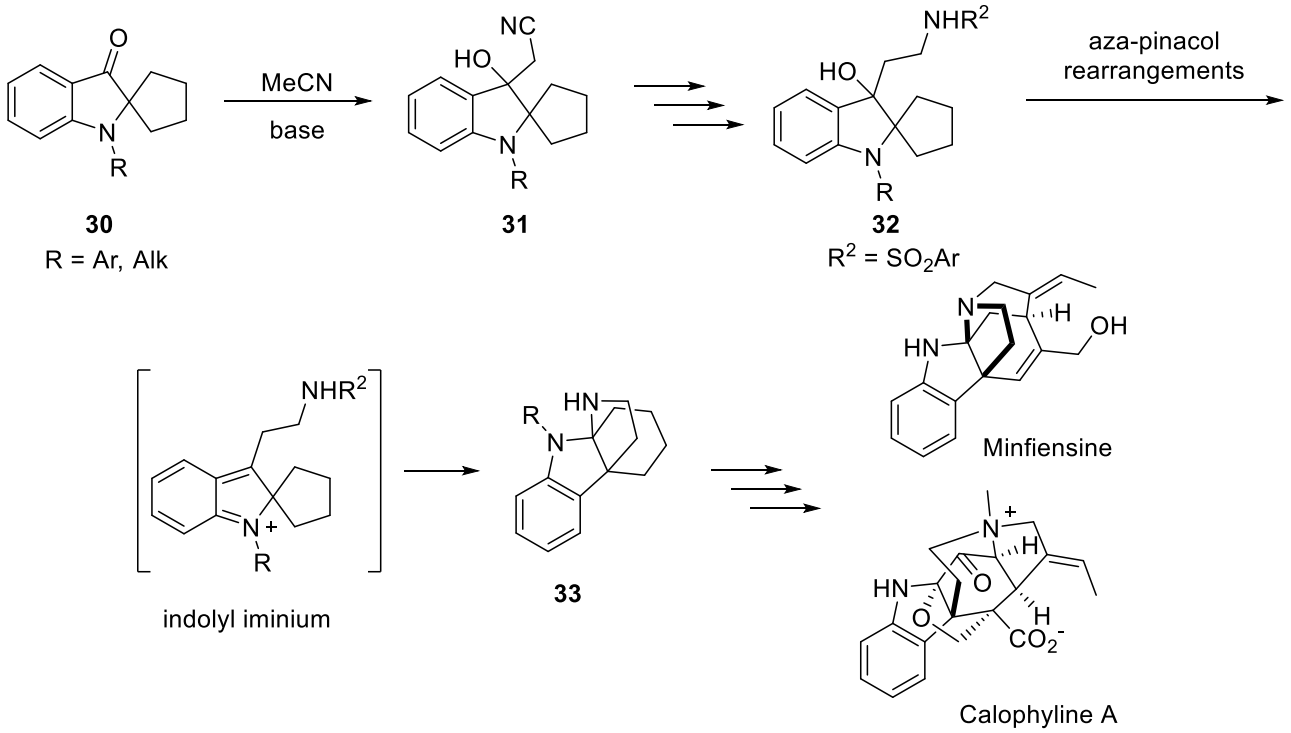


Figure 2.10

Moreover, an interesting application of spiropseudo-indoxyl derivatives was reported by Lin and co-workers in 2016. In particular, they synthesized a series of compounds active as spiro-type two-photon fluorescent dyes for sensing and bioimaging techniques (figure b) 2.10).[75]

Moreover, spiropseudo-indoxyl derivatives **30** are reported in literature as important intermediates for the synthesis of a particular class of alkaloids, called minfiensine and calophyline (scheme

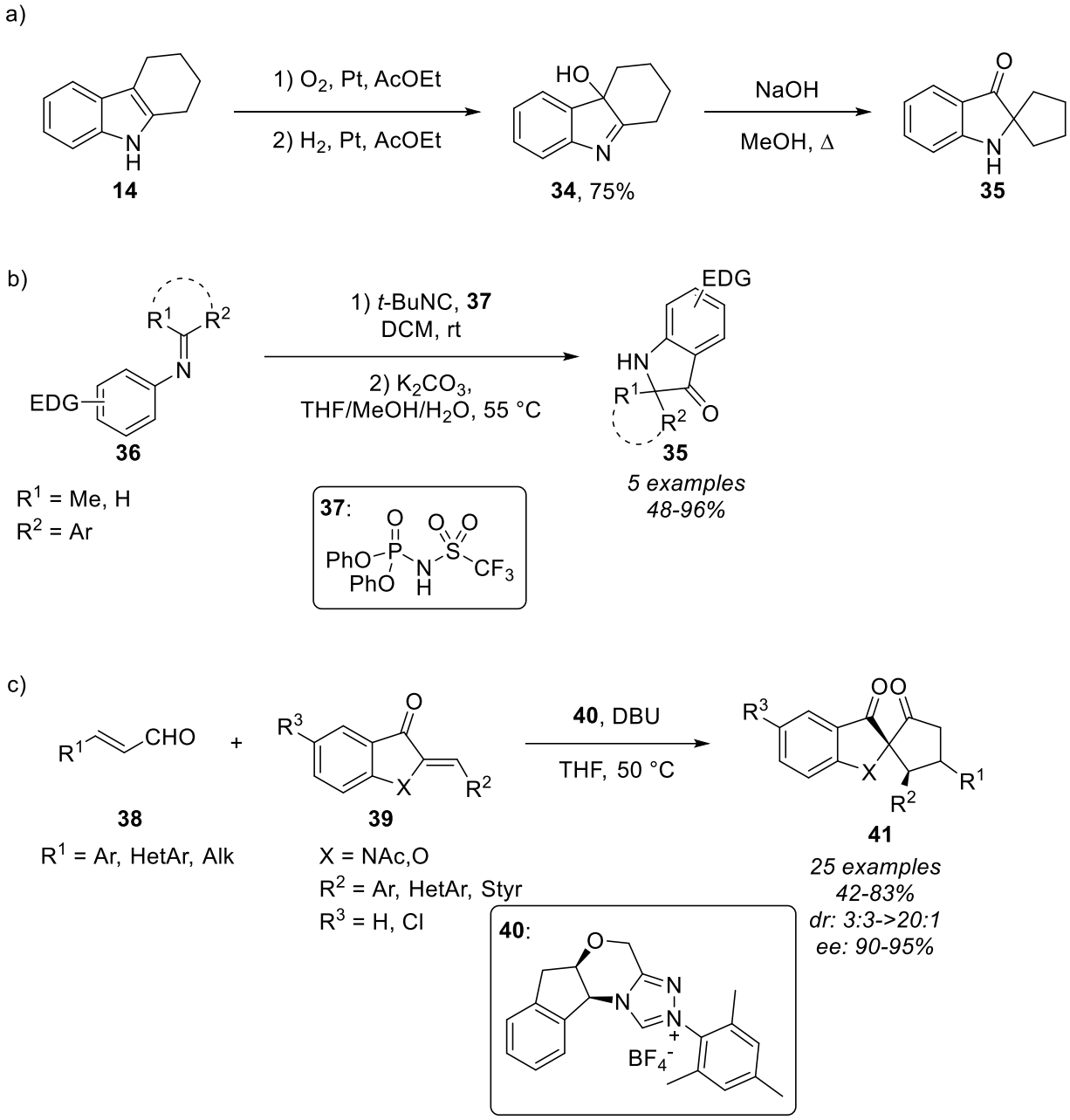
2.9).[76,77] In fact, spiropseudo-indoxyls **30** were employed as substrates in nucleophilic addition at the C-3 carbonyl to produce tertiary alcohol **31**. This latter took part in aza-pinacol rearrangement generating an indolyl iminium ion as intermediate, successively cyclized and functionalized in order to synthetize the tetracyclic core of both minfiensine and calophyline (scheme 2.9).



Scheme 2.9

Patrick and co-worker reported one of the first synthesis of indoxyl derivatives **35** in 1951. Tetrahydrocarbazole **14** underwent oxidation and semi-pinacol rearrangement catalyzed by acid or base giving rise to spiro[cyclopentane-1,2'-indolin]-3'-one **35** (scheme a) 2.10).[78] In 1993, Heathcock and co-worker reported the synthesis of Aristotelone following the same sequence of oxidative/reductive and semi-pinacol rearrangement of Patrick.[79] Over the years, the oxidation/semi-pinacol rearrangement sequence was performed using different type of oxidant sources, *meta*-chloroperbenzoic acid,[80–82] biocatalytic oxidative systems,[83] *N*-sulfonyloxaziridine-type oxidants,[84] aerobic photocatalysis.[85] Another interesting approach for the synthesis of indoxyl derivatives **35** was reported by Sorensen in 2009 proposing an interrupted Ugi reaction with imines **36** and isocianides (scheme b) 2.9).[86] The reaction occurred in two steps, the first was the Ugi reaction promoted by a phosphoric acid, while the second step was the basic hydrolysis of the imine obtained. However, the reaction took place only in the presence of electron rich anilines. Recently, in 2014 Glorius and co-workers reported one of the first efficient enantioselective N-heterocyclic

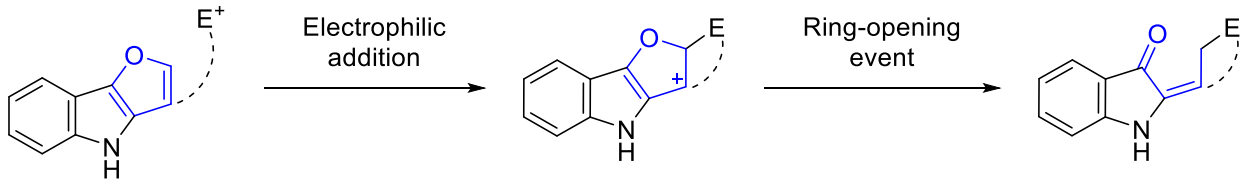
carbene catalyzed formal [3+2] annulation of α,β-unsaturated aldehydes **38** with azaaurones **39** (scheme c) 2.10) for the synthesis of the corresponding spiro derivatives **41**.[87]



Scheme 2.10

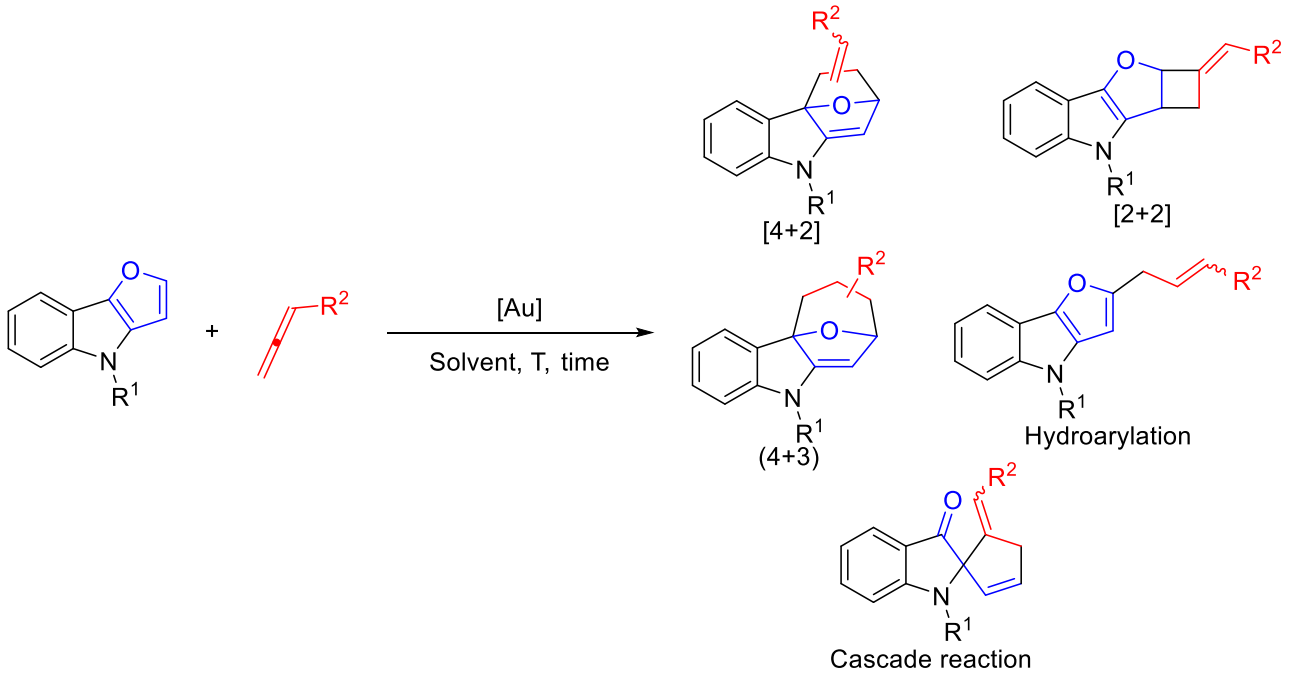
2.2.3 Objectives

Starting from our expertise in gold-catalyzed reaction of vinylindoles with allenes and given the structural analogy of these derivatives with 4*H*-furo[3,2-*b*]indoles, we decided to test the reactivity of 4*H*-furo[3,2-*b*]indoles with allenamides under gold catalysis. The aim was to develop a new cascade process including functionalization at the furan moiety, possibly followed by a ring-opening event (scheme 2.11).



Scheme 2.11

We started our investigation with the development of an efficient synthesis for 4*H*-furo[3,2-*b*]indoles bearing different functional groups. Then, we tested their reactivity in the presence of allenamides under gold catalysis. In principle, allenes can participate in these reactions as C2 or C3 synthons and their reactions with the rigid 4π-system of furoindoles could afford different (4+*n*) cyclization compounds as well as addition or isomerization reactions (Scheme 2.12).



Scheme 2.12

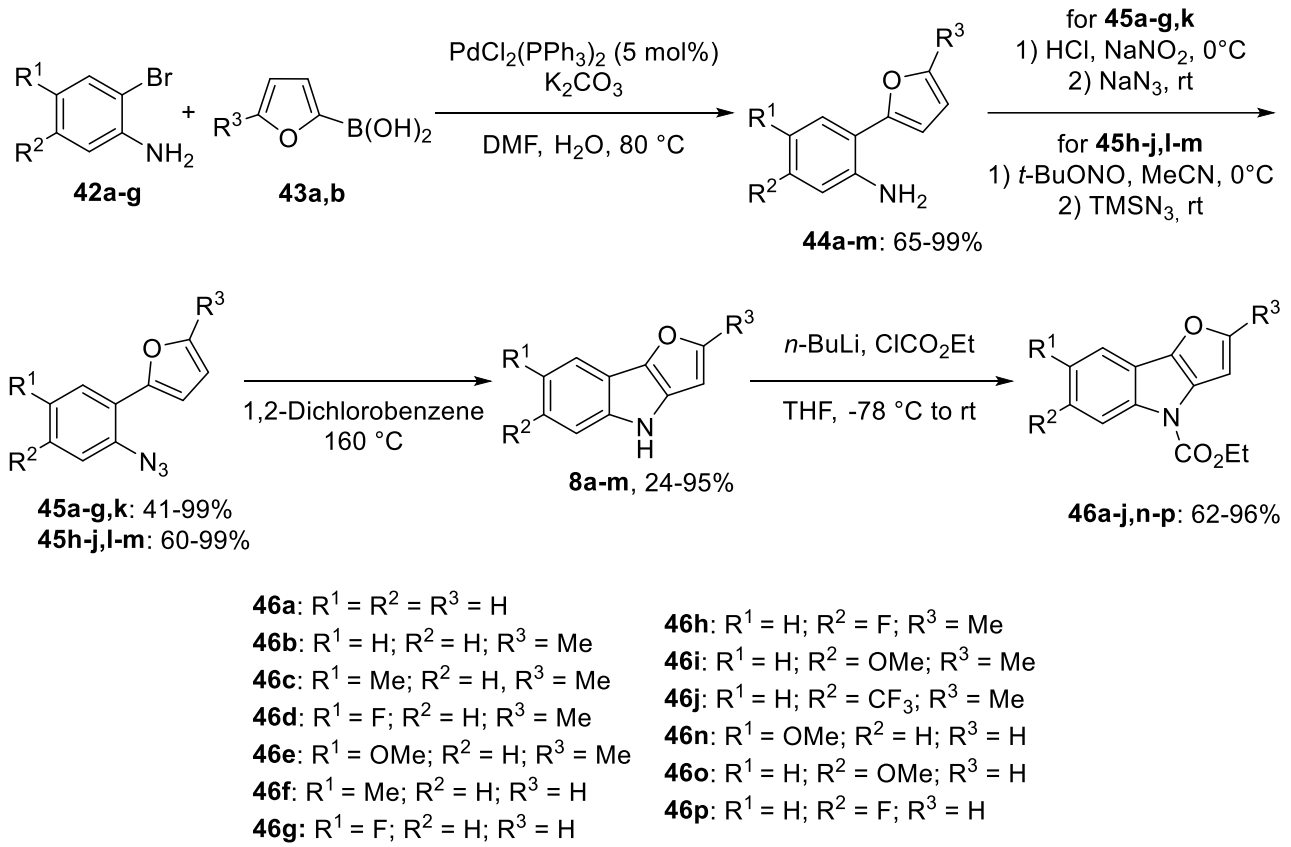
As reported before allenes are able to react with dienes in [4+2] cycloaddition leading to the formation of carbazole derivatives. However, the furan moiety could react as C2 synthon in a [2+2] cycloaddition reaction forming cyclobutane derivatives. Moreover, the (4+3) cycloaddition reaction could generate an interesting 7-member adduct, when the allene take parts in the cyclization as C3 synthon. Furthermore, it is important to take into consideration the possible rearrangement related to the furan moiety.[88,89] In fact, the addition of a suitable partner at C2 carbon of furan, could give rise to a ring-opening event with successive rearrangement. Finally, the electron rich furo moiety could undergo simple hydroarylation reactions with gold-activated electrophilic allenes. Thus, the study of the selectivity and the usefulness for these hypothetical transformations appears noteworthy.

2.2.4 Synthesis of starting materials

In this work of thesis, ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a-k,n-p**, as well as *N*-allenamides **11a-g**, both bearing groups with different electronic properties, have been synthetized and used.

2.2.4.1 Synthesis of 4H-furo[3,2-b]indole ***46a-k,n-p***

Searching in the literature, we noticed that the reported methodologies for the synthesis of furoindoles were poor in term of quantity and reaction yields. We started from the results reported by Sapi[90] and we adopted a modified procedure that comprises four different steps for the synthesis of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46** (scheme 2.13). The first step was a Suzuki-Miyaura cross-coupling reaction between 2-bromoanilines **42** and furan-2-ylboronic acids **43** under the conditions reported by Perumal.[91]



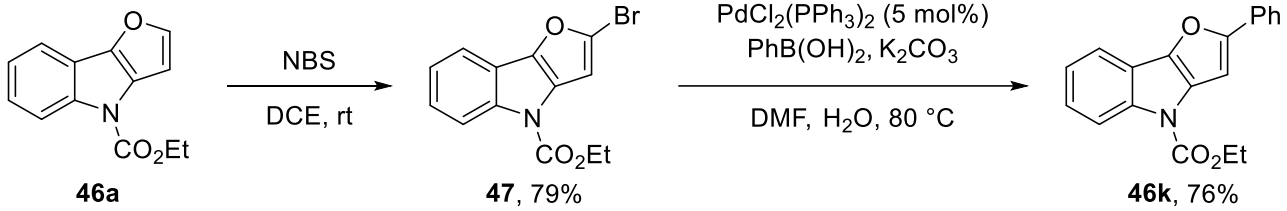
46a: $R^1 = R^2 = R^3 = H$
46b: $R^1 = H$; $R^2 = H$; $R^3 = Me$
46c: $R^1 = Me$; $R^2 = H$, $R^3 = Me$
46d: $R^1 = F$; $R^2 = H$; $R^3 = Me$
46e: $R^1 = OMe$; $R^2 = H$; $R^3 = Me$
46f: $R^1 = Me$; $R^2 = H$; $R^3 = H$
46g: $R^1 = F$; $R^2 = H$; $R^3 = H$
46h: $R^1 = H$; $R^2 = F$; $R^3 = Me$
46i: $R^1 = H$; $R^2 = OMe$; $R^3 = Me$
46j: $R^1 = H$; $R^2 = CF_3$; $R^3 = Me$
46n: $R^1 = OMe$; $R^2 = H$; $R^3 = H$
46o: $R^1 = H$; $R^2 = OMe$; $R^3 = H$
46p: $R^1 = H$; $R^2 = F$; $R^3 = H$

Scheme 2.13

The reaction required the use of bis(triphenylphosphine)palladium (II) dichloride as catalyst and was conducted in the presence of K_2CO_3 as base and DMF as solvent. The Suzuki-Miyaura cross-coupling gave rise to a series of 2-(furan-2-yl)anilines **44a-m** in good to excellent yields. Successively, the

synthesis of the corresponding azides **45** could be performed following two different strategies. The first involves, as reported by Tanaka, the classical formation of a diazonium salt by treatment of the aniline with $NaNO_2$ in acidic medium followed by treatment with NaN_3 and allowed for the synthesis of azides **45a-g,k**.[28] The second approach required the use of less hazardous, more stable and non-explosive reagents such as *tert*-butyl nitrite (*t*-BuONO) and azidotrimethylsilane ($TMSN_3$) and was adopted for the preparation of azides **45h-j,l-m**.[92] Then, for the preparation of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a-j,n-p**, a thermal ring closure in 1,2-dichlorobenzene[28] was required followed by protection of the nitrogen atom with an electron-withdrawing group using *n*-butyllithium and ethylchloroformate.[63]

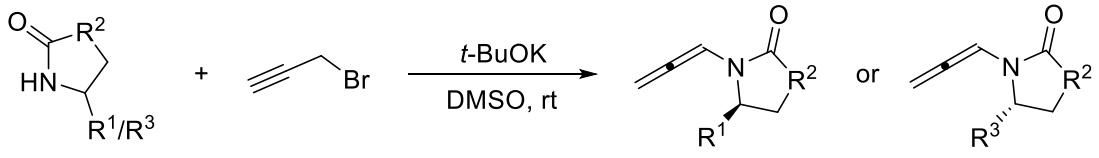
The synthesis of ethyl 2-phenyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46k** was achieved by bromination of compound **46a** at the C2 carbon atom of the furan moiety using *N*-bromosuccinimide followed by Suzuki-Miyaura cross-coupling reaction with phenylboronic acid under the same conditions reported before (scheme 2.14)



Scheme 2.14

*2.2.4.2 Synthesis of N-allenamides **11a-j***

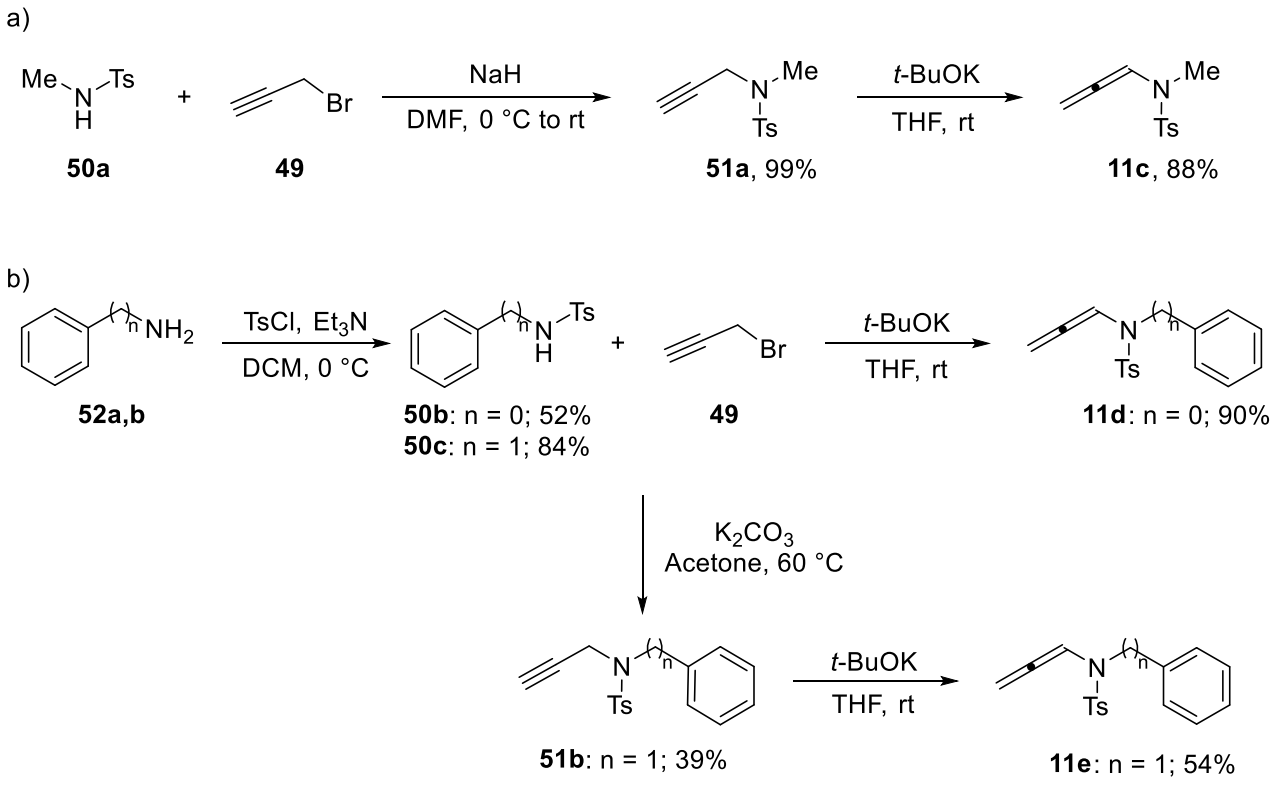
N-allenamides **11a-g** were synthetized following known procedures. Thus, the oxazolidinone derivatives **11a-b,g-j** were synthetized from the corresponding unsubstituted oxazolidinones **48a,b,g-j** in a two steps one pot-reaction using propargyl bromide **49** for the alkylation step and *t*-BuOK for the final isomerization step (scheme 2.15).[93,94]



11a: R^1 = H, R^2 = O; 52%
11b: R^1 = H, R^2 = CH_2; 40%
11g: R^1 = Bn, R^2 = O; 70%
11h: R^1 = Ph, R^2 = O; 40%
11i: R^3 = Ph, R^2 = O; 15%
11j: R^3 = *i*-Pr, R^2 = O; 80%

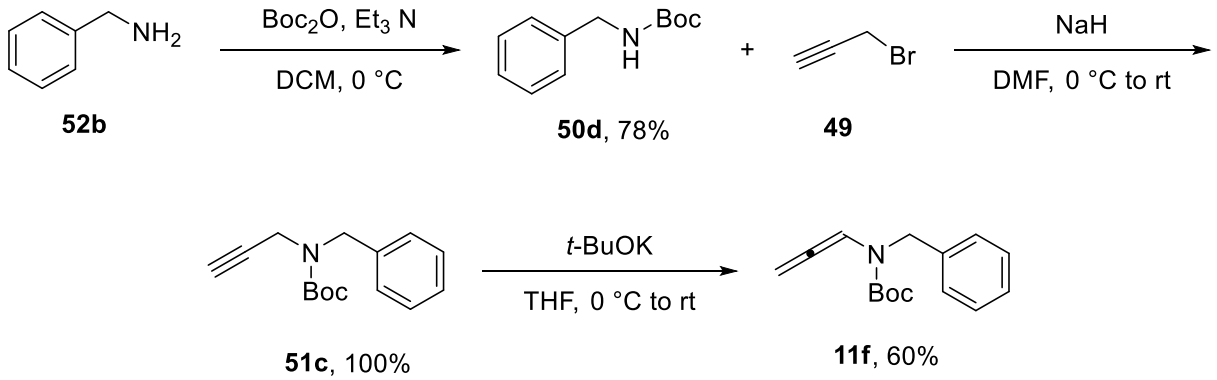
Scheme 2.15

The *N*-tosyl allenamides **11c-e** were synthetized following literature procedures *via* alkylation with propargyl bromide **49** and isomerization of the appropriate tosylamides under basic conditions (scheme 2.16).[95,96]



Scheme 2.16

The *N*-Boc allenamide **11f** was synthetized starting from benzyl amine with a procedure that involved *N*-protection with Boc_2O followed by alkylation and isomerization (scheme 2.17).[97]

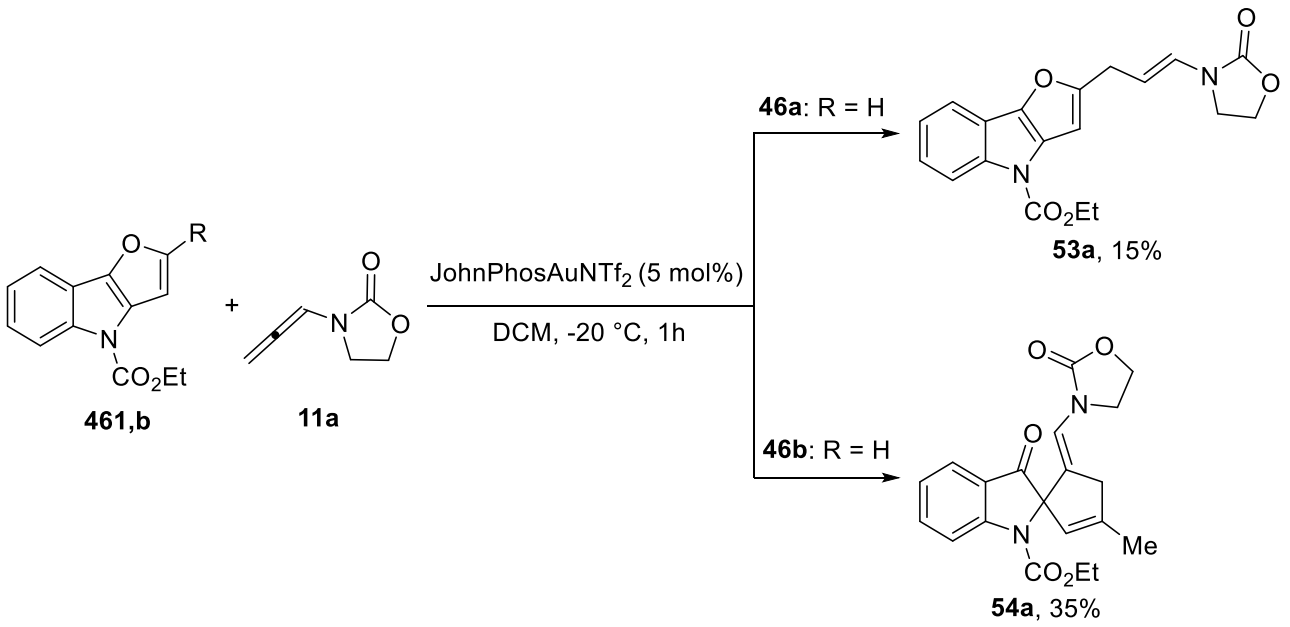


Scheme 2.17

2.2.5 Gold catalyzed cascade reactions between 4*H*-furo[3,2-*b*]indoles and *N*-allenamides

2.2.5.1 Initial studies

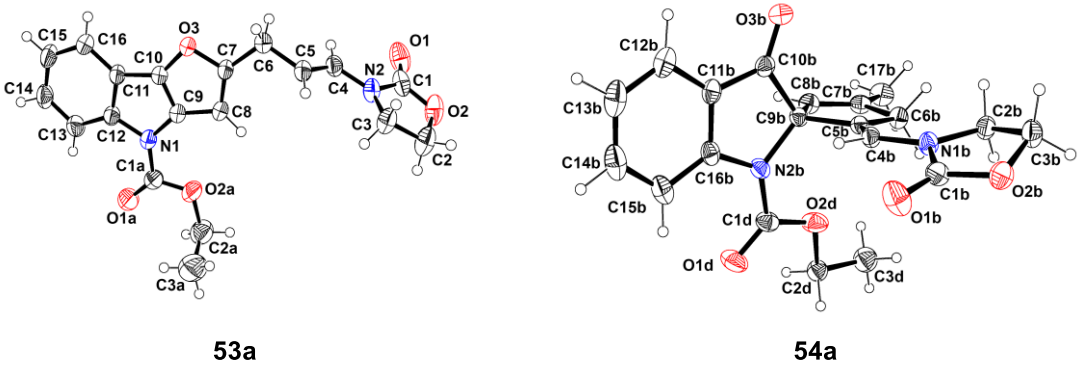
At the beginning, furoindoles **46a** and **46b** were chosen as models for the gold catalyzed transformation with allenamide **11a**. Two different furoindoles were employed to evaluate the influence of the C2 substitution, H *versus* Me, on the reaction outcome in the presence of a gold activated π-system. The C2 position on the furan moiety represents the nucleophilic site of the molecule and the substituent could modify its reactivity and, as a consequence, the entire reaction path. To start the investigation, JohnPhosAuNTf$_2$ was employed as catalyst with both furoindoles **46a,b** (scheme 2.18). The choice of the catalyst was based on previously reported studies on the reactivity of allenes with dienes.[59,62]



Scheme 2.18

Thus, employing the non-substituted furoindole **46a**, the obtained product was the predictable hydroarylated furoindole derivative **53a** although in low yield. This result was in accordance with previously reported literature examples for the allenes reactivity under gold catalysis. However, in the second case, the C2-methyl substituted furoindole **46b** afforded a more interesting and unexpected spiropseudo-indoxyl derivative **54a** isolated in 35% yield. Compound **54a** probably arises from a cascade reaction involving ring-opening and ring-closing events. Moreover, it is important to underline that the furan moiety, in both transformations, did not act as diene or two carbons

component of a cycloaddition reaction, unlike 2-vinylindoles[62,63]. On the contrary, it was inclined to present the reactivity of furan compounds.[71] The correct structures and the geometries around the double bond were established for both compounds, by analytical and spectroscopic data and confirmed by X-ray diffraction analysis of single crystal (figure 2.11).



53a **54a**

Figure 2.11

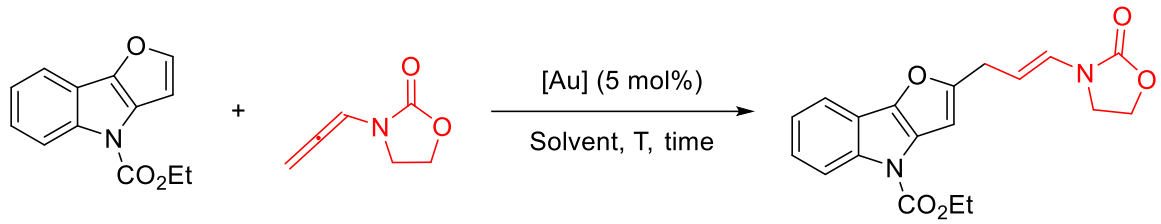
In these preliminary experiments, 4*H*-furo[3,2-*b*]indoles **46a-b** were reacted with 1.2 equivalents of allenamide **11a** in presence of 5 mol% of cationic gold(I) JohnPhosAuNTf$_2$ in dichloromethane at -20 °C for 1 hour. As reported in scheme 2.18, under these conditions, the hydroarylated product **53a** was isolated in 15% yield besides a complex mixture of unidentified products, while spirospeudo-indoxyl derivative **54a** was obtained in 35% yield beside unreacted furoindole **46a**.

It is worth to note that both products were obtained as single isomers in a chemo-, regio- and stereoselective way. In addition, the hydroarylated product **53a** was an unknown compound, never reported in literature, while the spiropseudo-indoxyl derivative **54a** revealed a new cascade reaction pathway for 4*H*-furo[3,2-*b*]indoles. Thus, for these reasons, we decided to carry out a more detailed study directed towards the identification of the reaction conditions that could increase the yields for each compound **53a** and **54a**.

*2.2.5.2 Screening of the reaction conditions for the synthesis of compound **53a***

For the synthesis of hydroarylated derivative **53a**, the evaluation for the best reaction conditions was pursued by reacting furoindole **46a** and allenaminde **11a** in the presence of different metal catalysts, solvents and reagents ratio. The obtained results are summarized in Table 2.1

*Table 2.1 Optimization of reaction conditions for the synthesis of **53a***



46a **11a** **53a**

Entry	46a/11a	[Au]	Solvent, M	T, °C	Time, min	53a[b] %
1	1/1.2	JohnPhosAuNTf$_2$	DCM, 0.05 M	- 20	60	15
2	1/1.2	IPrAuNTf$_2$	DCM, 0.05 M	- 20	60	n.r.[c]
3	1/1	(ArO)$_3$PAuNTf$_2$	DCM, 0.05 M	- 20	60	75
4	1.2/1	(ArO)$_3$PAuNTf$_2$	DCM, 0.05 M, 4Å ms	- 20	30	81
5	1.2/1	(ArO)$_3$PAuNTf$_2$	Toluene, 0.05 M, 4Å ms	- 20	15	90
6	1.2/1	HNTf$_2$ (20 mol%)	Toluene, 0.05 M, 4Å ms	- 20	15	n.r.[c]

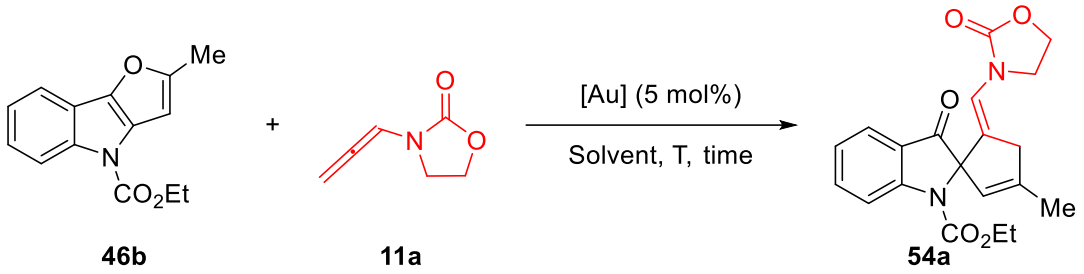
[a]All reactions were carried out using **46a** (0.2-0.24 mmol) and **11a** (0.2-0.24 mmol) in the stated solvent (0.05 M). [b] Isolated yield. [c]Complex mixture of unidentified products was observed besides starting materials. [d]Ar = 2,4-di-t-butylphenyl. IPr = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]. JohnPhos = (2-Biphenyl)di-tert-butylphosphine.

As reported before, the use of JohnPhosAuNTf$_2$ as catalyst in DCM at -20 °C gave rise, after 1 hour, to 15% yield of the desired product (entry 1). Successively an N-heterocyclic carbene IPrAuNTf$_2$ was employed, but the reaction did not take place and a series of unidentified products were detected besides the starting materials *via* ^{1}H-NMR analysis of the reaction mixture (entry 2). Changing the electronic features of the gold catalyst from poor electrophilic carbene complex to highly electrophilic triarylphosphite gold complex, a visible increase of the yield was observed and the hydroarylated product **53a** was obtained in 75% yield (entry 3). The addition of 4 Å molecular sieves and the use of a small excess of furoindole **46a** increased the yield to 81% (entry 4), but the best reaction yield (90%) was reached switching the solvent from DCM to toluene (entry 5). In order to verify the effective catalysis of the metal complex and the eventual influence of an acidic promoter, the reaction was reproduced in the presence of 20 mol% of trifluoromethanesulfonimide (HNTf$_2$) resulting in a complex mixture of unidentified products and starting materials (entry 6).

*2.2.5.3 Screening of the reaction conditions for the synthesis of compound **54a***

For the evaluation of the best reaction conditions for the synthesis of spiropseudo-indoxyl derivative **54a**, different metal catalysts, reactant ratios and solvents were tested. The obtained results are summarized in Table 2.2

*Table 2.2 Optimization of reaction conditions for the synthesis of **54a***



46b **11a** **54a**

Entry	46b/11a	Catalyst	Solvent, [M]	T, °C	Time, min	54a[b], %
1	1/1.2	JohnPhosAuNTf$_2$	DCM, 0.05 M	- 20	60	35%
2	1/1	(ArO)$_3$PAuNTf$_2$	DCM, 0.05 M	- 20	60	32%
3	1/1	IPrAuNTf$_2$	DCM, 0.05 M	- 20	180	57%
4	1/1	IPrAuNTf$_2$	Toluene, 0.05 M	- 20	180	n.r.[c]
5	1/1.2	IPrAuNTf$_2$	DCM, 0.05 M	- 20	60	68%
6	1/1.2	IPrAuSbF$_6$	DCM, 0.05 M	- 20	60	63%
7	1/1.2	HNTF$_2$ (20 mol%)	DCM, 0.05 M	- 20	60	n.r.[d]
8	1/1.5	[Rh(COD)Cl]$_2$	DCM, 0.05 M	- 20	24 h	n.r.[d]
9	1/1.5	PtCl$_2$	DCM, 0.05 M	- 20	24 h	n.r.[d]

[a]All reactions were carried out using **46b** (0.2 mmol) and **11a** (0.2-0.24 mmol) in the stated solvent (0.05 M). [b]Isolated yield. [c]Complex mixture of unidentified products was observed besides starting materials. [d]Starting **46b** (and **11a**) was (were) recovered unreacted at the end of the reaction (see text). [e]Ar = 2,4-di-t-butylphenyl, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, JohnPhos = (2-Biphenyl)di-tert-butylphosphine, [Rh(COD)Cl]$_2$ = chloro(1,5-cyclooctadiene)rhodium(I) dimer

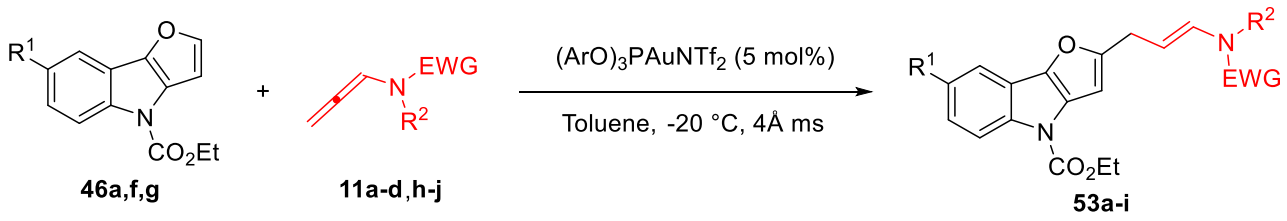
As reported before, the reaction performed under JohnPhosAuNTf$_2$ catalysis in DCM resulted in the isolation of compound **54a** in 35% yield (entry 1). Successively two different gold(I) catalysts were tested in DCM with equimolecular amounts of **46b**/**11a**. IPrAuNTf$_2$ gave better results than (ArO)$_3$PAuNTf$_2$ after 3h (entries 2 and 3). The variation of the solvent in favor of toluene led to a negative effect on the outcome of the reaction resulting in a complex mixture of unidentified

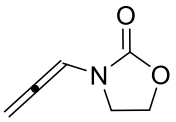
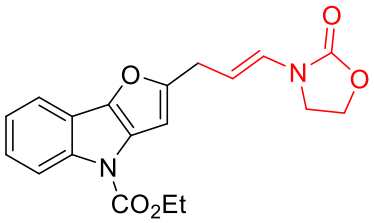
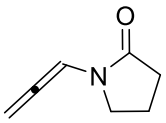
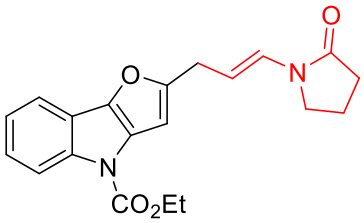
compounds and starting materials (entry 4). The best result in term of yield required the use of 1.2 equivalent of the allenamide **11a** with $IPrAuNTf_2$ (entry 5). In this transformation, the influence of the counterion was not so relevant, as demonstrated by a slight decrease in the yield choosing SbF_6 as counter anion (entry 6). In addition, the activity of $HNTf_2$ was tested to verify the real need of the metal catalyst to promote the reaction (entry 7). Finally, other transition metals were examined using an excess of allenamide **11a**. Rhodium and platinum were employed because of their well-known[53,98] ability of activation of allenes. However, product **54a** could not be isolated and **46b** and **11a** were recovered unreacted (entries 8 and 9).

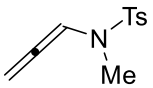
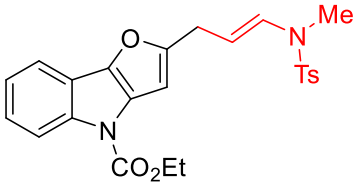
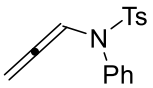
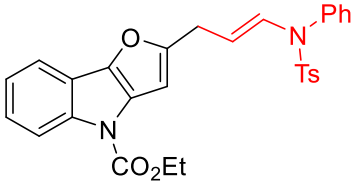
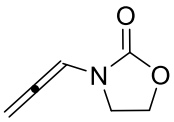
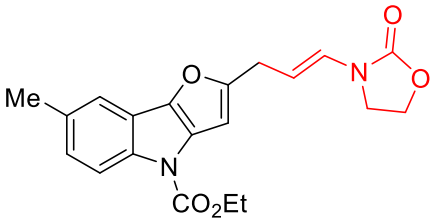
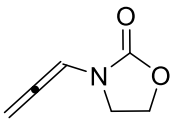
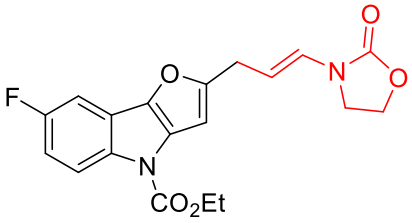
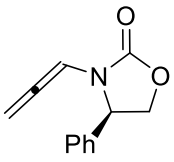
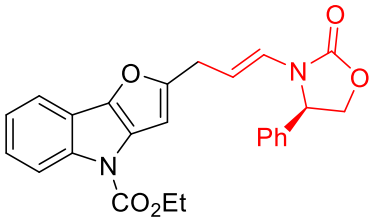
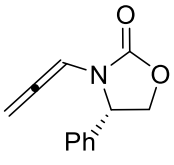
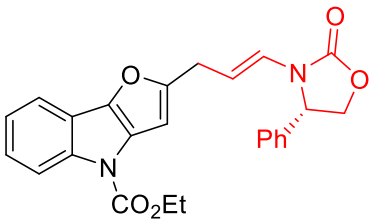
2.2.5.4 Scope for the synthesis of hydroarylated 4H-furo[3,2-b]indole derivatives ***53***

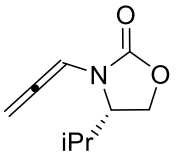
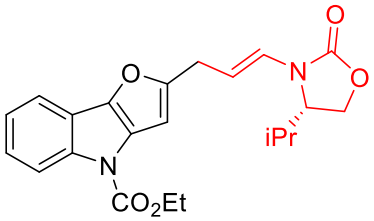
Having in hand the best reaction conditions for the synthesis of hydroarylated 4*H*-furo[3,2-*b*]indole derivatives **53a** (Table 2.1 entry 5), we next started to examine the scope and the limitation of the reaction between ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a-k** and *N*-allenamides **11a-d,h-j**. The results are summarized in Table 2.3

Table 2.3 Scope for the synthesis of compound ***53a-i***



Entry	46	R^1	11	Product	Yield,[b] %
1	**46a**	H	 **11a**	 **53a**	90
2	**46a**	H	 **11b**	 **53b**	80

3	**46a**	H	 **11c**	 **53c**	61[c]
4	**46a**	H	 **11d**	 **53d**	60[c]
5	**46f**	Me	 **11a**	 **53e**	70
6	**46g**	F	 **11a**	 **53f**	95
7	**46a**	H	 **11h**	 **53g**	90
8	**46a**	H	 **11i**	 **53h**	85

9	**46a**	H	 **11j**	 **53i**	92

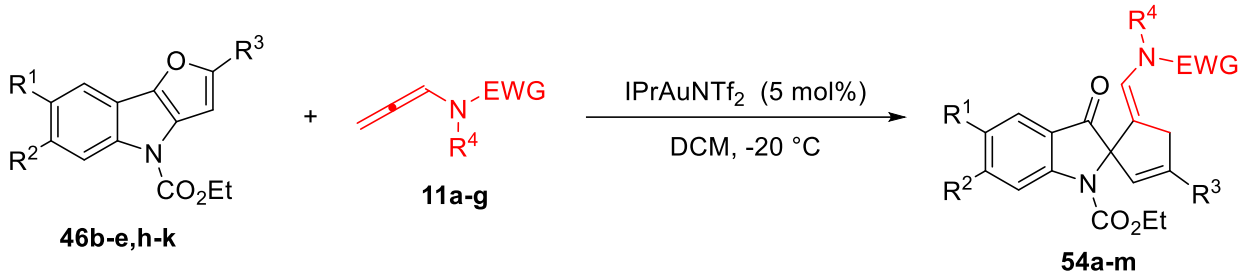
[a]All reactions were carried out using **46** (0.24 mmol), **11** (0.2 mmol), $(ArO)_3PAuNTf_2$ (5 mol%) in toluene (0.05 M), 4Å ms, -20 °C, 15 min. [b]Isolated yields. [c]Reactions carried out in toluene 0.01 M for 1h.

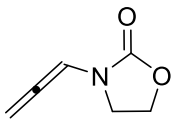
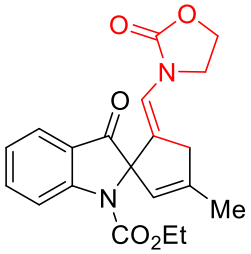
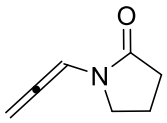
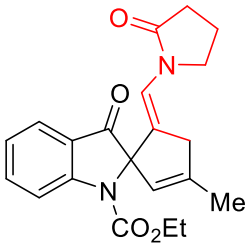
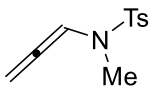
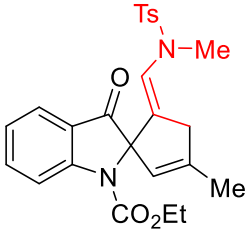
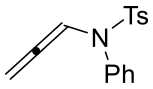
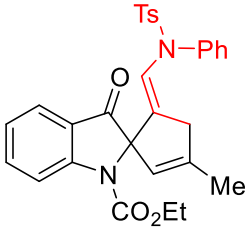
As reported before, the hydroarylated product **53a** was obtained in 90% yield, using the unsubstituted *N*-allenamide **11a** (see table 2.1 or table 2.3 entry 1). Successively, we start to evaluate the tolerance of the reaction in the presence of different *N*-allenamides. In particular, using similar pyrrolidone-derived *N*-allenamide **11b,** the formation of the product **53b** reached 80% of yield (entry 2). Changing the electron-withdrawing group in favor of *p*-toluenesulfonamide, the transformation took place in good yield, however it required the dilution of the reaction to 0.01 M in order to prevent the competitive [2+2] dimerization of allene. Therefore, using *N*-tosylallenamides **11c** and **11d** the corresponding products **53c** and **53d** were obtained with 61% and 60% yield, respectively (entries 3 and 4). Investigating the influence of different substituents on the indole moiety, ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46f** and **46g**, bearing respectively methyl and fluoro at the C7 carbon, were employed giving rise to the desired compounds in good yield (70% for **53e** and 95% for **53f**, entries 5 and 6). Finally, compound **46a** was tested with a series of enantiopure allenamides **11h-j** bearing *iso*-propyl or phenyl groups on the oxazolidinone moiety, obtaining the corresponding products **53g-i** in high yields and without loss of the stereochemical information (entries 7, 8 and 9). As reported before, the correct structure and the geometry around the double bond were confirmed for all compounds, by analytical and spectroscopic data and confirmed by analogy with the result of the X-ray diffraction analysis of single crystal performed for **53a** (figure 2.11).

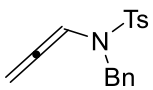
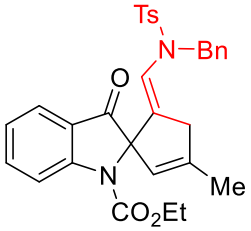
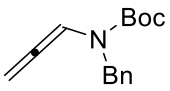
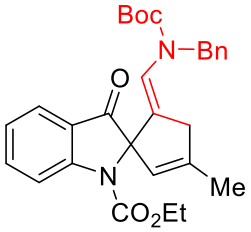
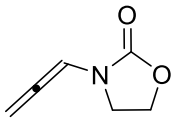
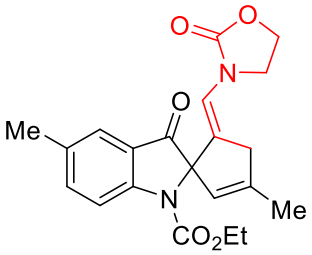
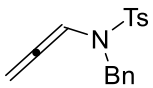
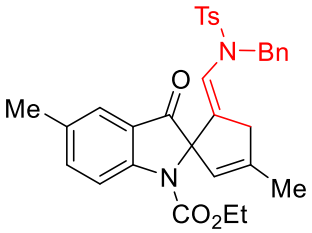
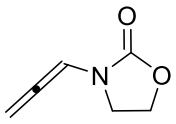
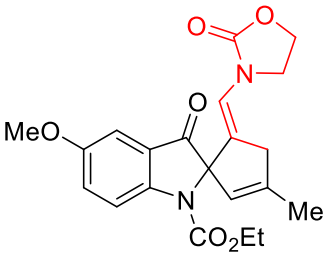
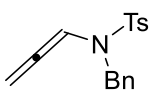
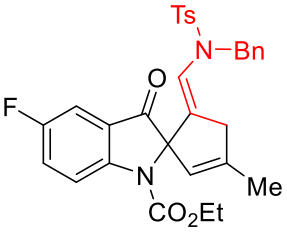
*2.2.5.5 Scope for the synthesis of sprirospeudo indoxyl derivatives **54***

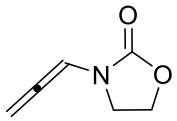
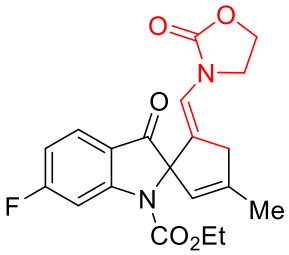
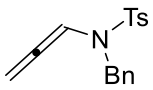
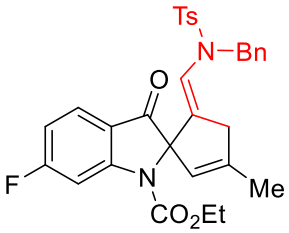
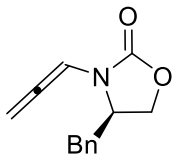
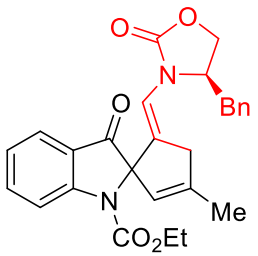
Then, the scope for the synthesis of sprirospeudo-indoxyl derivatives **54a-m** was developed using 4*H*-furo[3,2-*b*]indole-4-carboxylates **46b-e,h-k** and *N*-allenamides **11a-g** under the best reaction conditions reported before (Table 2.2, entry 5). The results are summarized in Table 2.4.

Table 2.4 Scope for the synthesis of compound ***54a-m***



Entry	46	R^1	R^2	R^3	11	Product	Yield,[b] %
1	**46b**	H	H	Me	 **11a**	 **54a**	68
2	**46b**	H	H	Me	 **11b**	 **54b**	61[c]
3	**46b**	H	H	Me	 **11c**	 **54c**	77
4	**46b**	H	H	Me	 **11d**	 **54d**	49

5	**46b**	H	H	Me	 **11e**	 **54e**	62
6	**46b**	H	H	Me	 **11f**	 **54f**	72[d]
7	**46c**	Me	H	Me	 **11a**	 **54g**	56[c]
8	**46c**	Me	H	Me	 **11e**	 **54h**	60[c,e]
9	**46e**	OMe	H	Me	 **11a**	 **54i**	44[c]
10	**46d**	F	H	Me	 **11e**		45[c]

11	**46h**	H	F	Me	 **11a**	 **54k**	52[c]
12	**46h**	H	F	Me	 **11e**	 **54l**	65[c]
13	**46b**	H	H	Me	 **11g**	 **54m**	49[c,e]

[a] All reactions were carried out using **46** (0.2 mmol), **11** (0.24 mmol), $IPrAuNTf_2$ (5 mol%) in DCM (0.05 M), -20 °C, 1-18 h. [b]Isolated yields. [c]1.5 eq. of **11** were used. [d]2.0 eq. of **11** were used. [e]Slow addition.

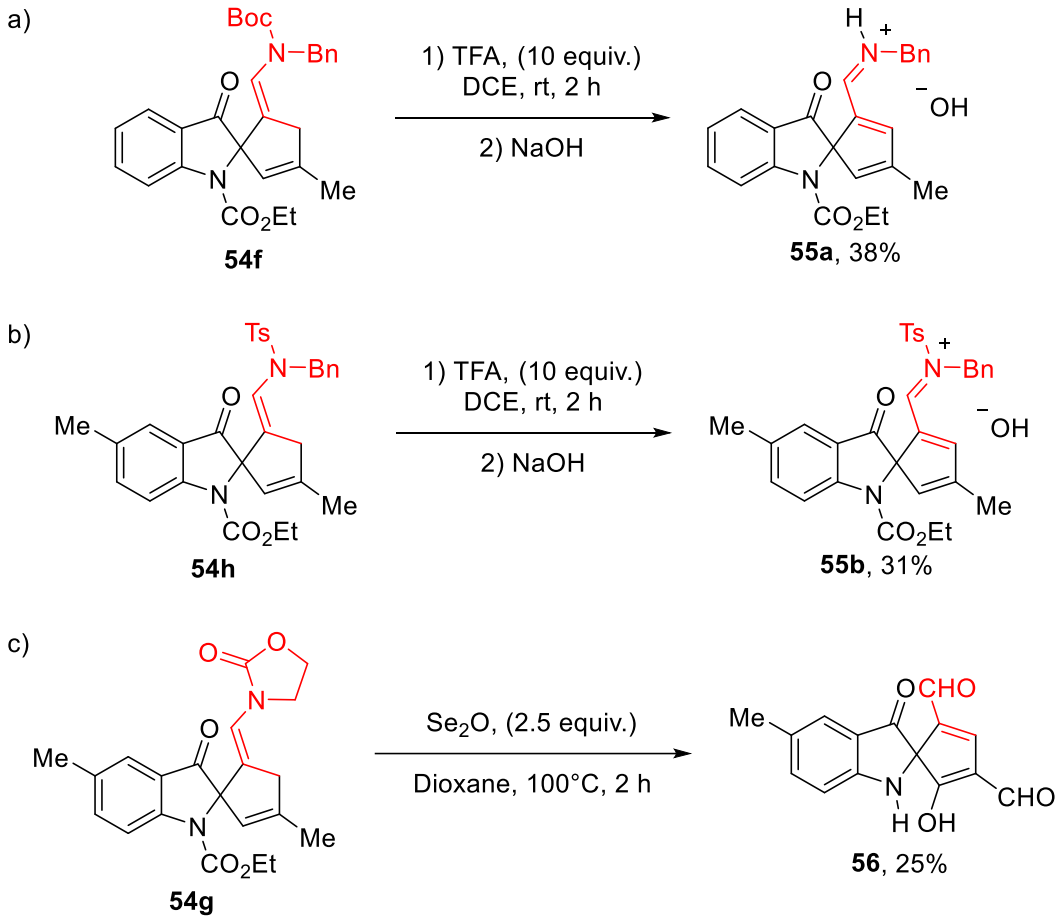
The result obtained for the reaction between **46b** and **11a** during the screening for the best reaction conditions is reported in entry 1. Then, the scope for this transformation started with the evaluation of the behavior of different allenamides **11b-f**. The first employed allenamide was the pyrrolidone derivative **11b** which led to the isolation of the corresponding product **54b** in 61% yield (entry 2). Successively, three allenamides bearing different *N*-aryl, *N*-alkyl tertiary tosylamides were tested. In the first case, using *N*,4-dimethyl-*N*-(2λ^5-propa-1,2-dien-1-yl)benzenesulfonamide **11c**, the corresponding product **54c** was isolated in a satisfying 77% yield (entry 3). However, the switch from phenyl group to methyl group on the nitrogen atom of allenamide (**11d**) negatively influenced the outcome of the reaction and the desired product **54d** was isolated in 49% besides unreacted indole **46b** and several unidentified side-products (entry 4). Benzylated allenamides, bearing tosyl (**11e**) or *t*-butoxycarbonyl (**11f**) substituents as electron-withdrawing groups were investigated, affording the corresponding products in good yield in both cases (62% yield for **54e** and 72% yield for **54f**, entries

5 and 6). Successively, the electronic features of different furoindoles were investigated with both type of allenamides, the oxazolidinone derivative **11a** and the *N*-tosyl-*N*-benzyl derivative **11e**. The study of electron-donating substituents on the indole moiety showed that weak ED methyl group at C7 was well tolerated with both allenamides **11a** and **11e**, giving the corresponding products **54g** and **54h** in 56 and 60% yields, respectively (entries 7 and 8). Unfortunately, strong ED group as a methoxyl negatively influenced the outcome of the reaction. In particular, when it is present at C7 position only allenamide **11a** gave rise to spiroindole **54i** in moderate 44% yield (entry 9). In addition, if the methoxyl group was shifted in C6, both allenamides **11a** and **11f** failed in the synthesis of spirpseudo-indoxyl compounds. Employing electron-withdrawing groups, the outcome of the reaction was different. In fact, furoindole derivative **46d** bearing a fluorine atom at C7 reacted with allenamide **11e** and not with **11a** leading to the isolation of compound **54j** in 45% yield (entry 10). As before, the fluorine atom was moved from C6 to C7 position (furoindole **46h**) and in this case an increase of the reactivity was reported with both the allenamides **11a** and **11e**, the reactions giving rise to the corresponding products **54k** and **54l** in 52% and 65% yields, respectively (entries 11 and 12). Moreover, stronger EW CF_3 group was tested (furoindole **46j**) resulting in a total inhibition of the reaction with both allenamides. The reported results underlined how ED and EW groups influence in an opposite way the reactivity of the C2 carbon of the furan moiety toward the electrophilic reactants. Another negative result was obtained using ethyl 2-phenyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46k** with allenamides **11a** and **11e**, probably due to steric effect. Finally, the enantiopure allenamide **11g** bearing a phenyl group on the ozaxolidinone moiety ((*R*)-4-benzyl-3-(propa-1,2-dien-1-yl)oxazolidin-2-one) was tested with **46b** giving rise to spiropseudo-indoxyl **54m** as a couple of diastereoisomers (13:1) in 49% yield (entry 13). The diastereoisomeric ratio was determined by NMR analysis. As reported before, the confirmation of the structures was made possible by analytical and spectral data analyses and by analogy with the results obtained with the employment of X-ray diffraction analysis of single crystal for compound **54a** (figure 2.11).

*2.2.5.6 Synthetic elaboration of spiropseudo-indoxyl **54***

In order to test the stability and the reactivity of these complex compounds, we carried out some simple synthetic elaborations. At the beginning, the stability under reductive conditions was examined. Compounds **54** were recovered unaltered after treatment with $NaBH_4$ and $LiALH_4$ for chemical reduction, but they resulted stable also under catalytic reductive conditions using H_2, Pd/C or H_2, Pt_2O. In particular, when compound **54e** was employed, the catalytic reductive condition did not allow for the cleavage of the benzyl moiety or for the reduction of the double bonds. More

surprisingly, these compounds did not undergo transformations under basic hydrolytic conditions. Successively, *N*-Boc derivative **54f** was treated with trifluoroacetic acid (TFA) followed by basic workup, in order to cleave the Boc protecting group. Surprisingly, the isolated product was the ammonium salt **55a** with an additional double bond. Compound **55a** was isolated in poor yield beside unidentified by-products (scheme a) 2.20). In addition, also the *N*,*N*-tosyl-benzyl derivative **54h** was treated under the same reaction conditions giving rise in poor yield to a similar ammonium salt **55b** bearing in this case both the protecting group on the nitrogen atom (scheme b) 2.20). The last tested transformation was the oxidation with Se_2O of compound **54g** resulting in the poly-oxidation product **56** with loss of the oxazolidinone moiety and bearing two additional aldehyde groups (scheme c) 2.20).

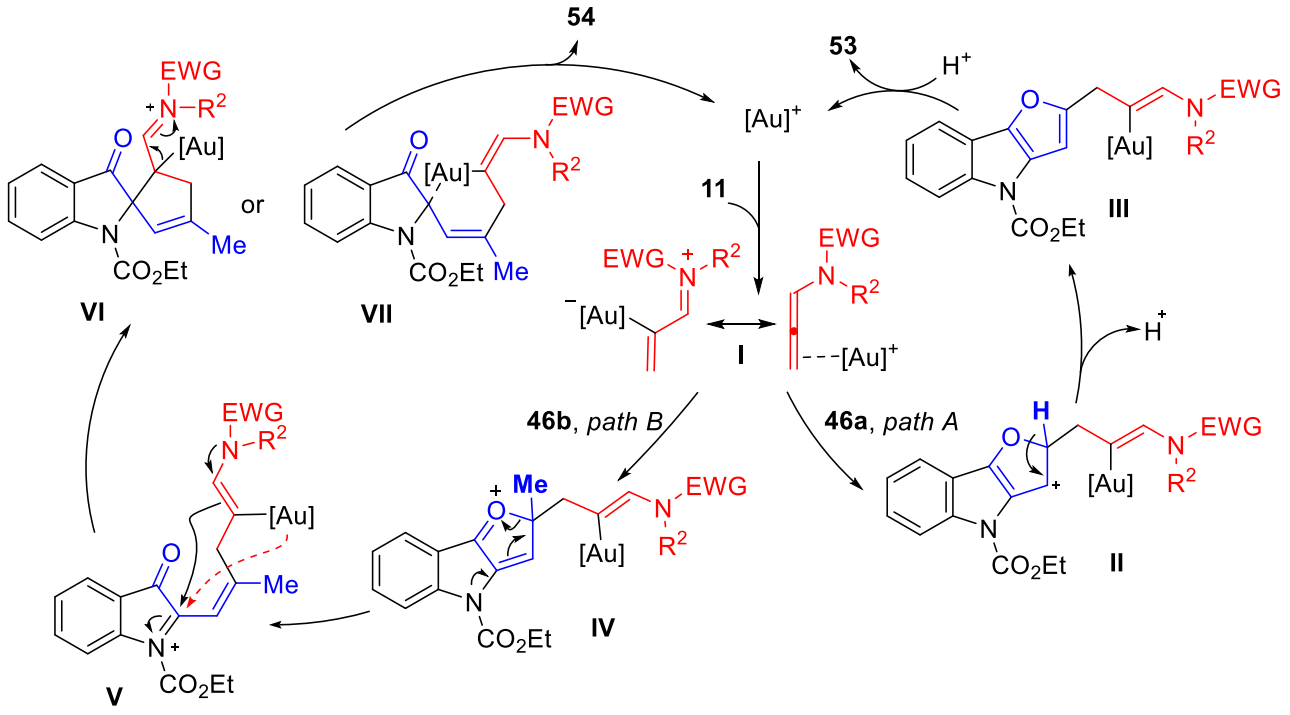


Scheme 2.20

2.2.5.7 Proposed mechanism

The proposed mechanism for the synthesis of compounds **53** and **54** starts in both cases with the activation of *N*-allenamide **11** by the cationic gold(I) catalyst generating the intermediate **I** that

undergo a nucleophilic addition to C2 carbon of the furan moiety. The following step depends on the group in C2 position of the furan moiety. In fact, when hydrogen is present, the cationic intermediate **II** undergoes loss of a proton to furnish intermediate **III**. Finally, the proton generated in the previous step is able to cleave the gold-carbon bond regenerating the cationic catalyst and forming the desired product **53** in a process called protodeauration (scheme 2.21 path A). The *trans*-selective hydroarylation mechanism is well-know and widely reported in literature.[64] However, when the substituent on the C2 position is a methyl group, after the nucleophilic attack (intermediate **IV**), the rearomatization cannot occur and the intermediate **IV** undergoes a rearrangement involving a furan ring-opening event[88,89] generating the iminium indole intermediate **V**. The subsequent cyclization can be promoted by the enaminone system providing the 6-member intermediate **VII** or assisted by gold *via* an electrostatic interaction with indole C2 forming the pseudo-metallacyclic intermediate **VI**. The final step is, for both the intermediates, the elimination of the gold catalyst generating the final spiropseudo-indoxyl product **54** (scheme 2.21 path B). In accordance with literature results, the intermediate **VII** better explains the stereochemistry of the synthetized products although in our investigation there are no evidence of the subsistence of intermediates **VI** and **VII**.[53,99]



Scheme 2.21

2.2.6 Experimental data

2.2.6.1 Preface

2.2.6.1.1 General methods

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

2.2.6.1.2 Reagents

This study was carried out using 4*H*-furo[3,2-*b*]indoles **46a-k**, which were prepared following the procedure described in section 2.2.4.1.
N-allenamides **11a-j** are known compounds and were prepared following the procedure 2.2.4.2 according to literature procedure.[93–97]
$AuCl_3$, $AgNTf_2$; $AgSbF_6$, JohnPhosAuCl, IPrAuCl were purchased from commercial suppliers and used as received; the rest of the gold catalysts were prepared following literature procedure.[41–43,100]

2.2.6.1.3 Solvents

Solvents, used for reactions sensitive to oxygen and hydrolysis, were purchased from commercial suppliers.

2.2.6.1.4 Immersion cooler

The immersion cooler *Julabo FT 402* was used for reactions carried out at -20 °C or -35 °C.

2.2.6.1.5 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade* 9385 60Å (230-400 mesh).
For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm).

2.2.6.1.6 NMR spectroscopy

^{1}H-NMR analyses were performed with a *Varian-Gemini 300* or with *Brucker 300, 500, 600 Avance* spectrometers at room temperature, respectively at 300, 500 or 600 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shift (δ) in ppm. The multiplicities of the proton spectra were described by following abbre*via*tions: s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double dublet).
^{13}C-NMR analyses were performed with the same instruments at 75.45, 125.75 MHz; APT sequences were used to distinguish the methane and methyl carbon signals from those arising from methylene and quaternary carbon atoms.
Two-dimensional NMR techniques (COSY, HSQC, HMBC, NOESY) were performed, where appropriate, to aid the correct assignment of structures.

2.2.6.1.7 Mass Spectroscopy

Low resolution MS spectra were recorded with *a FISONS MD 800* spectrometer with electron impact source and a *Thermo-Finnigan LCQ-advantage AP* electron spray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown
in brackets.

2.2.6.1.8 Melting points

The melting points of the solid products were measured in capillary tube with the device *StuarScientific* SMP3.

2.2.6.1.9 X-ray diffraction

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a DCM solution of **53a** and an ethyl acetate solution of **54a** at ambient temperature. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No.1874486-1874487). Copy may be obtained, free of charge, on application to CCDC e-mail:deposit@ccdc.cam.ac.uk.

2.2.6.2 Experimental data

2.2.6.2.1 General procedures for the synthesis of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates 46a–k,n-p.

According to the reaction sequence reported in Scheme 2.13, 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a-j,n-p** were synthesized in a four steps procedure according to the ensuing general procedures.

Step 1. To a N_2-flushed solution of furan-2-ylboronic acid **43** (1.5 equiv.), potassium carbonate (4.0 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%) in DMF and water (4.4:1), 2-bromoaniline **42** (1.0 equiv.) was added. The reaction mixture was heated at reflux for 3 h and then cooled at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent concentrated under vacuum. The crude was purified by flash column chromatography to yield the corresponding 2-(furan-2-yl)aniline **44**.

Step 2 (method A). To a solution of 2-(furan-2-yl)aniline **44** (1.0 equiv.), an aqueous solution of hydrochloric acid (15%) was added dropwise at 0° C. Then a solution of sodium nitrite (1.2 equiv.) in water was added dropwise. The mixture was stirred for 1 h at 0° C. Then a solution of sodium azide (2.4 equiv.) in water was added dropwise at 0° C and the mixture was stirred for 1 h at room temperature. The mixture was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate saturated solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography to yield the corresponding 2-(2-azidophenyl)furan **45**.

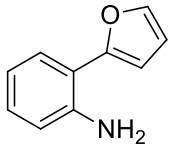
Step 2 (method B). To a solution of 2-(furan-2-yl)aniline **44** (1.0 equiv.) in CH_3CN (0.5 M) at 0° C *t*-BuONO (1.2 equiv.) was added, followed by $TMSN_3$ (1.2 equiv.) dropwise. The resulting solution was stirred at room temperature for 1 h and then was concentrated in vacuum. Purification by flash column chromatography yielded the corresponding 2-(2-azidophenyl)furan **45**.

Step 3. To a solution of 1,2-dichlorobenzene (final concentration 0.5 M) heated at 160° C, 2-(2-azidophenyl)furan **45** (1.0 equiv.) was added dropwise. The reaction mixture was stirred for 3 h. Then solvent was concentrated under vacuum. The crude was purified by flash column chromatography to yield the corresponding 4*H*-furo[3,2-*b*]indole **8**.

Step 4. To a N_2-flushed solution of appropriate 4*H*-furo[3,2-*b*]indole **8** (1.0 equiv.) in THF (0.1 M), a solution of *n*-butyllithium (1.6 M in hexane, 1.1 equiv.) was added dropwise at -78° C. The reaction mixture was stirred for 30 minutes. Ethyl chloroformate (1.5 equiv.) was added dropwise and the reaction was brought to room temperature and stirred for 2 h before of being quenched with ammonium chloride saturated solution. The organic layer was extracted with ethyl acetate, dried over

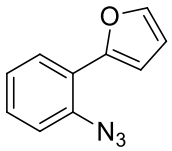
Na_2SO_4, filtered and the solvent concentrated under vacuum. The crude was purified by flash column chromatography to yield the corresponding ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46**.

2-(furan-2-yl)aniline (44a)



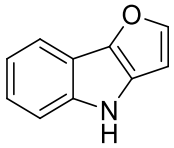
General procedure was followed using furan-2-ylboronic acid **43a** (487 mg, 4.35 mmol), potassium carbonate (1.60 g, 11.6 mmol), $PdCl_2(PPh_3)_2$ (102 mg, 0.145 mmol), 2-bromoaniline **42a** (500 mg, 2.9 mmol) in DMF (13 mL) and water (3 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 2-(furan-2-yl)aniline **44a** (344 mg, 98%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.54 - 7.43 (m, 2H), 7.11 (m, 1H), 6.83 - 6.69 (m, 2H), 6.58 (d, *J* = 3.4 Hz, 1H), 6.51 (dd, *J* = 3.3, 1.9 Hz, 1H), 4.35 (s, 2H). Data are in agreement with those reported in literature.[28]

2-(2-azidophenyl)furan (45a)



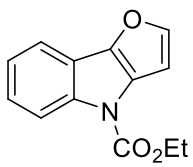
General procedure (method A) was followed using 2-(furan-2-yl)aniline **44a** (1.55 g, 9.76 mmol), a solution of HCl (1.96 mL, 64.42 mmol) in water (9 mL), a solution of sodium nitrite (1.62 g, 23.42 mmol) in water (7.6 mL), a solution of sodium azide (1.52 g, 23.42 mmol) in water (12.4 mL). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azidophenyl)furan **45a** (1.68 g, 93%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.85 (d, *J* = 7.7 Hz, 1H), 7.48 (s, 1H), 7.45 - 7.12 (m, 3H), 7.08 (d, *J* = 3.2 Hz, 1H), 6.51 (s, 1H). Data are in agreement with those reported in literature.[90]

4H-furo[3,2-b]indole (8a)



General procedure was followed using 1,2-dichlorobenzene (14.5 mL), 2-(2-azidophenyl)furan **45a** (1.63 g, 8.81 mmol). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 4*H*-furo[3,2-*b*]indole **8a** (1.02 g, 73%) as reddish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.71 (m, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.40 (m, 1H), 7.26 - 7.07 (m, 2H), 6.59 (d, *J* = 2.0 Hz, 1H), 5.30 (s, 1H). Data are in agreement with those reported in literature.[90]

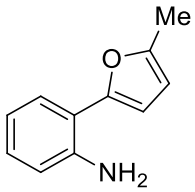
Ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate (46a)



General procedure was followed using 4*H*-furo[3,2-*b*]indole **8a** (250 mg, 1.6 mmol), *n*-butyllithium (1.6 M in hexane, 1.1 mL, 1.76 mmol), ethyl chloroformate (230 µL, 2.4 mmol) in THF (16 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded **46a** (277 mg, 75%) as orange solid (m.p. 60-61.9° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.34 (bs, 1H), 7.67 (m, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.35 - 7.25 (m, 2H), 6.82 (bs, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz,

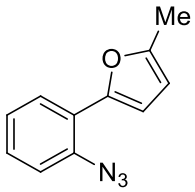
$CDCl_3$): 151.1 (C), 145.8 (CH), 143.5 (C), 138.8 (C), 129.5 (C), 124.0 (CH), 123.4 (CH), 118.1 (C), 116.4 (CH), 116.4 (CH), 103.1 (CH), 63.0 (CH_2), 14.5 (CH_3). **EI-MS**: m/z(%) = 229 (100) [M]. Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.99; H, 4.83; N, 6.12.

2-(5-methylfuran-2-yl)aniline (44b)



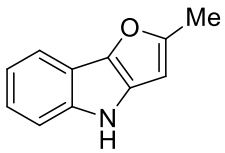
General procedure was followed using (5-methylfuran-2-yl)boronic acid **43b** (548 mg, 4.35mmol), potassium carbonate (1.60 g, 11.6 mmol), $PdCl_2(PPh_3)_2$ (102 mg, 0.145 mmol), 2-bromoaniline **42a** (500 mg, 2.9 mmol) in DMF (13 mL) and water (3 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 2-(5-methylfuran-2-yl)aniline **44b** (480 mg, 95%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.46 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 6.85 - 6.68 (m, 2H), 6.47 (d, *J* = 3.2 Hz, 1H), 6.10 (m, 1H), 4.44 (d, *J* = 0.7 Hz, 2H), 2.38 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 151.6 (C), 151.1 (C), 143.0 (C), 128.2 (CH), 127.2 (CH), 118.4 (CH), 116.60 (C), 116.58 (CH), 107.4 (CH), 107.3 (CH), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 174 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.35; H, 6.39; N, 8.10.

2-(2-azidophenyl)-5-methylfuran (45b)



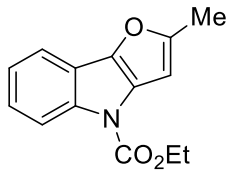
General procedure (method A) was followed using 2-(furan-2-yl)-4-methylaniline **44b** (2.14 g, 12.4 mmol), HCl (15%, 12.4 mL), a solution of sodium nitrite (1.03 g, 14.88 mmol) in water (31 mL), a solution of sodium azide (1.31 g, 20.2 mmol) in water (4.7 mL). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azidophenyl)-5-methylfuran **45b** (1.71 g, 69%) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.84 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.30 - 7.11 (m, 3H), 6.98 (d, *J* = 3.2 Hz, 1H), 6.09 (m, 1H), 2.39 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 152.2 (C), 148.3 (C), 134.9 (C), 127.8 (CH), 126.7 (CH), 125.3 (CH), 123.1 (C), 119.2 (CH), 111.9 (CH), 108.3 (CH), 14.1 (CH_3). Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.36; H, 4.54; N, 21.11.

2-methyl-4*H*-furo[3,2-*b*]indole (8b)



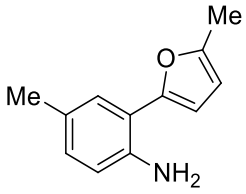
General procedure was followed using 1,2-dichlorobenzene (3.2 mL), 2-(2-azidophenyl)-5-methylfuran **45b** (400 mg, 2 mmol). Purification by flash column chromatography (SiO_2, hexane 100% to hexane/ethyl acetate 95:5), yielded 2-methyl-4*H*-furo[3,2-*b*]indole **8b** (269 mg, 79%) as reddish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.68 (m, 1H), 7.55 (bs, 1H), 7.37 (m, 1H), 7.18 - 7.08 (m, 2H), 6.21 (d, *J* = 1.0 Hz, 1H), 2.50 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.1 (C), 140.7 (C), 139.0 (C), 131.0 (C), 120.8 (CH), 119.7 (CH), 115.5 (CH), 114.8 (C), 112.0 (CH), 95.8 (CH), 14.9 (CH_3). **ESI(+)-MS**: m/z(%) = 172 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.26; H, 5.29; N, 8.17.

Ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46b)



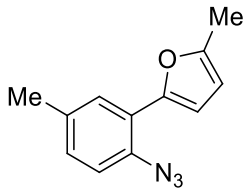
General procedure was followed using 2-methyl-4*H*-furo[3,2-*b*]indole **8b** (107 mg, 0.63 mmol), *n*-butyllithium (1.6 M in hexane, 430 µL, 0.69 mmol), ethyl chloroformate (90 µL, 0.95 mmol) in THF (6.2 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded **46b** (122 mg, 79%) as orange solid (m.p. 107.1-108.2° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.30 (s, 1H), 7.59 (m, 1H), 7.32 - 7.19 (m, 2H), 6.44 (s, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 2.49 (d, *J* = 0.8 Hz, 3H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.2 (C), 151.2 (C), 141.7 (C), 137.9 (C), 130.3 (C), 123.2 (CH), 123.1 (CH), 118.3 (C), 116.2 (CH), 115.6 (CH), 99.4 (CH), 62.9 (CH_2), 14.7 (CH_3), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 244 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.97; H, 5.40; N, 5.75.

4-methyl-2-(5-methylfuran-2-yl)aniline (44c)



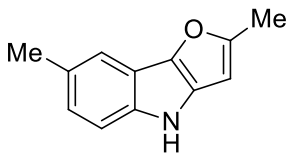
General procedure was followed using (5-methylfuran-2-yl)boronic acid **43b** (1.89 g, 15 mmol), potassium carbonate (5.50 g, 40 mmol), $PdCl_2(PPh_3)_2$ (350 mg, 0.5 mmol), 2-bromo-4-methylaniline **44b** (1.86 g, 10 mmol) in DMF (45 mL) and water (10 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 4-methyl-2-(5-methylfuran-2-yl)aniline **44c** (1.26 g, 65%) as orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.32 (m, 1H), 6.93 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 6.13 (m, 1H), 4.08 (bs, 2H), 2.40 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 151.6 (C), 151.0 (C), 140.4 (C), 129.0 (CH), 127.7 (C), 127.4 (CH), 116.8 (CH), 116.6 (C), 107.4 (CH), 107.3 (CH), 20.5 (CH_3), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 188 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.83; H, 6.99; N, 7,47.

2-(2-azido-5-methylphenyl)-5-methylfuran (45c)



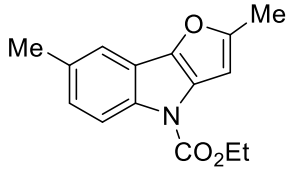
General procedure (method A) was followed using 4-methyl-2-(5-methylfuran-2-yl)aniline **44c** (1.22 g, 6.5 mmol), HCl (15%, 6.5 mL), a solution of sodium nitrite (538 mg, 7.8 mmol) in water (16 mL), a solution of sodium azide (689 mg, 10.6 mmol) in water (2.4 mL). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azido-5-methylphenyl)-5-methylfuran **45c** (1.06 g, 77%) as orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.63 (m, 1H), 7.14 - 7.03 (m, 2H), 6.94 (d, *J* = 3.3 Hz, 1H), 6.09 (m, 1H), 2.38 (m, 3H), 2.37 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 151.6 (C), 148.1 (C), 134.5 (C), 131.9 (C), 128.2 (CH), 126.8 (CH), 122.5 (C), 118.7 (CH), 111.4 (CH), 107.9 (CH), 20.9 (CH_3), 13.6 (CH_3). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.45; H, 5.19; N, 19.74.

2,7-dimethyl-4*H*-furo[3,2-*b*]indole (8c)



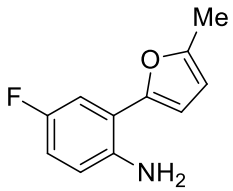
General procedure was followed using 1,2-dichlorobenzene (8.5 mL), 2-(2-azido-5-methylphenyl)-5-methylfuran **45c** (1.02 g, 4.81 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 2,7-dimethyl-4*H*-furo[3,2-*b*]indole **8c** (0.56 g, 63%) as reddish waxy solid. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.54 - 7.29 (m, 2H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.21 (d, *J* = 0.9 Hz, 1H), 2.52 (d, *J* = 0.9 Hz, 3H), 2.50 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 155.9 (C), 140.5 (C), 137.4 (C), 131.3 (C), 129.1 (C), 122.2 (CH), 115.4 (CH), 114.9 (C), 111.7 (CH), 95.9 (CH), 21.5 (CH_3), 15.0 (CH_3). **ESI(-)-MS**: m/z(%) = 184 (100) $[M-H]^-$. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.96; H, 6.00; N, 7.57.

Ethyl 2,7-dimethyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46c)



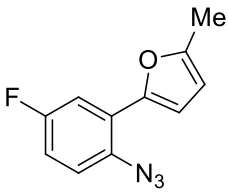
General procedure was followed using 2,7-dimethyl-4*H*-furo[3,2-*b*]indole **8c** (500 mg, 2.7 mmol), *n*-butyllithium (1.6 M in hexane, 1.85 mL, 2.97 mmol), ethyl chloroformate (388 μL, 4.05 mmol) in THF (28 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2), yielded **46c** (431 mg, 62%) as pink solid (m.p. 93.8-94.5° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.14 (s, 1H), 7.37 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.43 (s, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 2.45 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.0 (C), 151.1 (C), 141.6 (C), 136.1 (C), 132.8 (2xC), 124.2 (CH), 118.4 (C), 115.8 (CH), 115.8 (CH), 99.4 (CH), 62.7 (CH_2), 21.4 (CH_3), 14.7 (CH_3), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 258 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.93; H, 5.87; N, 5.45.

4-fluoro-2-(5-methylfuran-2-yl)aniline (44d)



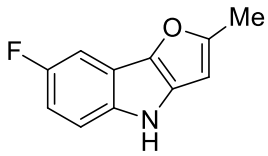
General procedure was followed using (5-methylfuran-2-yl)boronic acid **43b** (1.49 g, 11.8 mmol), potassium carbonate (4.40 g, 31.6 mmol), $PdCl_2(PPh_3)_2$ (273 mg, 0.39 mmol), 2-bromo-4-fluoroaniline **42c** (900 μL, 7.9 mmol) in DMF (35 mL) and water (8 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 4-fluoro-2-(5-methylfuran-2-yl)aniline **44d** (1.31 g, 87%) as orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.19 (dd, *J* = 9.9, 2.9 Hz, 1H), 6.79 (td, *J* = 8.4, 2.9 Hz, 1H), 6.66 (dd, *J* = 8.8, 4.9 Hz, 1H), 6.50 (d, *J* = 3.2 Hz, 1H), 6.10 (m, 1H), 4.14 (s, 2H), 2.38 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.2 (d, *J* = 235.3 Hz, C), 151.6 (C), 150.3 (d, *J* = 2.8 Hz, C), 138.8 (d, *J* = 2.0 Hz, C), 117.6 (d, *J* = 8.0 Hz, CH), 117.5 (C), 114.7 (d, *J* = 22.7 Hz, CH), 112.9 (d, *J* = 24.0 Hz, CH), 108.3 (CH), 107.5 (CH), 13.6 (CH_3). **ESI(+)-MS**: m/z (%) = 192 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33. Found: C, 68.91; H, 5.25; N, 7.54.

2-(2-azido-5-fluorophenyl)-5-methylfuran (45d)



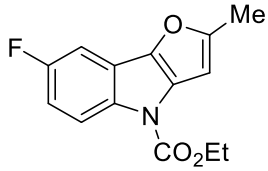
General procedure (method A) was followed using 4-fluoro-2-(5-methylfuran-2-yl)aniline **44d** (1.30 g, 6.7 mmol), HCl (15%, 6.7 mL), a solution of sodium nitrite (554 mg, 8.04 mmol) in water (18 mL), a solution of sodium azide (709 mg, 10.9 mmol) in water (2.5 mL). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azido-5-fluorophenyl)-5-methylfuran **45d** (881 mg, 61%) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.52 (dd, *J* = 10, 2.9 Hz, 1H), 7.13 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.02 (d, *J* = 3.3 Hz, 1H), 6.94 (ddd, *J* = 8.8, 7.5, 3.0 Hz, 1H), 6.11 (m, 1H), 2.41 - 2.33 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 160.0 (d, *J* = 243.4 Hz, C), 152.3 (C), 146.9 (C), 130.2 (C), 124.3 (C), 120.1 (d, *J* = 8.8 Hz, CH), 114.0 (d, *J* = 23.9 Hz, CH), 112.7 (d, *J* = 26.4 Hz, CH), 112.4 (CH), 108.2 (CH), 13.6 (CH_3). Anal. Calcd for $C_{11}H_8FN_3O$: C, 60.83; H, 3.71; N, 19.35. Found: C, 60.96; H, 3.72; N, 19.31.

7-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole (8d)



General procedure was followed using 1,2-dichlorobenzene (5.5 mL), 2-(2-azido-5-fluorophenyl)-5-methylfuran **45d** (668 mg, 3.08 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 7-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole **8d** (548 mg, 94%) as reddish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.53 (s, 1H), 7.34 - 7.22 (m, 2H), 6.86 (td, *J* = 9.1, 2.5 Hz, 1H), 6.20 (d, *J* = 0.9 Hz, 1H), 2.49 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 157.8 (d, *J* = 234.7 Hz, C), 156.9 (C), 140.6 (C), 135.5 (C), 133.0 (C), 114.6 (d, *J* = 10.8 Hz, C), 112.4 (d, *J* = 9.8 Hz, CH), 108.5 (d, *J* = 26.1 Hz, CH), 101.1 (d, *J* = 25.6 Hz, CH), 95.8 (CH), 14.9 (CH_3). **ESI(+)-MS**: m/z(%) = 190 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_8FNO$: C, 69.83; H, 4.26; N, 7.40. Found: C, 69.73; H, 4.25; N, 7.41.

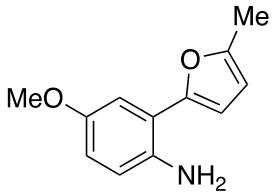
Ethyl 7-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46d)



General procedure was followed using 7-fluoro-4*H*-furo[3,2-*b*]indole **8d** (522 mg, 2.9 mmol), *n*-butyllithium (1.6 M in hexane, 2 mL, 3.2 mmol), ethyl chloroformate (416 µL, 4.35 mmol) in THF (30 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2), yielded **46d** (569 mg, 75%) as orange solid (m.p. 91-92° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.23 (s, 1H), 7.23 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.96 (dt, *J* = 9.1, 4.6 Hz, 1H), 6.44 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.50 (d, *J* = 1.0 Hz, 3H), 1.51 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.6 (d, *J* = 239.8 Hz, C), 157.0 (C), 150.9 (C), 141.0 (d, *J* = 3.4 Hz, C), 134.2 (C), 131.9 (d, *J* = 4.2 Hz, C), 118.8 (d, *J* = 10.8 Hz, C), 117.1 (d, *J* = 9.4 Hz, CH), 110.2 (d, *J* = 24.9 Hz, CH), 101.9 (d, *J* = 26.0 Hz, CH), 99.4 (CH), 63.0

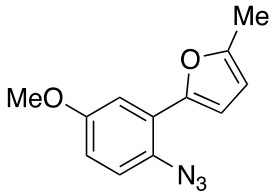
(CH_2), 14.8 (CH_3), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 262 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{12}FNO_3$: C, 64.36; H, 4.63; N, 5.36. Found: C, 64.25; H, 4.64; N, 5.35

4-methoxy-2-(5-methylfuran-2-yl)aniline (44e)



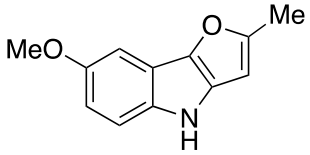
General procedure was followed using (5-methylfuran-2-yl)boronic acid **43b** (1.39 g, 11.1 mmol), potassium carbonate (4.09 g, 29.6 mmol), $PdCl_2(PPh_3)_2$ (260 mg, 0.37 mmol), 2-bromo-5-methoxyaniline **42d** (1.5 g, 7.4 mmol) in DMF (33 mL) and water (7.5 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 4-methoxy-2-(5-methylfuran-2-yl)aniline **44e** (1.19 g, 79%) as a red oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.05 (t, *J* = 1.7 Hz, 1H), 6.71 (d, *J* = 1.6 Hz, 2H), 6.50 (m, 1H), 6.09 (dt, *J* = 3.2, 1.0 Hz, 1H), 3.99 (bs, 2H), 3.79 (s, 3H), 2.38 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 152.7 (C), 151.3 (C), 151.1 (C), 136.4 (C), 118.2 (CH), 117.7 (C), 114.9 (CH), 111.7 (CH), 107.9 (CH), 107.4 (CH), 55.8 (CH_3), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 204 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.08; H, 6.47; N, 6.87.

2-(2-azido-5-methoxyphenyl)-5-methylfuran (45e)



General procedure (method A) was followed using 4-methoxy-2-(5-methylfuran-2-yl)aniline **44e** (850 mg, 4.2 mmol), HCl (15%, 4.2 ml), a solution of sodium nitrite (346 mg, 5.04 mmol) in water (10.5 mL), a solution of sodium azide (444 mg, 6.8 mmol) in water (1.7 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 99:1), yielded 2-(2-azido-5-methoxyphenyl)-5-methylfuran **45e** (242 mg, 25%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.35 (d, *J* = 2.9 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 3.2 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.09 (dd, *J* = 3.3, 1.0 Hz, 1H), 3.85 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.9 (C), 151.8 (C), 147.8 (C), 127.2 (C), 123.6 (C), 120.0 (CH), 113.7 (CH), 111.8 (CH), 110.9 (CH), 108.0 (CH), 55.6 (CH_3), 13.6 (CH_3). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.79; H, 4.82; N, 18.38.

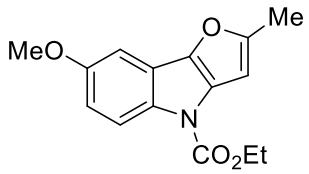
7-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole (8e)



General procedure was followed using 1,2- dichlorobenzene (3 mL), 2-(2-azido-5-methoxyphenyl)-5-methylfuran **45e** (220 mg, 0.96 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 7-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole **8e** (76 mg, 39%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.45 (bs, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.18 (d, *J* = 1.0 Hz, 1H), 3.87 (s, 3H), 2.49 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.2 (C), 154.1 (C), 140.8 (C), 134.2 (C), 132.1 (C), 114.8 (C), 112.7 (CH), 110.2 (CH),

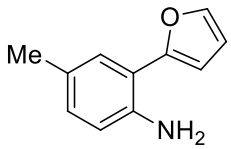
98.3 (CH), 95.9 (CH), 55.9 (CH_3), 14.9 (CH_3). **ESI(+)-MS**: m/z(%) = 202 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.88; H, 5.49; N, 6.98.

Ethyl 7-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46e)



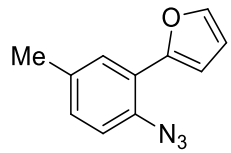
General procedure was followed using 7-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole **8e** (76 mg, 0.38 mmol), *n*-butyllithium (1.6 M in hexane, 260 µL, 0.42 mmol), ethyl chloroformate (56 µL, 0.58 mmol) in THF (11 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 99:1), yielded **46e** (80 mg, 77%) as white solid (m.p. 86.1-88.0° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.19 (bs, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.86 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.44 (bs, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 2.50 (d, *J* = 1.0 Hz, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.3 (C), 151.1 (C), 141.6 (C), 132.5 (C), 130.9 (C), 118.9 (C), 117.0 (CH), 110.8 (CH), 99.5 (CH), 99.4 (CH), 62.8 (CH_2), 55.7 (CH_3), 14.8 (CH_3), 14.5 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 274 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.17; H, 5.54; N, 5.11.

2-(furan-2-yl)-4-methylaniline (44f)



General procedure was followed using furan-2-ylboronic acid **43a** (1.95 g, 17.4 mmol), potassium carbonate (6.41 g, 46.4 mmol), $PdCl_2(PPh_3)_2$ (407 mg, 0.58 mmol), 2-bromo-4-methylaniline **42b** (2.16 g, 11.6 mmol) in DMF (52 mL) and water (12 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 97:3), yielded 2-(furan-2-yl)-4-methylaniline **44f** (1.87 g, 93%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.52 (m, 1H), 7.32 (d, *J* = 1.4 Hz, 1H), 6.96 (m, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 3.4 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.13 (bs, 2H), 2.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 153.6 (C), 141.2 (CH), 140.7 (C), 129.6 (CH), 127.9 (CH), 127.7 (C), 117.0 (CH), 116.3 (C), 111.3 (CH), 106.4 (CH), 20.4 (CH_3). **ESI(+)-MS**: m/z(%) = 174 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.43; H, 6.39; N, 8.10.

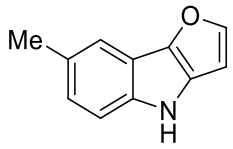
2-(2-azido-5-methylphenyl)furan (45f)



General procedure (method A) was followed using 2-(furan-2-yl)-4-methylaniline **44f** (1.84 g, 10.62 mmol), a solution of HCl (2.13 mL, 70.09 mmol) in water (9.7 mL), a solution of sodium nitrite (1.76 g, 25.49 mmol) in water (9.9 mL), a solution of sodium azide (1.66 g, 25.49 mmol) in water (13.5 mL). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azido-5-methylphenyl)furan **45f** (1.71 g, 80%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.66 (s, 1H), 7.47 (d, *J* = 1.0 Hz, 1H), 7.11 (s, 2H), 7.05 (d, *J* = 3.3 Hz, 1H), 6.50 (dd, *J* = 3.3, 1.8 Hz, 1H). 2.37 (s, 3H). **^{13}C NMR** (75 MHz,

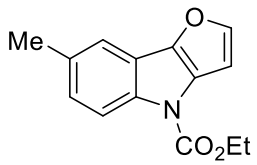
$CDCl_3$): 149.8 (C), 141.6 (CH), 134.6 (C), 132.4 (C), 128.8 (CH), 127.3 (CH), 122.2 (C), 118.8 (CH), 111.7 (CH), 110.2 (CH), 20.9 (CH_3). Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.47; H, 4.55; N, 21.08.

7-methyl-4*H*-furo[3,2-*b*]indole (8f)



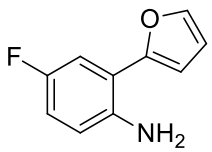
General procedure was followed using 1,2-dichlorobenzene (8 mL), 2-(2-azido-5-methylphenyl)furan **45f** (1.02 g, 5.09 mmol). Purification by flash column chromatography (SiO_2, hexane 100% to hexane/ethyl acetate 95:5), yielded 7-methyl-4*H*-furo[3,2-*b*]indole **8f** (834 mg, 95%) as reddish oil in a mixture with unidentified inseparable impurity. **^{1}H NMR** (300 MHz, $CDCl_3$) for 7-methyl-4*H*-furo[3,2-*b*]indole: 7.53 (m, 3H), 7.27 (m, 1H), 7.03 (m, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 2.48 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 145.6 (CH), 138.4 (C), 130.3 (C), 129.2 (C), 126.7 (C), 123.1 (CH), 116.1 (CH), 114.8 (C), 111.8 (CH), 99.4 (CH), 21.4 (CH_3). **ESI(+)-MS**: m/z(%) = 172 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.38; H, 5.31; N, 4.17.

Ethyl 7-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46f)



General procedure was followed using 7-methyl-4*H*-furo[3,2-*b*]indole **8f** (800 mg, 4.67 mmol), *n*-butyllithium (1.6 M in hexane, 3.2 mL, 5.14 mmol), ethyl chloroformate (668 µL, 7 mmol) in THF (46 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded **46f** (829 mg, 73%) as orange solid (m.p. 95-95.7° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.17 (bs, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.12 (dd, *J* = 8.5, 1.2 Hz, 1H). 6.79 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 151.0 (C), 145.6 (CH), 143.4 (C), 137.0 (C), 133.0 (C), 129.6 (C), 125.1 (CH), 118.2 (C), 116.4 (CH), 116.0 (CH), 103.0 (CH), 62.9 (CH_2), 21.3 (CH_3), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 266 (100) $[M+Na]^+$. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26; H, 5.40; N, 5.77.

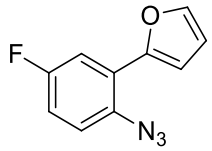
4-fluoro-2-(furan-2-yl)aniline (44g)



General procedure was followed using furan-2-ylboronic acid **43a** (2.65 g, 23.68 mmol), potassium carbonate (8.73 g, 63.16 mmol), $PdCl_2(PPh_3)_2$ (8.73 g, 63.16 mmol), 2-bromo-4-fluoroaniline **42c** (3.00 g, 15.79 mmol) in DMF (71 mL) and water (16 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 4-fluoro-2-(furan-2-yl)aniline **44g** (3.08 g, 100%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.50 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.20 (dd, *J* = 9.8, 2.9 Hz, 1H), 6.83 (ddd, *J* = 8.8, 7.9, 2.9 Hz, 1H), 6.68 (dd, *J* = 8.8, 4.8 Hz, 1H), 6.61 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.52 (dd, *J* = 3.4, 1.9 Hz, 1H), 4.18 (bs, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.1 (d, *J* = 235 Hz, C), 152.2 (d, *J* = 2.6 Hz, C), 141.6 (CH), 139.2 (d, *J*

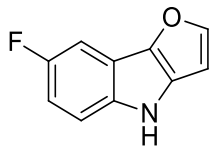
= 1.7 Hz, C), 117.7 (d, *J* = 7.8 Hz, CH), 117.0 (d, *J* = 7.8 Hz, C), 115.4 (d, *J* = 22.8 Hz, CH), 113.3 (d, *J* = 23.9 Hz, CH), 111.4 (CH), 107.2 (CH). **ESI(+)-MS**: m/z(%) = 178 (100) $[M+H]^+$. Anal. Calcd for $C_{10}H_8FNO$: C, 67.79; H, 4.55; N, 7.91. Found: C, 67.66; H, 4.56; N, 7.92.

2-(2-azido-5-fluorophenyl)furan (45g)



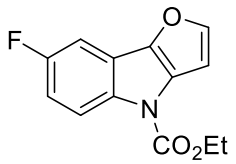
General procedure (method A) was followed using 4-fluoro-2-(furan-2-yl)aniline **44g** (3.02 g, 17.07 mmol), a solution of HCl (3.42 mL, 112.66 mmol) in water (15 mL), a solution of sodium nitrite (2.83 g, 40.97 mmol) in water (15 mL), a solution of sodium azide (2.66 g, 40.97 mmol) in water (22 mL). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azido-5-fluorophenyl)furan **45g** (1.42 g, 41%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.58 (dd, *J* = 9.8, 2.9 Hz, 1H), 7.50 (d, *J* = 1.1 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.01(ddd, *J* = 8.8, 7.5, 2.9 Hz, 1H), 6.54 (ddd, *J* = 3.5, 1.8, 0.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): 160.3 (d, *J* = 243 Hz, C), 149.2 (C), 142.8 (CH), 131.3 (d, *J* = 2.6 Hz, C), 124.4 (d, *J* = 8.7 Hz, C), 120.8 (d, *J* = 8.7 Hz, CH), 115.3 (d, *J* = 23.7 Hz, CH), 113.8 (d, *J* = 25.3 Hz, CH), 112.5 (CH), 111.9 (CH). Anal. Calcd for $C_{10}H_6FN_3O$: C, 59.12; H, 2.98; N, 20.68. Found: C, 59.23; H, 2.97; N, 20.60.

7-fluoro-4*H*-furo[3,2-*b*]indole (8g)



General procedure was followed using 1,2-dichlorobenzene (11 mL), 2-(2-azido-5-fluorophenyl)furan **45g** (1.37 g, 6.7 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 7-fluoro-4*H*-furo[3,2-*b*]indole **8g** (788 mg, 67%) as reddish wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.64 (bs, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.41 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.32 (dd, *J* = 8.9, 4.3 Hz, 1H), 6.99 (td, *J* = 9.1, 2.6 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): 158.2 (d, *J* = 235 Hz, C), 146.9 (CH), 142.5 (C), 136.8 (C), 132.2 (C), 114.9 (C), 113.1 (d, *J* = 9.7 Hz CH), 110.0 (d, *J* = 26.1 Hz, CH), 102.2 (d, *J* = 25.6 Hz, CH), 99.9 (CH). **ESI(-)-MS**: m/z(%) = 174 (100) $[M-H]^-$. Anal. Calcd for $C_{10}H_6FNO$: C, 68.57; H, 3.45; N, 8.00. Found: C, 68.54; H, 3.46; N, 7.99.

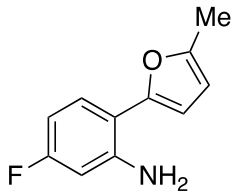
Ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate (46g)



General procedure was followed using 7-fluoro-4*H*-furo[3,2-*b*]indole **8g** (765 mg, 4.37 mmol), *n*-butyllithium (1.6 M in hexane, 3 mL, 4.81 mmol), ethyl chloroformate (627 µL, 6.55 mmol) in THF (43 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 99:1), yielded **46g** (855 mg, 79%) as orange solid (m.p. 60-61° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.27 (bs, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.03 (td, *J* = 9.1, 2.6 Hz, 1H), 6.82 (s, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.5 (d, *J* = 240 Hz, C), 150.9 (C),

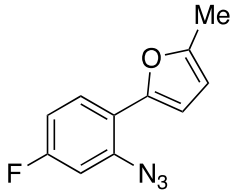
146.4 (CH), 142.8 (C), 135.0 (C), 131.0 (C), 118.6 (d, J = 10.9 Hz, C), 117.3 (d, J = 9.2 Hz, CH), 111.2 (d, J =25.3 Hz, CH), 103.1 (CH), 102.6 (d, J = 25.9 Hz, CH), 63.2 (CH_2), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 248 (100) $[M+H]^+$. Anal. Calcd for $C_{13}H_{10}FNO_3$: C, 63.16; H, 4.08; N, 5.67. Found: C, 63.24; H, 4.07; N, 5.68.

5-fluoro-2-(5-methylfuran-2-yl)aniline (44h)



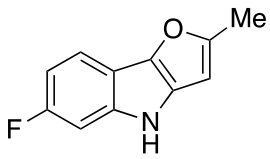
General procedure was followed using (5-methylfuran-2-yl)boronic acid **43b** (1.13 g, 9 mmol), potassium carbonate (3.30 g, 24 mmol), $PdCl_2(PPh_3)_2$ (211 mg, 0.3 mmol), 2-bromo-5-fluoroaniline **42e** (1.14 g, 6 mmol) in DMF (27 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 5-fluoro-2-(5-methylfuran-2-yl)aniline **44h** (907 mg, 79%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.39 (dd, J = 8.6, 6.4 Hz, 1H), 6.51 (dd, J = 8.4, 2.5 Hz, 1H), 6.47 (m, 1H), 6.42 (dd, J = 8.4, 2.8 Hz, 1H), 6.10 (m, 1H), 4.39 (bs, 2H), 2.39 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 163.0 (d, J = 243 Hz, C), 151.1 (C), 150.8 (C), 144.8 (C), 144.7 (d, J = 10.9 Hz, C), 129.0 (d, J = 10 Hz, CH), 112.9 (d, J = 2.6 Hz, C), 107.2 (d, J = 17.7 Hz, CH), 105.4 (d, J = 23 Hz, CH), 103.0 (CH), 102.6 (CH), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 192 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33. Found: C, 68.84; H, 5.25; N, 7.35.

2-(2-azido-4-fluorophenyl)-5-methylfuran (45h)



General procedure (method B) was followed using 5-fluoro-2-(5- methylfuran-2-yl)aniline **44h** (570 mg, 2.98 mmol), *t*-BuONO (0.53 ml, 4.47 mmol) and $TMSN_3$ (0.59 ml, 4.47 mmol) in CH_3CN (6 ml). Purification by flash column chromatography (SiO_2, hexane 100%), yielded 2-(2-azido-4-fluorophenyl)-5-methylfuran **45h** (390 mg, 60%) as a yellow wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.79 (dd, J = 8.6, 6.2 Hz, 1H), 6.96-6.87 (m, 3H), 6.10 (m, 1H), 2.38 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 161.7 (d, J = 249 Hz, C), 151.7 (C), 147.2 (C), 136.1 (d, J = 8 Hz, C), 127.9 (d, J = 11 Hz, CH), 119.2 (C), 112.2 (d, J = 22 Hz, CH), 110.9 (CH), 107.9 (CH), 106.1 (d, J = 24 Hz, CH), 13.6 (CH_3). Anal. Calcd for $C_{11}H_8FN_3O$: C, 60.83; H, 3.71; N, 19.35. Found: C, 61.04; H, 3.72; N, 19.29.

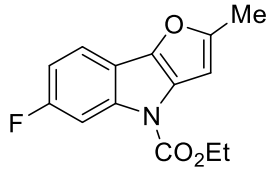
6-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole (8h)



General procedure was followed using 1,2-dichlorobenzene (4 mL), 2-(2-azido-4-fluorophenyl)-5-methylfuran **45h** (370 mg, 1.71 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 6-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole **8h** (221 mg, 68%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.67-7.48 (m, 2H), 7.08 (dd, J = 9.9, 2.1 Hz, 1H), 6.93 (m, 1H), 6.22 (d, J = 1.0 Hz, 1H), 2.50 (d, J = 0.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.3 (d, J = 237 Hz, C), 156.2 (C), 140.7 (C),

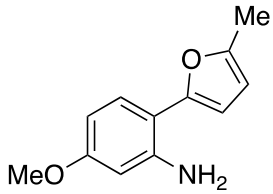
139.3 (d, J = 11.8 Hz, C), 131.5 (C), 116.3 (d, J = 10 Hz, CH), 112.1 (C), 108.4 (d, J = 24.4 Hz, CH), 99.2 (d, J = 26.6 Hz, CH), 96.4 (CH), 15.3 (CH_3). **ESI(+)-MS**: m/z(%) = 190 (100) $[M+H]^+$. Anal. Calcd for $C_{11}H_8FNO$: C, 69.84; H, 4.26; N, 7.40. Found: C, 7.02; H, 4.28; N, 7.37.

Ethyl 6-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46h)



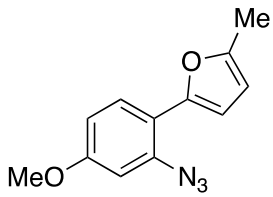
General procedure was followed using 6-fluoro-2-methyl-4*H*-furo[3,2-*b*]indole **8h** (208 mg, 1.1 mmol), *n*-butyllithium (1.6 M in hexane, 760 µL, 1.21 mmol), ethyl chloroformate (158 µL, 1.65 mmol) in THF (11 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 99:1 to 98:2), yielded **46h** (266 mg, 93%) as white solid (m.p. 100.9-102.8° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.04 (bs, 1H), 7.47 (dd, J = 8.6, 5.4 Hz, 1H), 7.01 (m, 1H), 6.41 (bs, 1H), 4.49 (q, J = 7.1 Hz, 2H), 2.47 (d, J = 0.9 Hz, 3H), 1.49 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.8 (d, J = 240 Hz, C), 156.0 (C), 150.9 (C), 141.1 (C), 130.4 (C), 115.9 (d, J = 9.6 Hz, CH), 114.9 (C), 111.0 (d, J = 24.2 Hz, CH), 104.1 (d, J = 29.2 Hz, CH), 99.4 (CH), 63.1 (CH_2), 14.7 (CH_3), 14.4 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 262 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{12}FNO_3$: C, 64.36; H, 4.63; N, 5.36. Found: C, 64.44; H, 4.61; N, 5.35.

5-methoxy-2-(5-methylfuran-2-yl)aniline (44i)



General procedure was followed using (5-methylfuran-2-yl)boronic acid **43b** (1.13 g, 9 mmol), potassium carbonate (3.30 g, 24 mmol), $PdCl_2(PPh_3)_2$ (211 mg, 0.3 mmol), 2-bromo-5-methoxyaniline **42f** (1.21 g, 6 mmol) in DMF (27 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 5-methoxy-2-(5-methylfuran-2-yl)aniline **44i** (903 mg, 74%) as a brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.35 (d, J = 8.6 Hz, 1H), 6.38 (dd, J = 8.6, 2.5 Hz, 1H), 6.33 (d, J = 3.1 Hz, 1H), 6.30 (d, J = 2.4 Hz, 1H), 6.05 (m, 1H), 4.31 (bs, 2H), 3.78 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 160.0 (C), 151.55 (C), 150.51 (C), 144.2 (C), 128.7 (CH), 110.4 (C), 107.1 (C), 106.1 (CH), 104.8 (CH), 101.6 (CH), 55.2 (CH_3), 13.8 (CH_3). **ESI(+)-MS**: m/z(%) = 204 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.08; H, 6.47; N, 6.91.

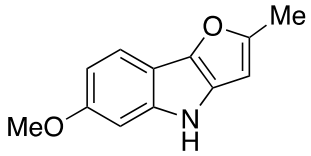
2-(2-azido-4-methoxyphenyl)-5-methylfuran (45i)



General procedure (method B) was followed using 5- methoxy-2-(5-methylfuran-2-yl)aniline **44i** (900 mg, 4.43 mmol), *t*-BuONO (0.79 ml, 6.65 mmol) and $TMSN_3$ (0.87 ml, 6.65 mmol) in CH_3CN (9 ml). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2), yielded 2-(2-azido-4-methoxyphenyl)-5-methylfuran **45i** (810 mg, 80%) as a yellow wax. **^{1}H NMR** (300 MHz,

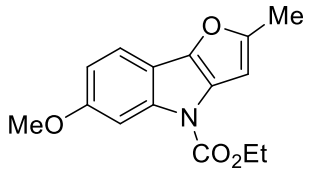
$CDCl_3$): 7.73 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.81 (d, *J* = 3.2 Hz, 1H), 6.78 – 6.73 (m, 2H), 6.08 (m, 1H), 3.87 (s, 3H), 2.38 (d, *J* = 0.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.1 (C), 151.0 (C), 148.1 (C), 135.8 (C), 127.6 (CH), 116.3 (C), 110.7 (CH), 109.6 (CH), 107.7 (CH), 104.6 (CH), 55.5 (CH_3), 13.6 (CH_3). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.79; H, 4.86; N, 18.37.

6-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole (8i)



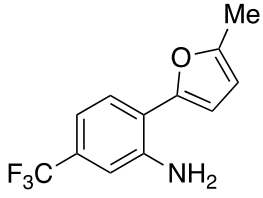
General procedure was followed using 1,2-dichlorobenzene (8 mL), 2-(2-azido-4-methoxyphenyl)-5-methylfuran **45i** (808 mg, 3.5 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1), yielded 6-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole **8i** (430 mg, 61%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.55 (m, 2H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.19 (s, 1H), 3.86 (s, 3H), 2.50 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 155.4 (C), 154.7 (C), 140.6 (C), 140.0 (C), 129.9 (C), 116.0 (CH), 109.8 (C), 108.6 (CH), 96.7 (CH), 96.0 (CH), 55.8 (CH_3), 14.9 (CH_3). **ESI(+)-MS**: m/z(%) = 202 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.88; H, 5.50; N, 6.94.

Ethyl 6-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46i)



General procedure was followed using 6-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole (395 mg, 1.91 mmol), *n*-butyllithium (1.6 M in hexane, 1.3 mL, 2.10 mmol), ethyl chloroformate (274 μL, 2.86 mmol) in THF (11 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded **1i** (447 mg, 86%) as white solid (m.p. 95.6-97.7 ° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.93 (bs, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.40 (bs, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 2.46 (d, *J* = 1.0 Hz, 3H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.8 (C), 154.9 (C), 151.2 (C), 141.7 (C), 139.1 (C), 129.0 (C), 116.0 (CH), 112.7 (C), 111.5 (CH), 101.5 (CH), 99.5 (CH), 62.8 (CH_2), 55.7 (CH_3), 14.6 (CH_3), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 274 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.84; H, 5.51; N, 5.14.

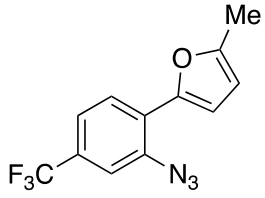
2-(5-methylfuran-2-yl)-5-(trifluoromethyl)aniline (44j)



General procedure was followed using (5- methylfuran-2-yl)boronic acid **43b** (1.13 g, 9 mmol), potassium carbonate (3.30 g, 24 mmol), $PdCl_2(PPh_3)_2$ (211 mg, 0.3 mmol), 2-bromo-5-(trifluoromethyl)aniline **42g** (1.44 g, 6 mmol) in DMF (27 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded 2-(5-methylfuran-2-yl)-5-(trifluoromethyl)aniline **44j** (1.37 mg, 95%) as a white wax. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.56 (d, *J* = 8.1 Hz, 1H), 7.02 (d, *J* =

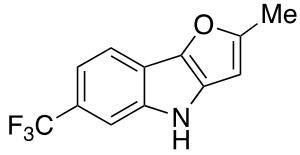
8.2 Hz, 1H), 6.98 (s, 1H), 6.58 (d, *J* = 3.3 Hz, 1H), 6.15 (m, 1H), 4.54 (bs, 2H), 2.42 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 152.0 (C), 150.4 (C), 142.8 (C), 129.9 (q, *J* = 33.8 Hz, C), 127.3 (CH), 122.2 (q, *J* = 272 Hz, C), 114.8 2 (q, *J* = 3.4 Hz, CH), 113.2 2 (q, *J* = 3.9 Hz, CH), 108.9 (CH), 107.7 (CH), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 242 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.91; H, 4.17; N, 5.83.

2-(2-azido-4-(trifluoromethyl)phenyl)-5-methylfuran (45j)



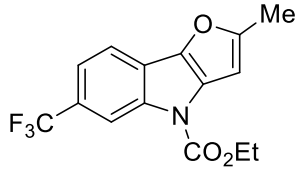
General procedure (method B) was followed using 2-(5-methylfuran-2-yl)-5-(trifluoromethyl)aniline **44j** (1.35 mg, 5.6 mmol), *t*-BuONO (1.0 ml, 8.4 mmol) and $TMSN_3$ (1.1 ml, 8.4 mmol) in CH_3CN (11 ml). Purification by flash column chromatography (SiO_2, hexane), yielded 2-(2-azido-4-(trifluoromethyl)phenyl)-5-methylfuran **45j** (1.33 g, 99%) as a yellow wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.92 (d, *J* = 8.6 Hz, 1H), 7.42-7.37 (m, 2H), 7.10 (d, *J* = 3.3 Hz, 1H), 6.14 (m, 1H), 2.39 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): 152.9 (C), 146.7 (C), 134.9 (C), 129.0 (q, *J* = 32.8 Hz, C), 129.1 (C), 126.4 (CH), 125.5 (C), 121.9 (q, *J* = 271 Hz, C), 121.6 (q, *J* = 3.9 Hz, CH), 115.7 (q, *J* = 3.8 Hz, CH), 113.7 (CH), 108.4 (CH), 13.6 (CH_3). Anal. Calcd for $C_{12}H_8F_3N_3O$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.11; H, 3.01; N, 15.69.

2-methyl-6-(trifluoromethyl)-4*H*-furo[3,2-*b*]indole (8j)



General procedure was followed using 1,2- dichlorobenzene (10.5 mL), 2-(2-azido-4-(trifluoromethyl)phenyl)-5-methylfuran **45j** (1.3 g, 4.9 mmol). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 90:10), yielded 2-methyl-6-(trifluoromethyl)-4*H*-furo[3,2-*b*]indole **8j** (873 mg, 74%) as reddish solid (m.p. 149.3-151.9 °C). **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.81 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.65 (m, 1H), 7.42 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.27 (d, *J* = 0.9 Hz, 1H), 2.54 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 158.0 (C), 140.0 (C), 137.6 (C), 133.6 (C), 125.2 (q, *J* = 271 Hz, C), 122.5 (q, *J* = 32 Hz, C), 116.7 (q, *J* = 3.9 Hz, CH), 116.3 (C), 115.5 (CH), 109.4 (q, *J* = 4.2 Hz, CH), 95.9 (CH), 15.0 (CH_3). **ESI(+)-MS**: m/z(%) = 240 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_8F_3NO$: C, 60.26; H, 3.37; N, 5.86. Found: C, 60.17; H, 3.38; N, 5.84.

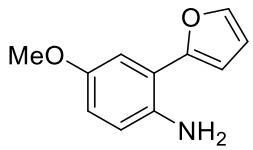
Ethyl 2-methyl-6-(trifluoromethyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (46j)



General procedure was followed using 2-methyl-6-(trifluoromethyl)-4*H*-furo[3,2-*b*]indole **8j** (500 mg, 2.1 mmol), *n*-butyllithium (1.6 M in hexane, 1.4 mL, 2.3 mmol), ethyl chloroformate (301 μL, 3.2 mmol) in THF (21 mL). Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5), yielded **46j** (628 mg, 96%) as yellow solid (m.p. 107.5-109.6 ° C). **^{1}H-NMR** (300 MHz,

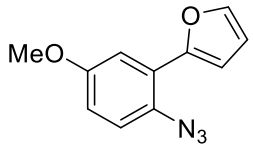
$CDCl_3$): 8.57 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.42 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.49 (d, *J* = 0.7 Hz, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 158.0 (C), 150.7 (C), 140.6 (C), 136.8 (C), 132.7 (C), 124.7 (q, *J* = 271 Hz, C), 124.7 (q, *J* = 31.4 Hz, C), 120.2 (q, *J* = 4.1 Hz, CH), 120.1 (C), 115.5 (CH), 113.6 (q, *J* = 4.3 Hz, CH), 99.4 (CH), 63.4 (CH_2), 14.8 (CH_3), 14.3 (CH_3). **ESI(+)-MS**: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}F_3NO_3$: C, 57.88; H, 3.89; N, 4.50. Found: C, 58.02; H, 3.88; N, 4.48.

2-(furan-2-yl)-4-methoxyaniline (44k)



To a N_2-flushed solution of furan-2-ylboronic acid **43a** (1.24 g, 11.1 mmol), potassium carbonate (4.09 g, 29.6 mmol), $PdCl_2(PPh_3)_2$ (260 mg, 0.37 mmol) in DMF (33 mL) and water (7.5 mL), 2-bromo-4-methoxyaniline **42d** (1.5 mg, 7.4 mmol) was added. The reaction mixture was heated at reflux for 3 h and then cooled at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent concentrated under reduced pression. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) to yield 2-(furan-2-yl)-4-methoxyaniline **44k** (1.34 g, 96%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.50 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.07 (dd, *J* = 2.5, 0.8 Hz, 1H), 6.74 – 6.71 (m, 2H), 6.61 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.9 Hz, 1H), 3.86 (bs, 2H), 3.79 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 152.98 (C), 152.61 (C), 141.40 (CH), 136.87 (C), 118.23 (CH), 117.17 (C), 115.51 (CH), 112.02 (CH), 111.36 (CH), 106.88 (CH), 55.81 (CH_3). **ESI(+)-MS**: m/z(%) = 190 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{11}NO_2$ [189.21]: C, 69.83; H, 5.86; N, 7.40; found C, 69.65; H, 5.88; N, 7.37.

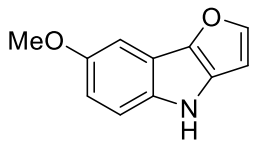
2-(2-azido-5-methoxyphenyl)furan (45k)



To a solution of 2-(furan-2-yl)-4-methoxyaniline **44k** (1.30 g, 6.9 mmol), an aqueous solution of hydrochloric acid (15%, 6.9 mL) was added dropwise at 0 °C. Then a solution of sodium nitrite (573 mg, 8.3 mmol) in water (19 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C. Then a solution of sodium azide (728 mg, 11.2 mmol) in water (2.6 mL) was added dropwise at 0 °C and the mixture was stirred for 1 h at room temperature. The mixture was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate saturated solution and brine. The organic layer was dried over Na_2SO_4 and the solvent concentrated under reduced pression. The crude was purified by flash column chromatography (SiO_2, hexane 100%) to yield 2-(2-azido-5-methoxyphenyl)furan **45k** (1.47 g, 99%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.47 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.38 (d, *J* = 2.9 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.10 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.85 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.85 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.89 (C), 149.47 (C), 141.74 (CH), 127.61 (C), 123.21

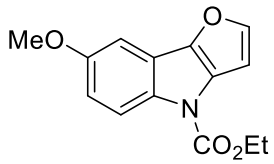
(C), 119.99 (CH), 114.44 (CH), 111.81 (CH), 111.21 (CH), 110.62 (CH), 55.61 (CH_3). **ESI(+)-MS**: Anal. Calcd. for $C_{11}H_9N_3O_2$ [215.21]: C, 61.39; H, 4.22; N, 19.53; found C, 61.67; H, 4.20; N, 19.48.

7-methoxy-4*H*-furo[3,2-*b*]indole (8k)



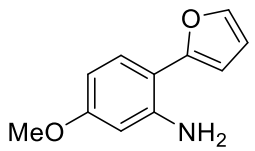
A solution of 2-(2-azido-5-methoxyphenyl)furan **45k** (1.34 g, 6.2 mmol) in 1,2-dichlorobenzene (4 mL) was added dropwise to 1,2-dichlorobenzene (8 mL) heated at 160 °C. The reaction mixture was stirred for 1 h. Then solvent was concentrated under reduced pression. The crude was purified by flash column chromatography (SiO_2, hexane/ ethyl acetate 95:5 to 9:1) to yield 7-methoxy-4*H*-furo[3,2-*b*]indole **8k** (279 mg, 24%) as brownish oil. **^{1}H NMR** (300 MHz, CD_2Cl_2): 7.69 (bs, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.32 (dd, J = 8.9, 0.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 8.9, 2.5 Hz, 1H), 6.62 (d, J = 2.1 Hz, 1H), 3.87 (s, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2):154.20 (C), 145.88 (CH), 142.22 (C), 135.10 (C), 131.10 (C), 114.49 (C), 112.91 (CH), 111.06 (CH), 99.52 (CH), 98.54 (CH), 55.71 (CH_3). **ESI(+)-MS**: m/z(%) = 188 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_9NO_2$ [187.19]: C, 70.58; H, 4.85; N, 7.48; found for C, 70.84; H, 4.86; N, 7.45.

Ethyl 7-methoxy-4H-furo[3,2-b]indole-4-carboxylate (46n)



To a N_2-flushed solution of 7-methoxy-4*H*-furo[3,2-*b*]indole **8k** (250 mg, 1.3 mmol) in tetrahydrofuran (13 mL), a solution of *n*-butyllithium (1.6 M in hexane, 893 µL, 1.43 mmol), was added dropwise at -78 °C. The reaction mixture was stirred for 30 minutes. Ethyl chloroformate (186 µL, 1.95 mmol) was added dropwise and the reaction was brought to room temperature and stirred for 2 h before of being quenched with ammonium chloride saturated solution. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and the solvent concentrated under reduced pression. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yield **46n** (288 mg, 86%) as orange solid (m.p. 74.5-76.2 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.20 (bs, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 2.6 Hz, 1H), 6.90 (dd, J = 9.1, 2.6 Hz, 1H), 6.79 (s, 1H), 4.50 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 156.31 (C), 151.04 (C) 145.85 (CH), 143.34 (C), 133.38 (C), 130.06 (C), 118.69 (C), 117.12 (CH), 111.80 (CH), 103.10 (CH), 99.87 (CH), 62.94 (CH_2), 55.72 (CH_3), 14.47 (CH_3) **ESI(+)-MS**: m/z(%) = 260 (100) $[M+H]^+$; Anal. Calcd. for $C_{14}H_{13}NO_4$ [259.26]: C, 64.86; H, 5.05; N, 5.40; found C, 65.09; H, 5.03; N, 5.42.

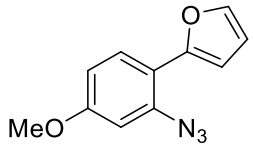
2-(furan-2-yl)-5-methoxyaniline (44l)



To a N_2-flushed solution of furan-2-ylboronic acid **43a** (1.24 g, 11.1 mmol), potassium carbonate (4.10 g, 29.7 mmol), $PdCl_2(PPh_3)_2$ (260 mg, 0.37 mmol) in DMF (33 mL) and water (7.5 mL), 2-bromo-5-methoxyaniline **42f** (1.5 mg,

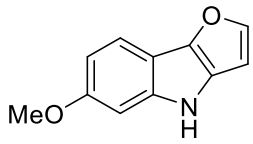
7.4 mmol) was added. The reaction mixture was heated at reflux for 3 h and then cooled at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yield 2-(furan-2-yl)-5-methoxyaniline **44l** (1.04 g, 74%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.49 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 6.51 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.48 (dd, *J* = 3.3, 0.5 Hz, 1H), 6.41 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.30 (d, *J* = 2.5 Hz, 1H), 4.25 (bs, 2H), 3.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 160.39 (C), 153.56 (C), 144.78 (C), 140.77 (CH), 129.08 (CH), 111.26 (CH), 109.84 (C), 105.17 (CH), 104.75 (CH), 101.45 (CH), 55.17 (CH_3). **ESI(+)-MS**: m/z(%) = 190 (100) $[M+H]^+$; $C_{11}H_{11}NO_2$ [189.21]: calcd. for: C 69.83, H 5.86, N 7.40; found: C, 69.65; H, 5.88; N, 7.37.

2-(2-azido-4-methoxyphenyl)furan (45l)



To a solution of 2-(furan-2-yl)-5-methoxyaniline **44l** (980 g, 5.17 mmol) in MeCN (10 mL) at 0 °C, *t*-BuONO (801 Mg, 7.77 mmol) was added, followed by $TMSN_3$ (895 Mg, 7.77) dropwise. The resulting solution was stirred at room temperature for 1 h and then concentrated in vacuum. The crude was purified by flash column chromatography (SiO_2, hexane 100%) to yield 2-(2-azido-4-methoxyphenyl)furan **45l** (614 Mg, 55%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.75 (m, 1H), 7.43 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.90 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.81 – 6.70 (m, 2H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.85 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.57 (C), 149.76 (C), 141.10 (CH), 136.32 (C), 128.11 (CH), 115.95 (C), 111.54 (CH), 110.71 (CH), 108.47 (CH), 104.59 (CH), 55.47 (CH_3). **ESI(+)-MS**: $C_{11}H_9N_3O_2$ [215.21]: calcd. for: C 61.39, H 4.22, N 19.53; found: C 61.57, H 4.20, N, 19.48.

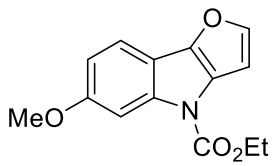
6-methoxy-4*H*-furo[3,2-*b*]indole (8l)



A solution of 2-(2-azido-4-methoxyphenyl)furan **45l** (590 Mg, 2.74 mmol) in 1,2-dichlorobenzene (2 mL) was added dropwise to 1,2-dichlorobenzene (4 mL) heated at 160 °C. The reaction mixture was stirred for 1 h. Then solvent was concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/ ethyl acetate 95:5) to yield 6-methoxy-4*H*-furo[3,2-*b*]indole **8l** (138 mg, 27%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.60 (d, *J* = 8.6 Hz, 1H), 7.53 (bs, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.84 (dd, J = 8.6, 2.1 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 3.86 (s, 3H). **^{13}C NMR** (75 MHz, CDC_3): 156.02 (C), 144.62 (CH), 142.46 (C), 141.04 (C), 128.93 (C), 116.77 (CH), 109.56 (C), 108.89 (CH), 99.50 (CH), 96.61 (CH), 55.70 (CH_3). **ESI(+)-MS**: m/z(%)

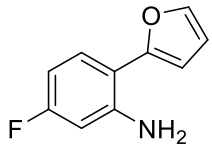
= 188 (100) $[M+H]^+$; $C_{11}H_9NO_2$ [187.19]: calcd. for: C 70.58, H 4.85, N 7.48; found: C 70.84, H 4.86, N 7.45.

Ethyl 6-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate (46o)



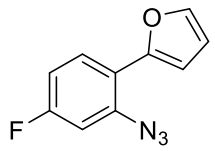
To a N_2-flushed solution of 6-methoxy-4*H*-furo[3,2-*b*]indole **8l** (98 mg, 0.52 mmol) in tetrahydrofuran (5 mL), a solution of *n*-butyllithium (1.6 M in hexane, 362 μL, 0.58 mmol), was added dropwise at -78 °C. The reaction mixture was stirred for 30 minutes. Ethyl chloroformate (75 μL, 0.78 mmol) was added dropwise and the reaction was brought to room temperature and stirred for 2 h before of being quenched with ammonium chloride saturated solution. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and the solvent concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield **46o** (114 mg, 85%) as orange solid (m.p. 70-72 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.94 (bs, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.76 (s, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 157.40 (C), 151.10 (C), 144.62 (CH), 143.54 (C), 139.97 (C), 128.19 (C), 116.76 (CH), 112.33 (C), 111.71 (CH), 103.12 (CH), 101.40 (CH), 62.92 (CH_2), 55.68 (CH_3), 14.40 (CH_3). **ESI(+)-MS**: m/z(%) = 260 (100) $[M+H]^+$; $C_{14}H_{13}NO_4$ [259.26]: calcd. for: C 64.86, H 5.05, N 5.40; found: C 64.71, H 5.03, N 5.42.

5-fluoro-2-(furan-2-yl)aniline (44m)



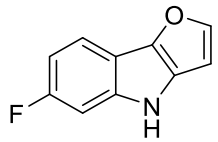
To a N_2-flushed solution of furan-2-ylboronic acid **43a** (1.32 g, 11.8 mmol), potassium carbonate (4.36 g, 31.5 mmol), $PdCl_2(PPh_3)_2$ (276 mg, 0.39 mmol) in DMF (35 mL) and water (8 mL), 2-bromo-5-fluoroaniline **42e** (1.50 mg, 7.89 mmol) was added. The reaction mixture was heated at reflux for 3 h and then cooled at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yield 5-fluoro-2-(furan-2-yl)aniline **44m** (1.21 g, 87%) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.48 (t, *J* = 1.2 Hz, 1H), 7.39 (dd, *J* = 8.6, 6.4 Hz, 1H), 6.59 – 6.33 (m, 3H), 4.43 (bs, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): 163.29 (d, *J* = 245.4 Hz, C), 152.76 (C), 145.10 (d, *J* = 10.9 Hz, C), 141.24 (CH), 129.43 (d, *J* = 10.1 Hz, CH), 112.54 (d, *J* = 2.5 Hz, C), 111.31 (CH), 106.12 (CH),105.39 (d, *J* = 22.1 Hz, CH), 102.87 (d, *J* = 24.8 Hz, CH). **ESI(+)-MS**: m/z(%) = 178 (100) $[M+H]^+$; $C_{10}H_8FNO$ [177.18]: calcd. for: C 67.79, H 4.55, N 7.91; found: C 67.97, H 4.56, N 7.093.

2-(2-azido-4-fluorophenyl)furan (45m)



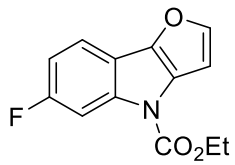
To a solution of 5-fluoro-2-(furan-2-yl)aniline **44m** (1.18 g, 6.65 mmol) in CH_3CN (13 mL) at 0 °C, *t*-BuONO (1.03 g, 9.97 mmol) was added, followed by $TMSN_3$ (1.15 g, 9.97) dropwise. The resulting solution was stirred at room temperature for 1 h and then concentrated in vacuum. The crude was purified by flash column chromatography (SiO_2, hexane 100%) to yield 2-(2-azido-4-fluorophenyl)furan **45m** (1.02 g, 76%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.80 (m, 1H), 7.46 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.99 (m, 1H), 6.96 – 6.86 (m, 2H), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): 162.05 (d, *J* = 249.4 Hz, C), 148.90 (C), 141.69 (CH), 136.69 (d, *J* = 8.3 Hz, C), 128.40 (d, *J* = 9.0 Hz, CH), 119.02 (C), 112.24 (d, *J* = 21.6 Hz, CH), 111.68 (CH), 109.76 (CH), 106.12 (d, *J* = 25.2 Hz, CH). **ESI(+)-MS**: $C_{10}H_6FN_3O$ [203.18]: calcd. for: C 59.12, H 2.98, N 20.68; found: C 59.04, H 2.99, N 20.66.

6-fluoro-4*H*-furo[3,2-*b*]indole (8m)



A solution of 2-(2-azido-4-fluorophenyl)furan **45m** (983 mg, 4.84 mmol) in 1,2-dichlorobenzene (3.5 mL) was added dropwise to 1,2-dichlorobenzene (7 mL) heated at 160 °C. The reaction mixture was stirred for 1 h. Then solvent was concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/ ethyl acetate 95:5) to yield 6-fluoro-4*H*-furo[3,2-*b*]indole **8m** (650 mg, 76%) as brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.77 – 7.61 (m, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 9.8, 2.2 Hz, 1H), 6.97 (td, *J* = 9.2, 2.2 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.38 (d, *J* = 238.1 Hz, C), 145.52 (CH), 142.03 (C), 140.00 (d, *J* = 11.9 Hz, C), 130.21 (C), 116.77 (d, *J* = 10.0 Hz, CH), 111.55 (C), 108.24 (d, *J* = 24.5 Hz, CH), 99.54 (CH), 98.95 (d, *J* = 26.6 Hz, CH). **ESI(+)-MS**: m/z(%) = 176 (100) $[M+H]^+$; $C_{10}H_6FNO$ [175.16]: calcd. for: C 68.57, H 3.45, N 8.00; found: C 68.48, H 3.46, N 8.02.

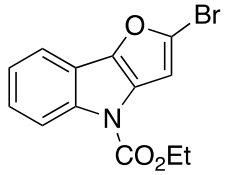
Ethyl 6-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate (46p)



To a N_2-flushed solution of 6-fluoro-4*H*-furo[3,2-*b*]indole **8m** (538 mg, 3.07 mmol) in tetrahydrofuran (30 mL), a solution of *n*-butyllithium (1.6 M in hexane, 2.1 mL, 3.36 mmol), was added dropwise at -78 °C. The reaction mixture was stirred for 30 minutes. Ethyl chloroformate (728 µL, 4.58 mmol) was added dropwise and the reaction was brought to room temperature and stirred for 2 h before of being quenched with ammonium chloride saturated solution. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and the solvent concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield **46p** (672 mg, 89%) as orange solid (m.p. 53-55 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.07 (bs, 1H), 7.57 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.06 (td, *J* = 8.9, 2.4 Hz, 1H), 6.80 (s, 1H), 4.53 (q, *J* = 7.1 Hz,

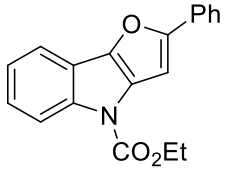
2H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) : 160.27 (d, *J* = 240.9 Hz, C), 150.82 (C), 145.58 (CH), 142.87 (C), 139.07 (C), 129.57 (C), 116.78 (d, *J* = 9.7 Hz, CH), 114.64 (C), 111.20 (d, *J* = 24.3 Hz, CH), 104.23 (d, *J* = 29.2 Hz, CH), 103.08 (CH), 63.30 (CH_2), 14.41 (CH_3). **ESI(+)-MS**: m/z(%) = 248 (100) $[M+H]^+$; $C_{13}H_{10}FNO_3$ [247.23]: calcd. for: C 63.16, H 4.08, N 5.67; found: C 63.39, H 4.08, N 5.68.

Ethyl 2-bromo-4*H*-furo[3,2-*b*]indole-4-carboxylate (47)



To a N_2 flushed solution of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (150 mg, 0.65 mmol) in 1,2-dichloroethane (6.5 mL), *N*-bromosuccinimide (116 mg, 0.65 mmol) and DMF (7 µL) were added. The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with $Na_2S_2O_3$ saturated solution and extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield ethyl 2-bromo-4*H*-furo[3,2-*b*]indole-4-carboxylate **47** (159 mg, 79%) as white solid (m.p. 96-98° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.32 (bs, 1H), 7.64 (m, 1H), 7.44-7.06 (m, 2H), 6.80 (s, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 150.8 (C), 143.4 (C), 137.6 (C), 129.6 (C), 125.0 (C), 124.3 (CH), 123.6 (CH), 117.6 (C), 116.3 (CH), 116.2 (CH), 105.1 (CH), 63.3 (CH_2), 14.5 (CH_3). Anal. Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55. Found: C, 50.49; H, 3.28; N, 4.54.

Ethyl 2-phenyl-4*H*-furo[3,2-*b*]indole-4-carboxylate (46k)

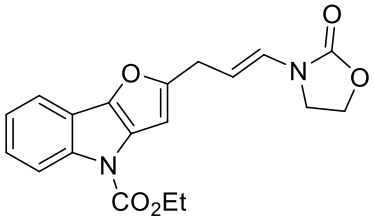


To a N_2-flushed solution of phenylboronic acid (67 mg 0.54 mmol), potassium carbonate (249 mg, 1.8 mmol.), $PdCl_2(PPh_3)_2$ (16 mg, 0.02 mmol) in DMF (2 mL) and water (0.6 mL), ethyl 2-bromo-4*H*-furo[3,2-*b*]indole-4-carboxylate **47** (140 mg 0.45 mmol)was added. The reaction mixture was heated at reflux for 1.5 h and then cooled at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield **46k** (105 mg, 76%) as white solid (m.p. 114-116° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.32 (bs, 1H), 7.81 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.69 (m, 1H), 7.48-7.38 (m, 2H), 7.38-7.21 (m, 3H), 7.06 (bs, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 157.3 (C), 151.1 (C), 142.9 (C), 138.5 (C), 131.1 (C), 128.8 (2xCH), 127.8 (CH), 123.9 (2xCH), 123.8 (CH), 123.5 (CH), 118.0 (C), 116.31 (CH), 116.29 (CH), 97.8 (CH), 63.1 (CH_2), 14.5 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 306 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.86; H, 4.97; N, 4.58.

2.2.6.2.2 General procedure for the synthesis of compounds 53a-i

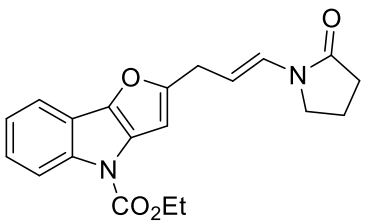
To a N_2-flushed solution of appropriate ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a,f,g** (1.2 equiv.) and $(ArO)_3PAuNTf_2$ (5 mol%) in anhydrous toluene and in the presence of 200 mg of 4 Å MS, a solution of the appropriate *N*-allenamide **11a-d**,**h-j** (1.0 equiv.) in toluene was added dropwise at -20 °C. The reaction mixture was stirred for 15 minutes, quenched with PPh_3 (15 mol%) and filtered through a pad of celite. The crude was purified by flash chromatography to yield the corresponding hydroarylated product **53a-i**.

(*E*)-ethyl 2-(3-(2-oxooxazolidin-3-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53a)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (25 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.05 mmol) in anhydrous toluene (3+1 mL) at -20° C. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) yielded **53a** (64 mg, 90%), as a pink solid (m.p. 139.5-141° C). **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.31 (bs, 1H), 7.64 (m, 1H), 7.37 - 7.21 (m, 2H), 6.88 (d, *J* = 14.2 Hz, 1H), 6.58 (s, 1H), 5.07 (dt, *J* = 14.2, 7.1 Hz, 1H), 4.56 - 4.34 (m, 4H), 3.79 - 3.65 (m, 2H), 3.63 (d, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 158.5 (C), 155.2 (C), 151.0 (C), 141.9 (C), 138.0 (C), 130.2 (C), 126.3 (CH), 123.3 (CH), 123.2 (CH), 118.0 (C), 116.1 (CH), 115.7 (CH), 105.5 (CH), 99.2 (CH), 63.1 (CH_2), 62.3 (CH_2), 42.5 (CH_2), 29.8 (CH_2), 14.2 (CH_3). **EI-MS**: m/z(%) = 354 (100) [M]. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.63; H, 5.13; N, 7.92.

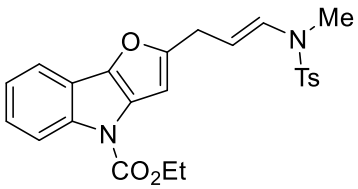
(*E*)-ethyl 2-(3-(2-oxopyrrolidin-1-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53b)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), 1-(propa-1,2-dien-1-yl)pyrrolidin-2-one **11b** (25 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.05 mmol) in anhydrous toluene (3+1 mL) at -20° C. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) yielded **53b** (58 mg, 80%), as a pink solid (m.p. 141.4-142.9° C). **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.31 (bs, 1H), 7.63 (m, 1H), 7.35 - 7.26 (m, 2H), 7.09 (d, *J* = 14.4 Hz, 1H), 6.57 (s, 1H), 5.17 (dt, *J* = 14.3, 7.1 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 3.63 (d, *J* = 7.1 Hz, 2H), 3.55 (dd, *J* = 8.8, 5.6 Hz, 2H), 2.47 (t, *J* = 8.1 Hz, 2H), 2.18 - 2.06 (m, 2H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 172.9 (C), 158.9 (C), 151.0 (C), 141.9 (C), 138.0 (C), 130.3 (C), 126.0 (CH), 123.2 (2xCH), 118.1 (C), 116.1 (CH), 115.7 (CH), 106.1 (CH), 99.2 (CH), 63.1 (CH_2), 45.2 (CH_2), 31.1 (CH_2), 30.2 (CH_2), 17.5 (CH_2),

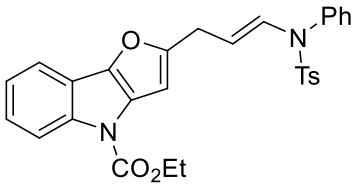
14.2 (CH_3). **ESI(+)-MS**: m/z(%) = 576 (100) $[M+Na]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.84; H, 5.79; N, 7.34.

(*E*)-ethyl 2-(3-(*N*,4-dimethylphenylsulfonamido)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (3c)



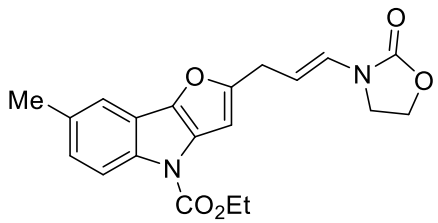
General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), *N*,4-dimethyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11c** (45 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.05 mmol) in anhydrous toluene (6+4 mL) at -20° C. The reaction mixture was stirred for 1 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **53c** (66 mg, 61%), as a wax. **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.31 (bs, 1H), 7.73 - 7.60 (m, 3H), 7.39-7.27 (m, 4H), 6.99 (d, *J* = 14.0 Hz, 1H), 6.52 (s, 1H), 4.96 (dt, *J* = 14.1, 7.1 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 3.58 (d, *J* = 7.1 Hz, 2H), 2.91 (s, 3H), 2.44 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 158.7 (C), 151.0 (C), 144.1 (C), 141.9 (C), 137.9 (C), 134.5 (C), 130.3 (CH), 129.7 (2xCH), 127.0 (2xCH), 123.3 (CH), 123.2 (CH), 118.0 (C), 116.2 (CH), 115.6 (CH), 105.9 (CH), 99.1 (CH), 63.1 (CH_2), 32.3 (CH_3), 29.7 (CH_2), 21.2 (CH_3), 14.2 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 453 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_5S$: C, 63.70; H, 5.35; N, 6.19. Found: C, 63.62; H, 5.36; N, 6.18.

(*E*)-ethyl-2-(3-(4-methyl-*N*-phenylphenylsulfonamido)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53d)



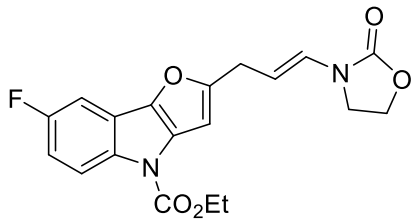
General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), 4-methyl-*N*-phenyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11d** (57 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.05 mmol) in anhydrous toluene (6+4 mL) at -20° C. The reaction mixture was stirred for 1 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **53d** (62 mg, 60%), as a pink solid (m.p. 148.5-151°C). **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.27 (bs, 1H), 7.62-7.54 (m, 3H), 7.43 - 7.24 (m, 7H), 7.18 (dt, *J* = 13.9, 1.2 Hz, 1H), 7.08 - 6.95 (m, 2H), 6.40 (s, 1H), 4.63 - 4.42 (m, 3H), 3.49 (d, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 158.4 (C), 151.0 (C), 144.1 (C), 141.8 (C), 137.9 (C), 136.7 (C), 135.8 (C), 131.3 (CH), 130.1 (2xCH), 129.6 (2xCH), 129.4 (2xCH), 128.9 (CH), 127.4 (2xCH), 123.2 (CH), 123.2 (CH), 118.0 (C), 116.1 (CH), 115.6 (CH), 107.0 (CH), 99.1 (CH), 63.0 (CH_2), 29.7 (CH_2), 21.3 (CH_3), 14.2 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 537 (100) $[M+Na]^+$. Anal. Calcd for $C_{29}H_{26}N_2O_5S$: C, 67.69; H, 5.09; N, 5.44. Found: C, 67.53; H, 5.08; N, 5.45.

(*E*)-ethyl 7-methyl-2-(3-(2-oxooxazolidin-3-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53e)



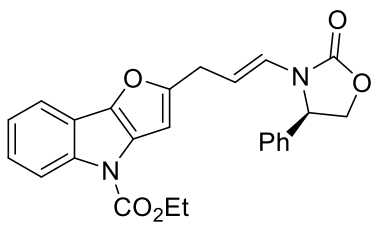
General procedure was followed using ethyl 7-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46f** (58 mg, 0.24 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (25 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.05 mmol) in anhydrous toluene (3+1 mL) at -20° C. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) yielded **53e** (52 mg, 70%), as a pink solid (m.p. 121.2-122.7° C). **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.17 (bs, 1H), 7.43 (s, 1H), 7.12 (dd, *J* = 8.5, 1.1 Hz, 1H).), 6.87 (d, *J* = 14.2 Hz, 1H), 6.56 (s, 1H), 5.06 (dt, *J* = 14.2, 7.1 Hz, 1H), 4.56 - 4.41 (m, 4H), 3.75 (dd, *J* = 8.9, 7.2 Hz, 2H), 3.62 (d, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 1.51 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 158.3 (C), 155.2 (C), 151.0 (C), 141.8 (C), 136.2 (C), 133.0 (C), 126.2 (CH), 124.4 (CH), 118.1 (C), 115.7 (2xCH), 105.5 (CH), 99.2 (CH), 62.9 (CH_2), 62.3 (CH_2), 42.5 (CH_2), 29.8 (CH_2), 21.0 (CH_3), 14.2 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 391 (100) $[M+Na]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.33; H, 5.49; N, 7.58.

(*E*)-ethyl 7-fluoro-2-(3-(2-oxooxazolidin-3-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53f)



General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46g** (59 mg, 0.24 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (25 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.05 mmol) in anhydrous toluene (3+1 mL) at -20° C. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 4:1) yielded **53f** (71 mg, 95%), as a pink solid (m.p. 172.6-173.1° C). **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.24 (s, 1H), 7.28 (m, 1H), 6.99 (td, *J* = 9.2, 2.7 Hz, 1H), 6.85 (d, *J* = 14.3 Hz, 1H), 6.54 (s, 1H), 5.03 (dt, *J* = 14.2, 7.1 Hz, 1H), 4.54 - 4.39 (m, 4H), 3.73 (dd, *J* = 8.9, 7.2 Hz, 2H), 3.64 - 3.57 (m, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 159.5 (d, *J* = 239.4 Hz, C). 159.4 (C), 155.2 (C), 150.8 (C), 145.9 (C),134.2 (C), 126.4 (CH), 118.6 (d, *J* = 10.8 Hz, C), 117.1 (d, *J* = 9.4 Hz, CH), 110.2 (d, *J* = 24.9 Hz, CH), 105.2 (CH), 101.8 (d, *J* = 26.0 Hz, CH), 99.2 (CH), 63.2 (CH_2), 62.3 (CH_2), 42.5 (CH_2), 29.8 (CH_2), 14.2 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 395 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{17}FN_2O_5$: C, 61.29; H, 4.60; N, 7.52. Found: C, 61.24; H, 4.59; N, 7.53.

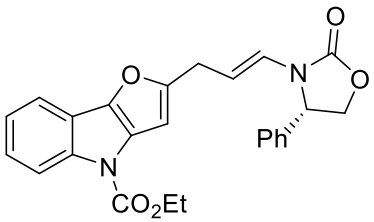
(*R*,*E*)-ethyl 2-(3-(2-oxo-4-phenyloxazolidin-3-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53g)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), ((*R*)-4-phenyl-3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11h** (40 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.01 mmol) in anhydrous toluene (3+1 mL) at -20 °C.

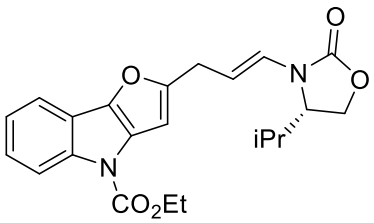
Purification by flash chromatography (SiO_2, hexane/ethyl acetate 8:2) to yield the desired product **53g** (78 mg, 90%) as a pink solid (m.p. 136.5 - 137.2 °C). **^{1}H-NMR** (300 MHz, CD_2Cl_2): 8.27 (s, 1H), 7.63-753 (m, 1H), 7.47 – 7.22 (m, 7H), 6.80 (dt, *J* = 14.5, 1.0 Hz, 1H), 6.31 (s, 1H), 5.08 (dd, *J* = 9.0, 5.3 Hz, 1H), 4.84 (dt, *J* = 14.4, 7.2 Hz, 1H), 4.73 (t, *J* = 8.9 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.13 (m,, 1H), 3.44 (m, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (75 MHz, CD_2Cl_2): 158.36 (C), 155.54 (C), 150.95 (C), 141.82 (C), 138.21 (C), 137.93 (C), 130.12 (C), 129.24 (2xCH), 128.69 (CH), 126.02 (2xCH), 125.27 (CH), 123.20 (CH), 117.98 (C), 116.12 (CH), 115.64 (CH), 107.42 (CH), 99.05 (CH), 70.65 (CH_2), 63.03 (CH_2), 58.52 (CH), 30.03 (CH_2), 14.30 (CH_3). **ESI(+)-MS**: m/z(%) = 453 (90%) $[M+Na]^+$; $C_{25}H_{22}N_2O_5$ [430.45].

(*S,E*)-ethyl 2-(3-(2-oxo-4-phenyloxazolidin-3-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53h)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), ((*S*)-4-phenyl-3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11i** (40 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.01 mmol) in anhydrous toluene (3+1 mL) at -20 °C. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 8:2) to yield the desired product **53h** (74 mg, 85%), as a pink solid (m.p. 133.3 - 135.9 °C). **^{1}H-NMR** (300 MHz, CD_2Cl_2): 8.27 (s, 1H), 7.63-753 (m, 1H), 7.47 – 7.22 (m, 7H), 6.80 (dt, *J* = 14.5, 1.0 Hz, 1H), 6.31 (s, 1H), 5.08 (dd, *J* = 9.0, 5.3 Hz, 1H), 4.84 (dt, *J* = 14.4, 7.2 Hz, 1H), 4.73 (t, *J* = 8.9 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.13 (m,, 1H), 3.44 (m, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (75 MHz, CD_2Cl_2): 158.36 (C), 155.54 (C), 150.95 (C), 141.82 (C), 138.21 (C), 137.93 (C), 130.12 (C), 129.24 (2xCH), 128.69 (CH), 126.02 (2xCH), 125.27 (CH), 123.20 (CH), 117.98 (C), 116.12 (CH), 115.64 (CH), 107.42 (CH), 99.05 (CH), 70.65 (CH_2), 63.03 (CH_2), 58.52 (CH), 30.03 (CH_2), 14.30 (CH_3). **ESI(+)-MS**: m/z(%) = 453 (90%) $[M+Na]^+$; $C_{25}H_{22}N_2O_5$ [430.45].

(*S,E*)-ethyl 2-(3-(4-isopropyl-2-oxooxazolidin-3-yl)allyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (53i)



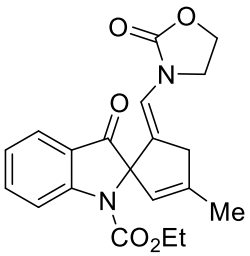
General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (55 mg, 0.24 mmol), (*S*)-4-isopropyl-3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11j** (34 mg, 0.2 mmol), $(ArO)_3PAuNTf_2$ (11 mg, 0.01 mmol) in anhydrous toluene (3+1 mL) at -20 °C. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) to yield the desired product **53b** (73 mg, 92%), as a pink solid (m.p. 80 - 84.8 °C). **^{1}H-NMR** (300 MHz, CD_2Cl_2) δ 8.29 (s, 1H), 7.66-7.58 (m, 1H), 7.34-7.24 (m, 2H), 6.73 (dt, *J* = 14.5, 1.2 Hz, 1H), 6.53 (s, 1H), 5.20 (dt, *J* = 14.4, 7.1 Hz, 1H), 4.50 (d, *J* = 7.1 Hz, 2H), 4.35-4.20 (m, 2H), 4.10-4.03

(m, 1H), 3.60 (dd, *J* = 7.1, 1.1 Hz, 2H), 2.53 – 2.34 (m, 1H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.03 – 0.78 (m, 6H). **^{13}C-NMR** (75 MHz, CD_2Cl_2): 158.58 (C), 155.37(C), 150.94 (C), 141.91 (C), 137.95 (C), 130.20 (C), 125.22 (CH), 123.22 (CH), 123.20 (CH), 118.02 (CH_2), 116.11 (CH), 115.64 (CH), 109.99 (C), 106.15 (CH), 99.20 (CH), 63.01 (CH_2), 58.40 (CH), 30.17 (CH_2), 26.23 (CH), 17.49 (CH_3), 14.20 (CH_3), 13.60 (CH_3). **ESI(+)-MS**: m/z(%) = 397 (90%) $[M+Na]^+$; $C_{22}H_{24}N_2O_5$ [396.44].

2.2.6.2.3 General Procedure for the Synthesis of Compounds 54a-m.

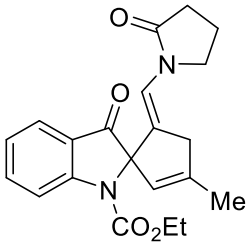
To a N_2-flushed solution of ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b-e**,**h-k** (1 equiv.) and $IPrAuNTf_2$ (5 mol%) in anhydrous dichloromethane, a solution of *N*-allenamide **11a-g** (1.2 equiv.) in dichloromethane was added dropwise at -20° C. The reaction mixture was stirred for the stated time at -20° C and then quenched with PPh_3 (15 mol%). The solvent was removed under vacuum and the crude residue was purified by flash column chromatography to yield the desired product **54a-m**.

(*E*)-ethyl 3-methyl-3'-oxo-5-((2-oxooxazolidin-3-yl)methylene)spiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54a)



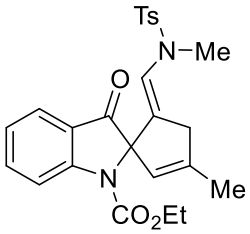
General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (30 mg, 0.24 mmol) and $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 1 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) yielded **54a** (50 mg, 68%) as a yellowish wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.46 (bs, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.30 (m, 1H, overlapping with the signal of C_6D_6), 6.79 (t, *J* = 7.4 Hz, 1H), 6.44 (s, 1H), 4.95 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.35 (m, 2H), 3.18 (m, 2H), 2.85 (m, 1H), 2.73 (m, 1H), 1.78 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 198.0 (C), 155.4 (C), 153.0 (C), 151.6 (C), 145.4 (C), 137.1 (CH), 124.6 (CH), 123.4 (CH), 123.3 (CH), 122.3 (C), 118.5 (CH), 116.8 (CH), 82.8 (C) 61.6 (CH_2), 61.2 (CH_2), 43.4 (CH_2), 40.0 (CH_2), 16.5 (CH_3), 14.0 (CH_3). One quaternary carbon is missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 489 (100) $[M+Na]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.29; H,.5.46: N, 7.59.

(*E*)-ethyl-3-methyl-3'-oxo-5-((2-oxopyrrolidin-1-yl)methylene)spiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54b)



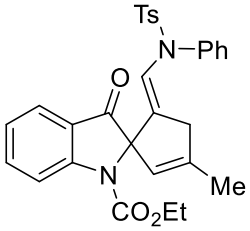
General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol), 1-(propa-1,2-dien-1-yl)pyrrolidin-2-one **11b** (37 mg, 0.3 mmol) and IPrAuNTf$_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 3 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) yielded **54b** (45 mg, 61%) as yellowish wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.50 (bs, 1H), 7.79 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.32 (m, 1H), 6.93 - 6.67 (m, 2H), 4.99 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.41 - 3.20 (m, 2H), 3.10 (m, 1H), 2.97 (m, 1H), 1.93 - 1.81 (m, 2H), 1.78 (s, 3H), 1.21 - 1.11 (m, 2H), 1.03 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 198.1 (C), 172.3 (C), 153.1 (C), 151.6 (C), 145.5 (C), 137.0 (CH), 124.6 (CH), 123.3 (CH), 123.3 (CH), 122.4 (C), 118.3 (CH), 116.8 (CH), 83.1 (C), 61.4 (CH_2), 46.2 (CH_2), 40.6 (CH_2), 29.6 (CH_2), 17.4 (CH_2), 16.5 (CH_3), 14.0 (CH_3). One quaternary carbon is missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 367 (100) $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 69.03; H, 6.04; N, 7.66.

(*E*)-ethyl-5-((N,4-dimethylphenylsulfonamido)methylene)-3-methyl-3'-oxospiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (4c)



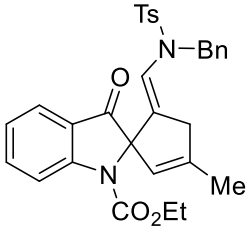
General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol), *N*,4-dimethyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11c** (53 mg, 0.24 mmol) and IPrAuNTf$_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 3 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **54c** (72 mg, 77%) as yellowish wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.69 (bs, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.29 (m, 1H, overlapping with the signal of C_6D_6), 6.91 (d, *J* = 8.1 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 5.62 (bs, 1H), 4.87 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.54 - 3.24 (m, 2H), 2.55 (s, 3H), 1.93 (s, 3H), 1.63 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 197.2 (C), 153.3 (C), 151.9 (C), 146.2 (C), 143.1 (C), 137.0 (CH), 134.4 (C), 129.5 (2xCH), 127.6 (2xCH), 124.4 (CH), 123.3 (CH), 122.5 (CH), 122.4 (CH), 122.4 (C), 116.7 (CH), 82.0 (C), 61.9 (CH_2), 40.5 (CH_2), 36.2 (CH_3), 20.8 (CH_3), 16.3 (CH_3), 13.8 (CH_3). One quaternary carbon is missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 489 (100) $[M+Na]^+$. Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 64.36; H, 5.62; N, 6.00. Found: C, 64.18; H, 5.63; N, 5.99.

(*E*)-ethyl 3-methyl-5-((4-methyl-*N*-phenylphenylsulfonamido)methylene)-3'-oxospiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (4d)



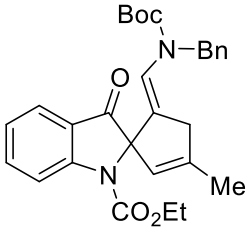
General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol), 4-methyl-*N*-phenyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11d** (69 mg, 0.24 mmol) and IPrAuNTf$_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 18 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **54d** (52 mg, 49%) as yellowish oil. **^{1}H NMR** (300 MHz, C_6D_6): 8.75 (bs, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.39 - 7.20 (m, 3H, overlapped with the signal of C_6D_6), 7.10 - 6.91 (m, 3H), 6.79 (dd, *J* = 12.3, 4.7 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 2H), 4.83 (d, *J* = 1.4 Hz, 1H), 4.26 - 4.12 (m, 2H), 2.93 - 2-63 (m, 2H), 1.84 (s, 3H), 1.45 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 197.3 (C), 153.4 (C), 151.9 (C), 145.6 (C), 143.2 (C), 140.1 (C), 137.1 (CH), 135.8 (C), 129.4 (2xCH), 128.8 (2xCH), 128.1 (CH), 127.6 (2xCH), 127.0 (2xCH), 124.6 (CH), 123.3 (CH), 122.8 (CH), 122.2 (C), 122.0 (CH), 116.9 (CH), 82.2 (C), 61.8 (CH_2), 40.1 (CH_2), 20.8 (CH_3), 16.1 (CH_3), 13.8 (CH_3). One quaternary carbon is missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 551 (100) $[M+Na]^+$. Anal. Calcd for $C_{30}H_{28}N_2O_5S$: C, 68.16; H, 5.34; N, 5.30. Found: C, 68.07; H, 5.33; N, 5.29.

(*E*)-ethyl 5-((*N*-benzyl-4-methylphenylsulfonamido)methylene)-3-methyl-3'-oxospiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54e)



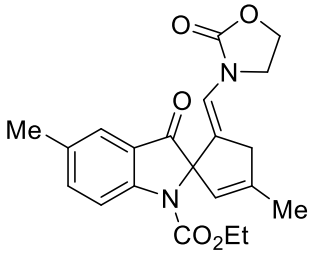
General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol), *N*-benzyl-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11e** (72 mg, 0.24 mmol) and IPrAuNTf$_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 18 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **54e** (67 mg, 62%) as white thick wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.73 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 3H), 7.33 - 7.19 (m, 4H, overlapped with the signal of C_6D_6), 7.17 - 7.06 (m, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.76 (t, *J* = 7.4 Hz, 1H), 5.21 (s, 1H), 4.77 (d, *J* = 1.5 Hz, 1H), 4.22 (dq, *J* = 10.4, 7.1 Hz, 1H), 4.05 (d, *J* = 13.9 Hz, 1H), 3.98- 3.81 (m, 2H), 3.51 - 3.23 (m, 2H), 1.95 (s, 3H), 1.51 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 196.5 (C), 153.4 (C), 151.9 (C), 146.5 (C), 143.1 (C), 136.9 (CH), 136.5 (C), 135.5 (C), 129.5 (2xCH), 128.9 (2xCH), 128.5 (2xCH), 127.7 (3xCH), 124.3 (CH), 123.2 (CH), 122.4 (C), 121.9 (CH), 120.8 (CH), 116.7 (CH), 111.1 (C), 81.6 (C), 61.9 (CH_2), 54.5 (CH_2), 40.7 (CH_2), 20.8 (CH_3), 16.1 (CH_3), 13.5 (CH_3). **ESI(+)-MS**: m/z (%) = 543 (100) $[M+H]^+$. Anal. Calcd for $C_{31}H_{30}N_2O_5S$: C, 68.61; H, 5.57; N, 5.16. Found: C, 68.73; H, 5.56; N, 5.17.

(*E*)-ethyl 5-((benzyl(tert-butoxycarbonyl)amino)methylene)-3-methyl-3'-oxospiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54f)



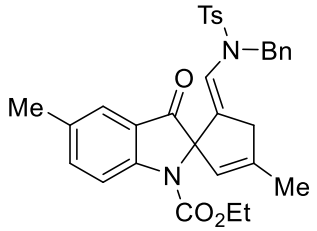
To a N_2-flushed solution of ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol) and $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in 3 mL of anhydrous dichloromethane, a solution of *tert*-butyl benzyl(propa-1,2-dien-1-yl)carbamate **11f** (45 mg, 0.2 mmol) in 1 mL of dichloromethane was added dropwise at -20° C. The reaction mixture was stirred for 1 h. Then another solution of *tert*-butyl benzyl(propa-1,2-dien-1-yl)carbamate **11f** (45 mg, 0.2 mmol) in 1 mL of dichloromethane was added dropwise at -20° C. The reaction was stirred for 1 h, then quenched with PPh_3 and the solvent was removed under vacuum. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **54f** (70 mg, 72%) as yellow thick wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.67 (bs, 1H), 7.81 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.39 - 7.03 (m, 6H, overlapping with the signal of C_6D_6), 6.78 (t, *J* = 7.2 Hz, 1H), 6.60 (bs, 1H), 4.92 (d, *J* = 1.4 Hz, 1H), 4.67 (bs, 2H), 4.23 - 3.91 (m, 2H), 3.28 - 2.94 (m, 2H), 1.61 (d, *J* = 0.9 Hz, 3H), 1.36 (s, 9H), 0.93 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 197.6 (C), 153.3 (C), 151.8 (C), 145.4 (C), 139.1 (C), 136.8 (CH), 128.4 (2xCH), 127.0 (3xCH), 124.5 (CH), 123.1 (CH), 123.0 (CH), 122.6 (CH), 122.5 (C), 116.7 (CH), 80.4 (C), 61.3 (CH_2), 49.4 (CH_2), 40.2 (CH_2), 29.9 (C) 27.8 (3xCH_3), 16.3 (CH_3), 13.8 (CH_3). Two quaternary carbons are missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 511 (100) $[M+Na]^+$. Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 71.47; H, 6.61; N, 5.72.

(*E*)-ethyl 3,5'-dimethyl-3'-oxo-5-((2-oxooxazolidin-3-yl)methylene)spiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54g)



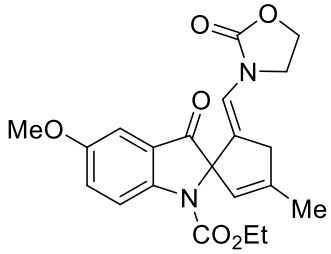
General procedure was followed using ethyl 2,7-dimethyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46c** (52 mg, 0.2 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (38 mg, 0.3 mmol) and $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 1 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 3:1 to 1:1) yielded **54g** (43 mg, 56%) as yellowish wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.42 (bs, 1H), 7.63 (s, 1H), 7.15 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.50 (s, 1H), 5.01 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.39 - 3.25 (m, 2H), 3.2 - 3.08 (m, 2H), 2.90 - 2.78 (m, 1H), 2.75 - 2.64 (m, 1H), 2.02 (s, 3H), 1.80 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 198.1 (C), 155.4 (C), 151.6 (C), 151.2 (C), 145.2 (C), 138.3 (CH), 133.1 (C), 124.5 (CH), 123.5 (CH), 122.4 (C), 118.4 (CH), 116.6 (CH), 83.0 (C), 61.5 (CH_2), 61.2 (CH_2), 43.4 (CH_2), 40.0 (CH_2), 20.1 (CH_3), 16.5 (CH_3), 14.0 (CH_3). One quaternary carbon is missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 405 (100) $[M+Na]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.84; H, 5.79; N, 7.34.

(*E*)-ethyl 5-((*N*-benzyl-4-methylphenylsulfonamido)methylene)-3,5'-dimethyl-3'-oxospiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54h).



To a N_2-flushed solution of ethyl 2,7-dimethyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46c** (52 mg, 0.2 mmol) and IPrAu(NTf_2 (8.7 mg, 0.01 mmol) in 3 mL of anhydrous dichloromethane, a solution of *N*-benzyl-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11e** (90 mg, 0.30 mmol) in 1 mL of dichloromethane was added dropwise in 12 h with the syringe pump at -20° C. The reaction mixture was stirred for 18 h. Then the reaction was quenched with PPh_3 and the solvent was removed under vacuum. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **54h** (65 mg, 60%) as yellow thick oil. **^{1}H NMR** (300 MHz, C_6D_6): 8.53 (bs, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.48 (s, 1H), 7.21 - 7.04 (m, 4H overlapping with the signal of C_6D_6), 7.04 - 6.92 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 5.10 (s, 1H), 4.67 (d, *J* = 1.5 Hz, 1H), 4.09 (dq, *J* = 10.4, 7.1 Hz, 1H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.89 - 3.70 (m, 2H), 3.35 - 3.10 (m, 2H), 1.85 (s, 3H), 1.80 (s, 3H), 1.38 (d, *J* = 1.0 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 196.3 (C), 151.7 (C), 151.4 (C), 146.1 (C), 142.9 (C), 137.8 (CH), 136.4 (C), 135.5 (C), 132.7 (C), 129.4 (2xCH), 128.7 (2xCH), 128.3 (2xCH), 127.5 (2xCH), 127.5 (CH), 124.0 (CH), 122.4 (C), 122.0 (CH), 120.6 (CH), 116.3 (CH), 81.7 (C), 61.6 (CH_2), 54.4 (CH_2), 40.5 (CH_2), 20.6 (CH_3), 19.9 (CH_3), 16.0 (CH_3), 13.3 (CH_3). One quaternary carbon is missing, probably overlapping with C_6D_6. **ESI(+)-MS**: m/z (%) = 579 (100) $[M+Na]^+$. Anal. Calcd for $C_{32}H_{32}N_2O_5S$: C, 69.04; H, 5.79; N, 5.03. Found: C, 68.97; H, 5.80; N, 5.04.

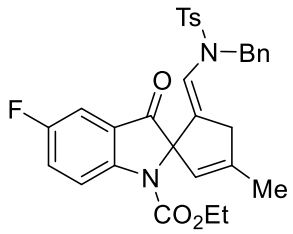
(*E*)-ethyl 5'-methoxy-3-methyl-3'-oxo-5-((2-oxooxazolidin-3-yl)methylene)spiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (4i)



General procedure was followed using ethyl 7-methoxy-2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46e** (55 mg, 0.2 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (38 mg, 0.3 mmol) and IPrAuNTf$_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 3 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) yielded **54i** (35 mg, 44%) as yellowish wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.32 (bs, 1H), 7.14 (d, *J* = 2.8 Hz, 1H), 7.01 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.45 (bs, 1H), 4.89 (bs, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.15-2.92 (m, 7H), 2.64 (m, 1H), 2.47 (m, 1H), 1.65 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 198.1 (C), 156.5 (C), 155.3 (C), 151.4 (C), 147.7 (C), 144.7 (C), 126.3 (CH), 124.0 (C), 123.5 (CH), 122.8 (C), 118.4 (CH), 118.0 (CH), 105.2 (CH), 83.1 (C), 61.3 (CH_2), 60.9 (CH_2), 54.7

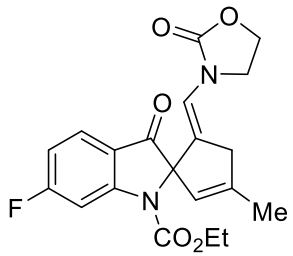
(CH_3), 43.1 (CH_2), 39.9 (CH_2), 16.4 (CH_3), 13.9 (CH_3). **ESI(+)-MS:** m/z (%) = 399 (100) $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 62.91; H, 5.58; N, 7,05.

(*E*)-ethyl 5-((*N*-benzyl-4-methylphenylsulfonamido)methylene)-5'-fluoro-3-methyl-3'-oxospiro[cyclopent[2]ene-1,2'-indoline]-1'-carboxylate (54j)



General procedure was followed using ethyl 7-fluoro-2-dimethyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46d** (52 mg, 0.2 mmol), *N*-benzyl-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11e** (90 mg, 0.3 mmol) $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 18 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **54j** (55 mg, 45%) as yellow thick oil. **^{1}H NMR** (300 MHz, C_6D_6): 8.51 (bs, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.41 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.31 - 7.19 (m, 4H), 7.12 (m, 1H), 7.00 - 6.87 (m, 3H), 5.19 (s, 1H), 4.76 (d, *J* = 1.5 Hz, 1H), 4.26 - 3.80 (m, 4H), 3.46 - 3.22 (m, 2H), 1.96 (s, 3H), 1.52 (d, *J* = 0.9 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 195.8 (C), 158.9 (d, *J* = 245.3 Hz, C), 151.8 (C), 149.6 (C), 146.8 (C), 143.2 (C), 136.4 (C), 135.4 (C), 129.6 (2xCH), 128.8 (2xCH), 128.5 (2xCH), 127.7 (CH), 127.6 (2xCH), 124.1 (d, *J* = 24.0 Hz, CH), 123.3 (d, *J* = 7.0 Hz, C), 121.6 (CH), 120.9 (CH), 118.0 (d, *J* = 7.2 Hz, CH), 111.1 (C), 109.6 (d, *J* = 22.9 Hz, CH), 82.1 (C), 62.0 (CH_2), 54.5 (CH_2), 40.6 (CH_2), 20.8 (CH_3), 16.1 (CH_3), 13.5 (CH_3). **ESI(+)-MS**: m/z (%) = 561 (100) $[M+H]^+$; Anal. Calcd for $C_{31}H_{29}FN_2O_5S$: C, 66.41; H, 5.21; N, 5.00. Found: C, 66.31; H, 5.20; N, 4.99.

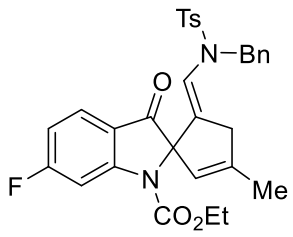
(*E*)-ethyl-6'-fluoro-3-methyl-3'-oxo-5-((2-oxooxazolidin-3-yl)methylene)spiro[cyclopentane-1,2'-indolin]-2-ene-1'-carboxylate (54k)



General procedure was followed using ethyl 6-fluoro-2-methyl-4*H*-furo[3,2-b]indole-4-carboxylate **46h** (52.2 mg, 0.2 mmol), 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **11a** (38 mg, 0.3 mmol) and $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at -20° C for 3 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) yielded **54k** (40 mg, 52%) as white wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.85 (bs, 1H), 7.74 (dd, *J* = 8.5, 5.8 Hz, 2H), 6.89 (td, *J* = 8.5, 2.2 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 1H), 5.16 (d, *J* = 1.5 Hz, 2H), 4.39 (t, *J* = 8.0 Hz, 2H), 4.28 (m, 2H), 4.08 (m, 2H), 3.44 (s, 2H), 1.94 (s, 3H), 1.31 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 197.2 (C), 169.0 (d, *J* = 257 Hz, C), 156.0 (C), 151.3 (C), 146.7 (C), 145.3 (C), 127.1 (d, *J* = 12.2 Hz, CH), 122.9 (C), 122.4 (CH), 118.9 (CH), 118.3 (C), 111.9 1 (d, *J* = 25.2 Hz, CH) , 104.5 1 (d, *J* = 28 Hz, CH), 83.5 (C), 62.3 (CH_2), 62.1 (CH_2), 44.2 (CH_2), 40.0 (CH_2), 16.9

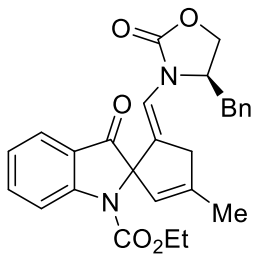
(CH_3), 14.3 (CH_3). **ESI(+)-MS**: m/z (%) = 387 (100) $[M+H]^+$; Anal. Calcd for $C_{20}H_{19}FN_2O_5$: C, 62.17; H, 4.96; N, 7.25. Found: C, 62.33; H, 4.94; N, 7.23.

(*E*)-ethyl-5-(((*N*-benzyl-4-methylphenyl)sulfonamido)methylene)-6'-fluoro-3-methyl-3'-oxospiro[cyclopentane-1,2'-indolin]-2-ene-1'-carboxylate (54l)



General procedure was followed using ethyl 6-fluoro-2-dimethyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46h** (52 mg, 0.2 mmol), *N*-benzyl-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide **11e** (90 mg, 0.3 mmol), and $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in anhydrous dichloromethane (3+1 mL) at −20 °C for 24 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1−8:2) yielded **54l** (73 mg, 65%) as a yellow thick oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.94 (d, J = 9.9 Hz, 1H), 7.71 (dd, *J* = 8.5, 5.7 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.40−7.11 (m, 7H), 6.86 (td, *J* = 8.5, 2.2 Hz, 1H), 5.04 (d, *J* = 1.5 Hz, 2H), 4.27−4.04 (m, 3H), 3.74 (bs, 1H), 3.26−2.97 (m, 2H), 2.39 (s, 3H), 1.81 (d, *J* = 1.2 Hz, 3H), 1.04 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 195.5 (C), 168.8 (d, *J* = 257 Hz, C), 154.7 (d, *J* = 14.1 Hz, C), 151.5 (C), 147.32 (C), 143.74 (C), 135.88 (C), 134.54 (C), 129.7 (2×CH), 128.47 (2×CH), 128.37 (2×CH), 127.78 (CH), 127.33 (2×CH), 126.62 (d, *J* = 11.8 Hz, CH), 121.29 (CH), 120.70 (CH), 118.21 (C), 111.58 (d, *J* = 24.4 Hz, CH), 104.14 (d, *J* = 29.2 Hz, CH), 82.20 (C), 62.26 (CH_2), 54.08 (CH_2), 40.34 (CH_2), 21.49 (CH_3), 16.73 (CH_3), 13.64 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-MS**: m/z (%) = 561 (100) $[M+H]^+$. Anal. Calcd for $C_{31}H_{29}FN_2O_5S$: C, 66.41; H, 5.21; N, 5.00. Found: C, 66.52; H, 5.21; N, 4.38.

Ethyl (*R*,*E*)-5-(((R)-4-benzyl-2-oxooxazolidin-3-yl)methylene)-3-methyl-3'-oxospiro[cyclopentane-1,2'-indolin]-2-ene-1'-carboxylate (54m)

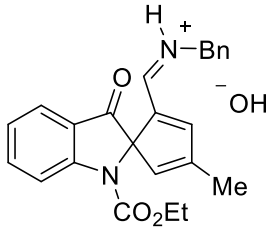


To a N_2-flushed solution of 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49 mg, 0.2 mmol) and $IPrAuNTf_2$ (8.7 mg, 0.01 mmol) in 3 mL of anhydrous dichloromethane, a solution of (*R*)-4-benzyl-3-($2\lambda^5$-propa-1,2-dien-1-yl)oxazolidin-2-one **11g** (65 mg, 0.3 mmol) in 1 mL of dichloromethane was added dropwise in 12 h with the syringe pump at -20° C. The reaction mixture was stirred for 18 h. Then the reaction was quenched with PPh_3 and the solvent was removed under vacuum. Purification by flash chromatography (SiO_2, toluene/ethyl acetate 3:1) yielded **54m** (45 mg, 49%, *dr* = 13:1) as clear thick oil. Given data refers to major isomer**. ^{1}H NMR** (500 MHz, $CDCl_3$): 7.88 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.39-7.24 (m, 4 H), 7.23-7.16 (m, 2H), 7.12 -7.06 (m, 2H), 6.12 (t, *J* = 1.5 Hz, 1H), 5.21 (m, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.72 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.62 (m, 1H), 3.51 (m, 1H), 3.44 (m, 1H), 3.33 (dd, *J* = 20.2, 1.0 Hz, 1H), 2.98 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.38 (m, 1H),

1.95 (d, J = 1.3 Hz, 3H), 1.45 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 174.9 (C), 155.8 (C), 150.8 (C), 144.3 (C), 140.8 (C), 138.7 (C), 135.5 (C), 129.7 (C), 129.1 (2xCH), 128.84 (2xCH), 128.76 (CH), 127.1 (CH), 126.2 (CH), 125.0 (CH), 124.6 (CH), 118.2 (CH), 114.8 (CH), 66.2 (CH_2), 64.1 (C), 63.5 (CH_2), 58.9 (CH), 43.0 (CH_2), 37.5 (CH_2), 16.6 (CH_3), 14.2 (CH_3). **ESI(+)-MS**: m/z(%) = 459 (100) $[M+H]^+$; Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.94; H, 5.71; N, 6.09.

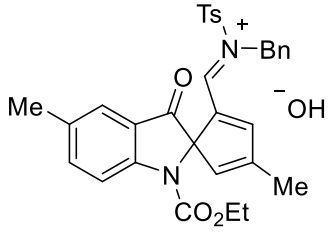
2.2.6.2.4 Preparation of products 55a,b and 56.

(*Z*)-*N*-((1'-(ethoxycarbonyl)-3-methyl-3'-oxospiro[cyclopentane-1,2'-indoline]-2,4-dien-5-yl)methylene)-1-phenylmethanaminium hydroxide (55a)



To solution of **45f** (62 mg, 0.13 mmol) in dichloromethane (1 ml) TFA (0.1 ml) was added dropwise at room temperature and the resulting mixture was stirred for 1 h at room temperature. Then it was quenched with 1M NaOH solution (10 ml) and extracted with dichloromethane (3 x 10 ml). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **55a** (20 mg, 38%) as yellow thick oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 12.65 (bs, 1H), 8.66 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 13.4 Hz, 1H), 7.55 (m, 1H), 7.49-7.34 (m, 6H), 7.08 (t, J = 7.3 Hz, 1H), 6.88 (s, 1H), 6.79 (s, 1H), 4.76 (d, J = 5.7 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.32 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 189.4 (C), 153.8 (C), 153.3 (CH), 141.2 (CH), 137.2 (C), 136.3 (C), 135.1 (CH), 130.8 (CH), 130.7 (2 x CH), 130.6 (C), 129.1 (2 x CH), 129.3 (C), 128.2 (CH), 127.5 (CH), 125.7 (C), 121.4 (CH), 120.1 (CH), 117.7 (C), 61.02 (CH_2), 53.35 (CH_2), 14.60 (CH_3), 14.23 (CH_3). **ESI(+)-MS:** m/z (%) = 411 (100) $[M+Na]^+$.

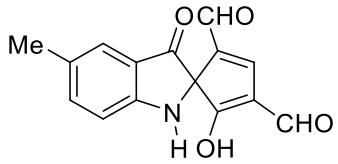
(*Z*)-*N*-((1'-(ethoxycarbonyl)-3,5-dimethyl-3'-oxospiro[cyclopentane-1,2'-indoline]-2,4-dien-5-yl)methylene)-1-tosyl-1-phenylmethanaminium hydroxide (55b)



To solution of **54h** (50 mg, 0.09 mmol) in dichloromethane (1 ml) TFA (0.1 ml) was added dropwise at room temperature and the resulting mixture was stirred for 5 h at room temperature. Then it was quenched with 1M NaOH solution (10 ml) and extracted with dichloromethane (3 x 10 ml). Purification by flash chromatography (SiO_2, toluene/ethyl acetate 98:2) yielded **55b** (16 mg, 31%) as yellow thick oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 9.55 (s, 1H), 9.05 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 1.7 Hz, 1H), 7.35-7.20 (m, 8H), 6.61 (d, J = 1.5 Hz, 1H), 6.22 (s, 1H), 5.10 (s, 2H), 4.21 (d, J = 7.1 Hz, 3H), 2.43 (s, 3H), 2.31 (s, 3H), 1.92 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 193.8 (C), 154.0

(C), 145.2 (C), 142.7 (CH), 139.9 (C), 139.7 (CH), 136.7 (C), 135.4 (C), 134.9 (C), 134.2 (C), 133.1 (CH), 132.0 (CH), 130.5 (C), 130.2 (2 x CH), 128.9 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 127.1 (C), 126.1 (2 x CH), 121.7 (CH), 120.4 (C), 120.0 (CH), 61.0 (CH_2), 51.5 (CH_2), 21.6 (CH_3), 20.7 (CH_3), 15.06 (CH_3)., 14.57 (CH_3). **ESI(+)-MS:** m/z (%) = 579 (100) $[M+Na]^+$.

2-hydroxy-5'-methyl-3'-oxospiro[cyclopentane-1,2'-indoline]-2,4-diene-3,5-dicarbaldehyde (56)

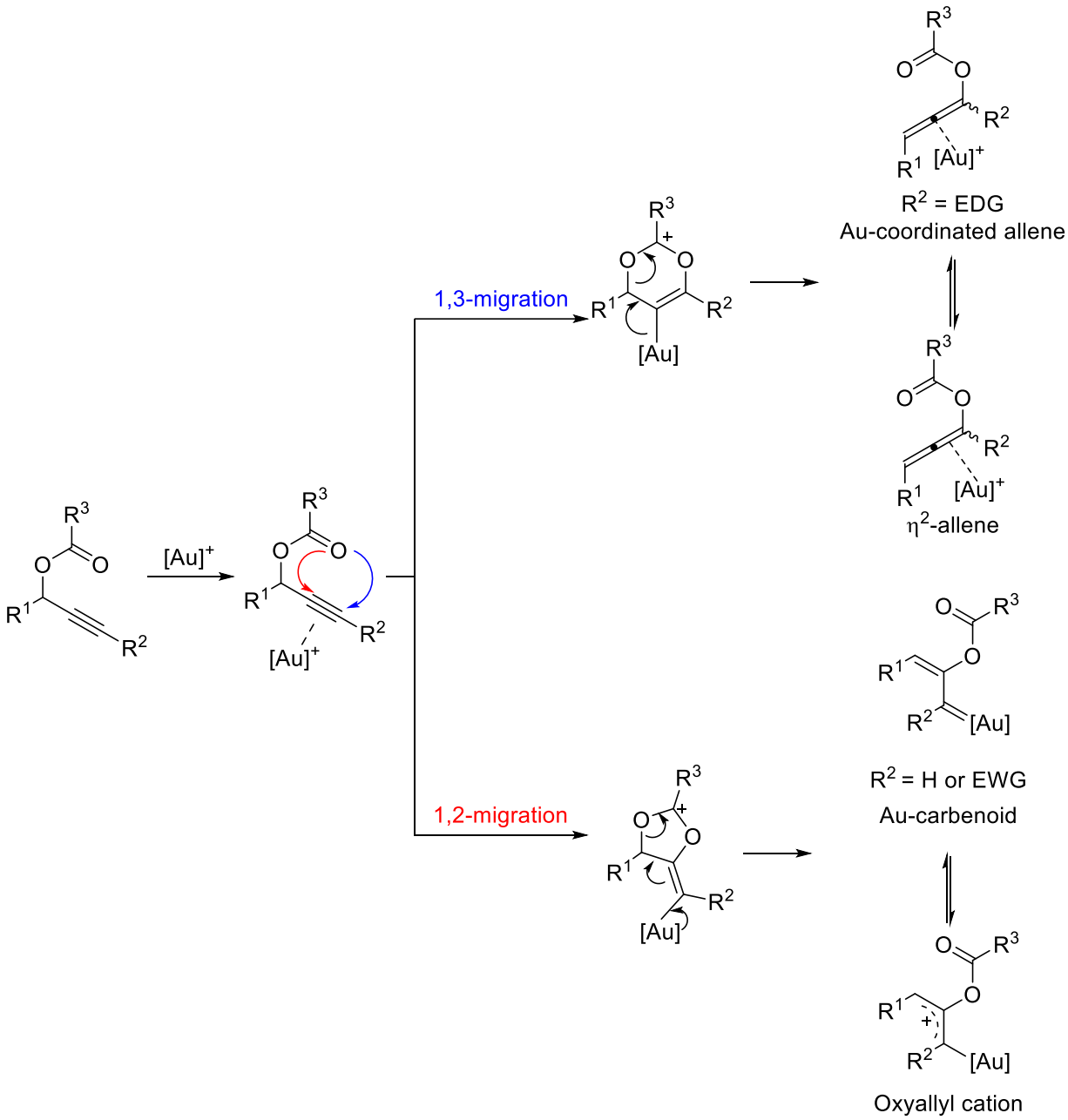


To a suspension of **54g** (43 mg, 0.1 mmol) in 1,4-dioxane (0.4 ml) SeO_2 (27 mg, 0.25 mmol) was added and the mixture was stirred at 100 °C for 2.5 h. Then it was filtered over a pad of celite and concentrated in vacuum. Purification by flash chromatography (SiO_2 hexane/ethyl acetate 3:1) yielded **56** (7 mg, 25%) as yellow thick oil. **^{1}H NMR** (500 MHz, DMSO): 13.38 (s, 1H), 9.93 (s, 1H), 9.34 (s, 1H), 8.29 (m, 2H), 8.10 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 2.53 (s, 3H). **^{13}C NMR** (125 MHz, DMSO): 185.3 (CH), 185.2 (CH), 160.8 (C), 144.4 (CH), 143.9 (C), 137.0 (C), 134.6 (CH), 134.2 (C), 122.7 (CH), 119.8 (CH), 118.9 (C), 116.5 (C), 115.8 (C), 113.4 (C) 21.33 (CH_3). **ESI(-)-MS:** m/z (%) = 252 (100) $[M-OH]^-$.

2.3 Synthesis of 2-alkenylidene-3-oxoindoles through a cascade reaction between propargyl esters and 4*H*-furo[3,2-*b*]indoles

2.3.1 Gold activation of propargyl esters in cyclization reactions

Propargyl esters are a particular class of alkynes in which the usual gold activation of the π system is followed by an intramolecular cascade process affording gold activated allenes or gold carbenes depending upon the substituent's array around the triple bond. These gold intermediate complexes take part in cycloisomerization, cycloaddition and cyclization reactions for the synthesis of compounds with high molecular complexity.[46] Thus, after the coordination with the carbophilic gold catalyst, the triple bond undergoes an intramolecular nucleophilic attack by the carbonyl oxygen of the ester giving rise to a cyclic intermediate (scheme 2.22).[101] The cyclization can occur with a 6-*endo*-dig or a 5-*exo*-dig mechanism and results, respectively, in a 1,3-acyloxy migration or in a 1,2-acyloxy migration of the ester moiety. The 1,3-acyloxy migration affords a gold-coordinated allene and the nature of substituents on the allene determine the η^1 or η^2 character of the complex and thus the reactivity.[102] The 1,2 acyloxy migration results in the formation of a gold carbene specie that has been proven to exist as a continuum with the isomeric oxyallyl cationic specie.[103–105]

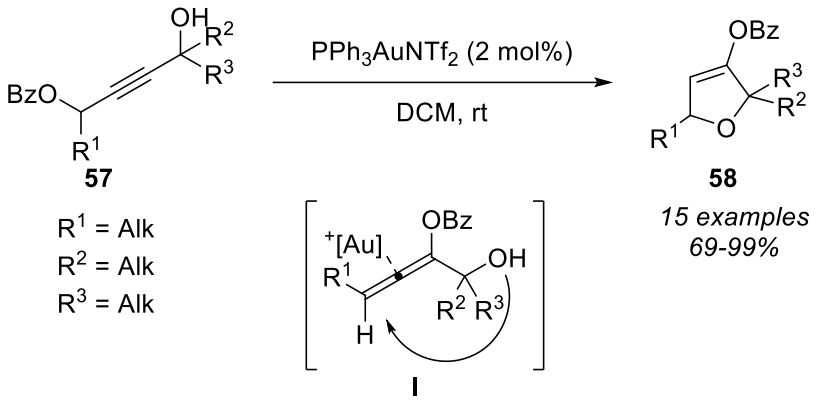


Scheme 2.22

The electrophilicity of the two carbon atoms of the triple bond modulates the rearrangement mode of propargyl esters. When an internal and neutral propargyl ester is employed, the principal rearrangement involves 1,3 migration, while [2,3] rearrangement is relevant with terminal alkynes and the internal ones bearing EW groups.[106,107]

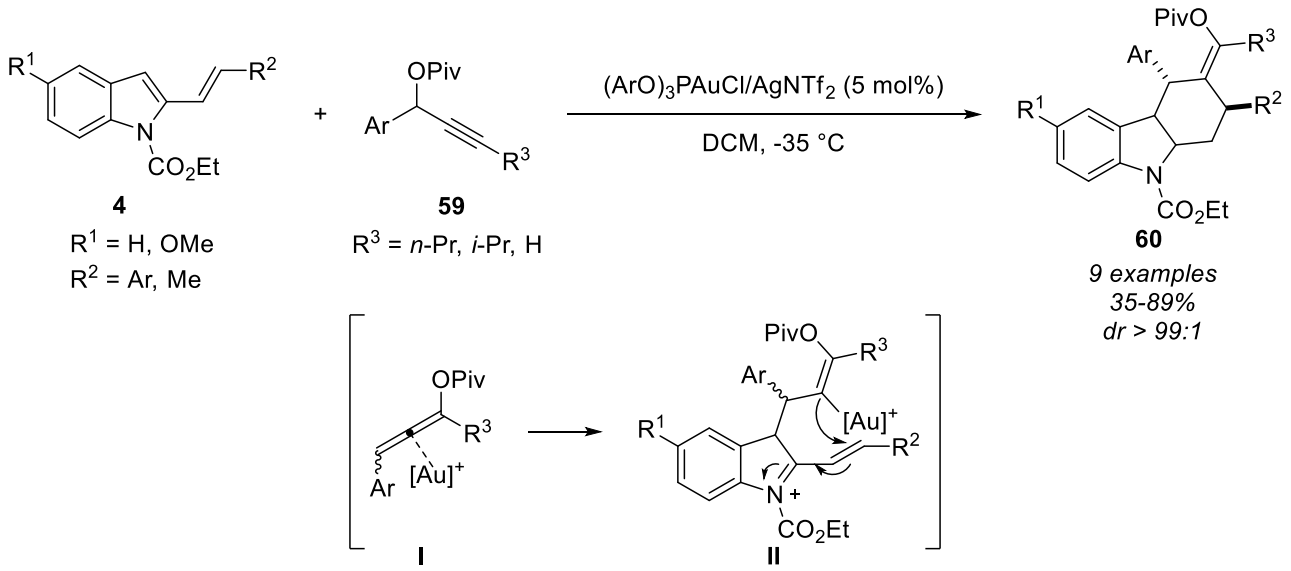
One of the first example that involves the 1,3-migration mechanism was developed in 2006 by Gagosz and co-workers. They proposed the synthesis of functionalized 2,5-dihydrofurans **58** starting from butynediol monobenzoates **57** under PPh_3AuNTf_2 catalysis (scheme 2.23).[108] In this reaction the

propargyl ester undergoes a [3,3]-rearrangement with subsequent nucleophilic attack of the alcohol oxygen on the allene intermediate forming the dihydrofuran.



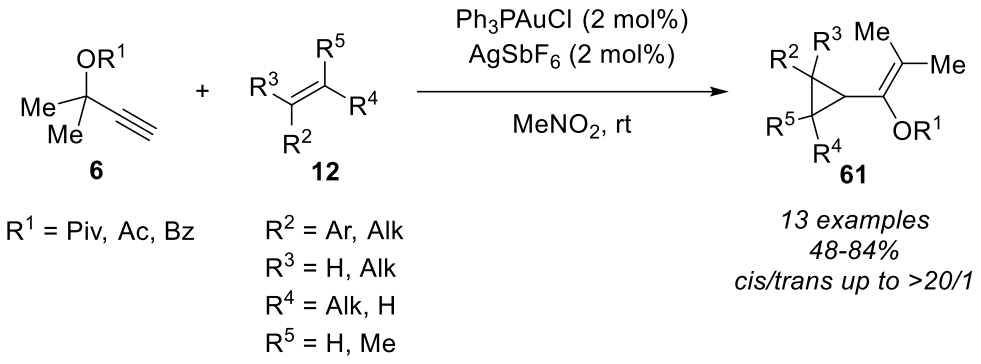
Scheme 2.23

In 2016, the formation of allenyl esters was exploited by our research group for the synthesis of tetrahydrocarbazoles **60** starting from 2-vinylindoles **4** and propargyl esters **59** (scheme 2.24).[109] In this transformation, the gold catalyst promotes not only the [3,3]-rearrangement of the propargyl ester **59** but also the [4+2] cycloaddition reaction with the diene in a new cascade process. In addition, initial studies on the enantioselective version of this cascade reaction were reported and good enantiomeric ratios could be achieved using chiral phosphoramidites as gold(I) ligands.



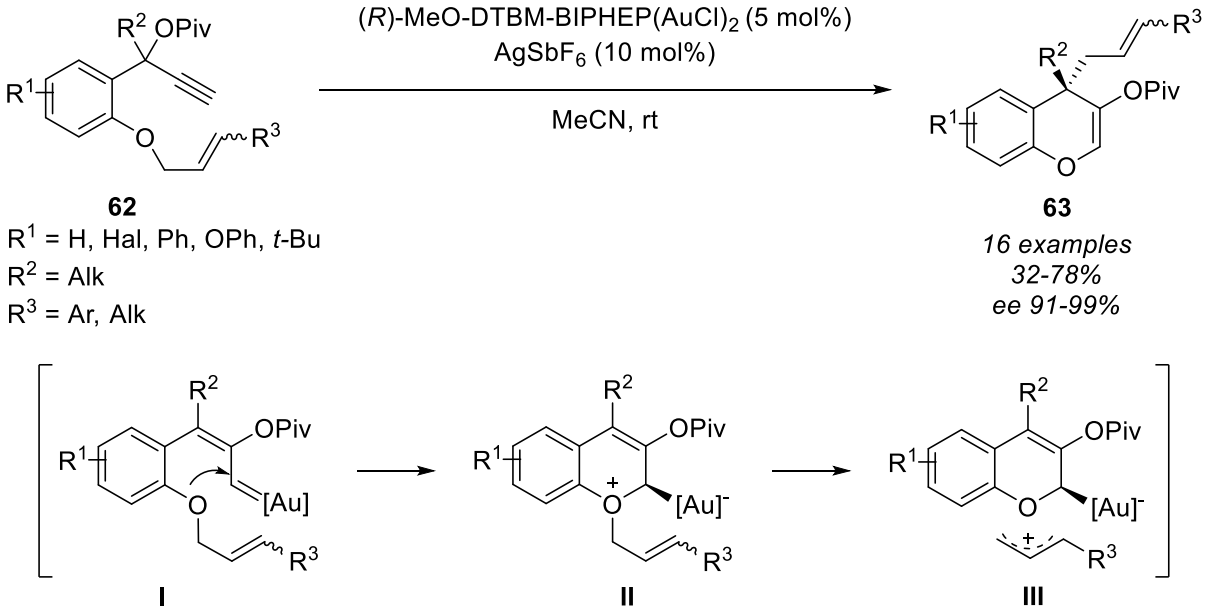
Scheme 2.24

Moving to the 1,2-migration, in 2005, the research group of Toste reported the cyclopropanation of styrenes and methylstyrenes **12** using 2-methylbut-3-yn-2-yl pivalate **6** as gold carbene source demonstrating also the concerted mechanism of these cyclizations (scheme 2.25).[100]



Scheme 2.25

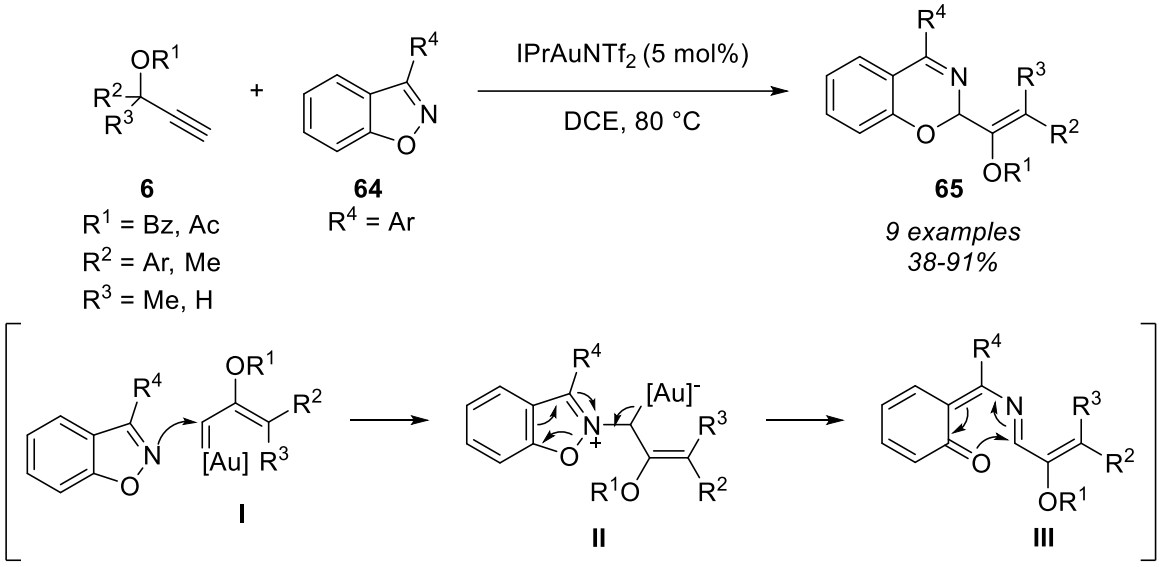
Successively in 2009, Toste proposed an enantioselective intramolecular cyclization of propargyl esters **62** affording benzopyrans **63** (scheme 2.26).[110] With these particular propargyl esters, after the *in situ* generation of gold carbene **I**, the olefin cyclopropanation is suppressed in favor of a competing intramolecular nucleophilic attack followed by formal 2,3-rearrangement of the formed oxonium ylide **II** allowing for the formation of benzopyran derivatives **63**.



Scheme 2.26

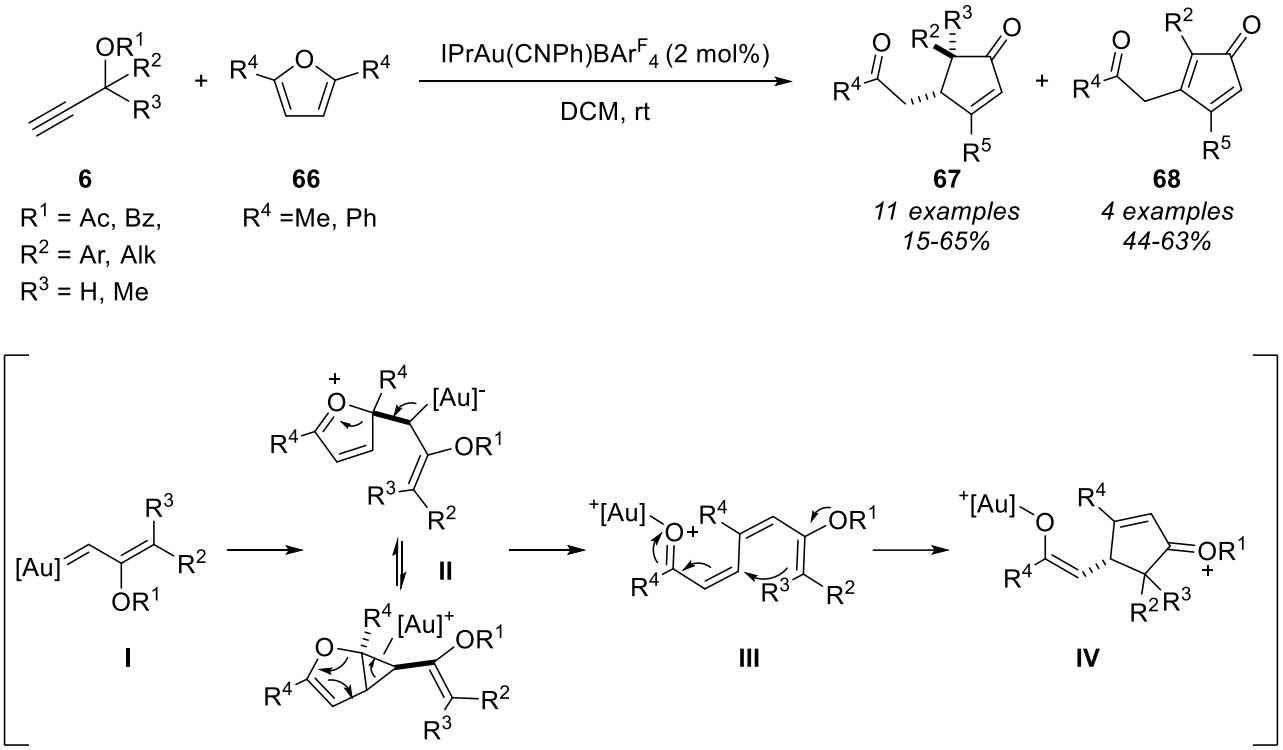
Moreover, in 2018, Liu and co-workers proposed the synthesis of benzo[*e*][1,3]oxazines **65** by intermolecular [5+1] annulation reaction between propargyl esters **6** and benzo[*d*]isoxazoles **64**

(scheme 2.27).[111] The gold carbene intermediate **I** generated from propargyl esters under gold catalysis undergoes the nucleophilic attack of the nitrogen atom of benzo[*d*]isoxazoles followed by rearrangement of the isoxazole nucleus and by a final cyclization step.



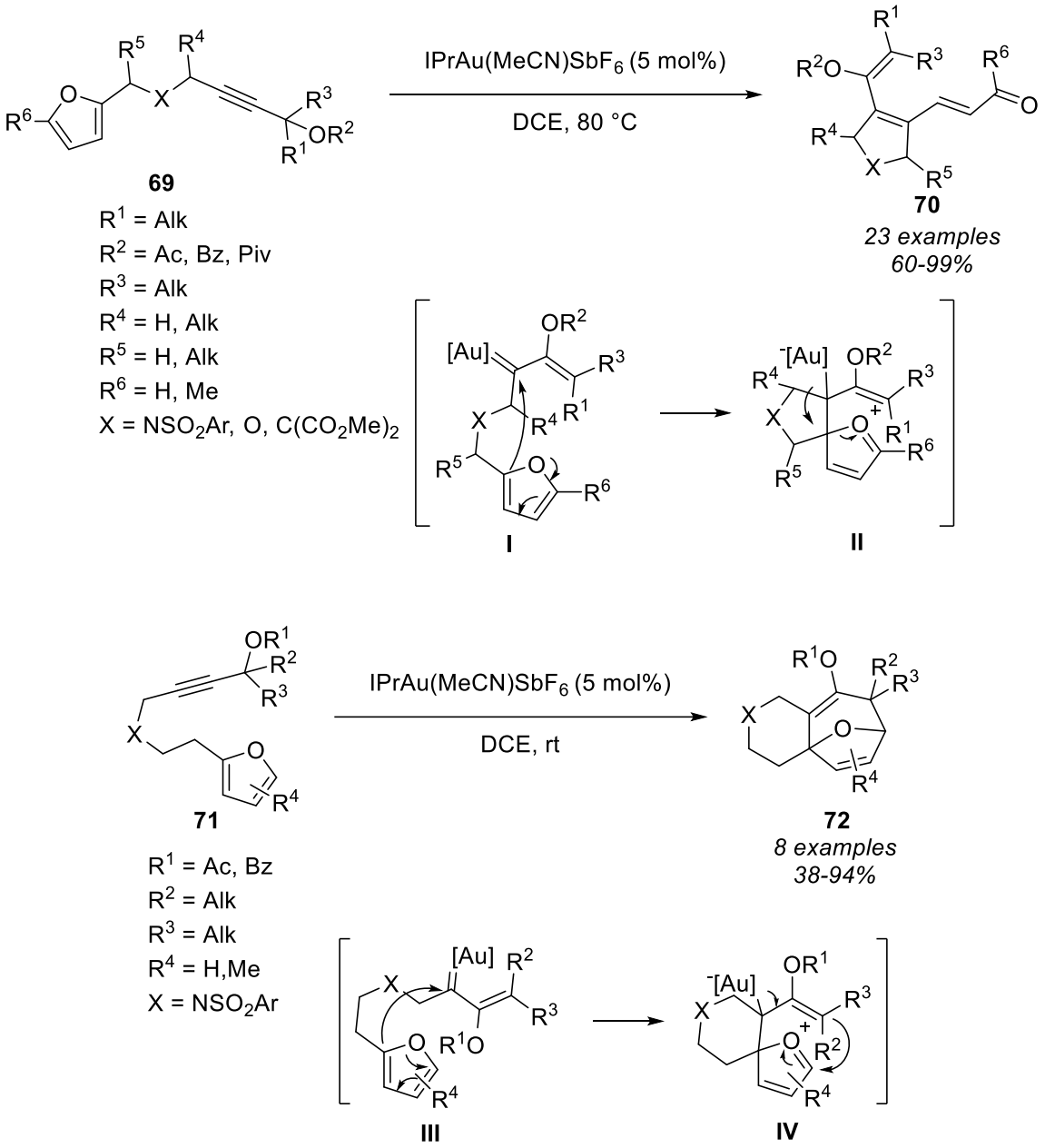
Scheme 2.27

More recently, the reactivity of propargyl esters and of their gold activated carbene intermediates was tested with furan derivatives. This strategy allowed for the increase of molecular complexity in different transformations. In particular, in 2014 Echavarren and co-workers reported the intermolecular reaction of gold carbenes with furan compounds **66** (scheme 2.28).[89] This transformation involved the furan ring rearrangement and led to the synthesis of functionalized cyclopentenones **67** or cyclopentadienyl carboxylates **68**. After the formation of gold carbene intermediate **I**, the cyclopropanated furan **II** undergoes a ring opening rearrangement with the generation of intermediate **III**. Successively, intermediate **III** is involved in a Mukaiyama–Michael-type cyclization leading to cyclopentenones **67** or cyclopentadienyl benzoates **68**.



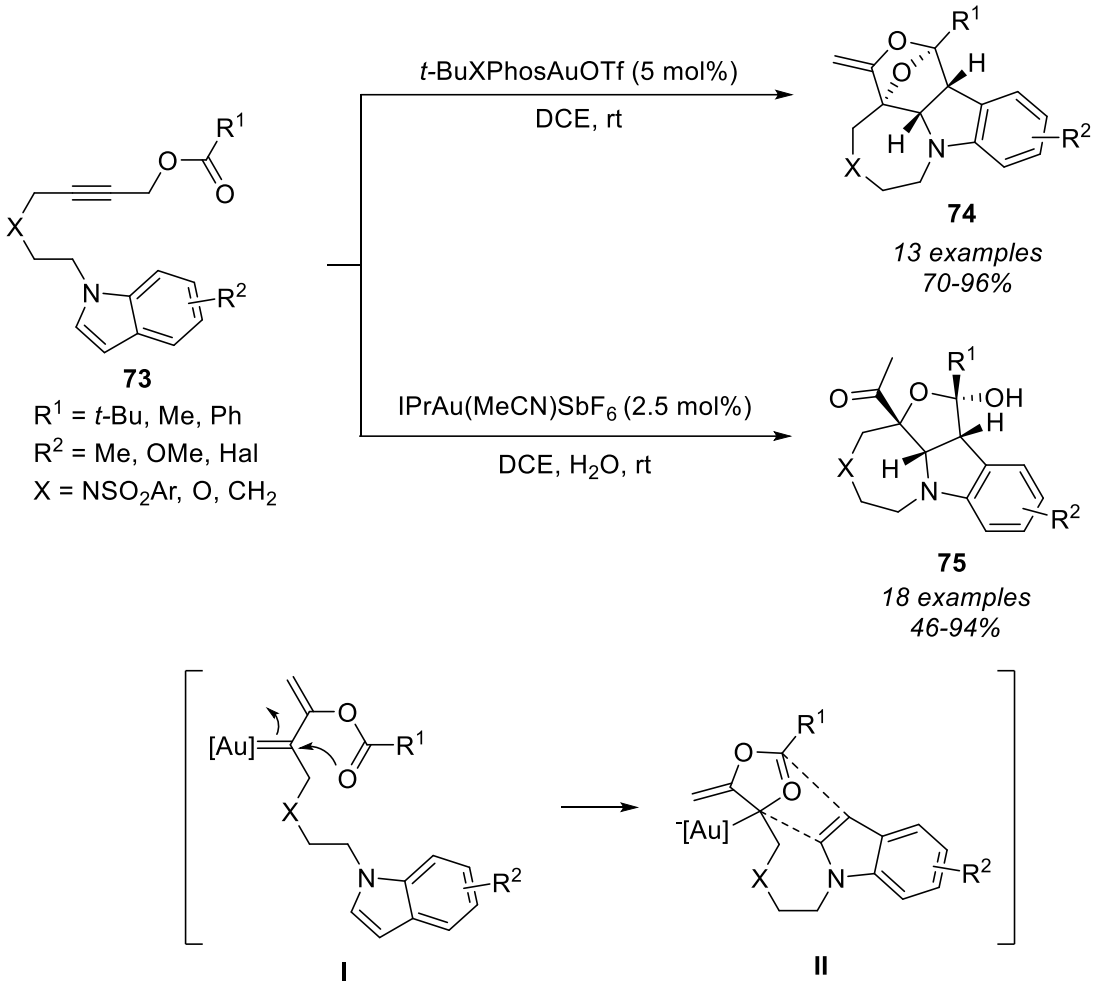
Scheme 2.28

Then, in 2015, Shi and co-workers proposed the synthesis of α,β-unsaturated aldehydes and ketones **70** and the formation of (4+3) cycloaddition products **72** from furan tethered propargyl esters **69** and **71** under gold catalysis (scheme 2.29).[112] They demonstrated that gold carbene generated from the 1,2-acyloxy migration of propargyl esters could induce the rearrangement of the tethered furan moiety followed by intramolecular nucleophilic attack (intermediate **I** and **II**) or by intramolecular cycloaddition (intermediate **III** and **IV**) depending on the length of the tether and the steric hindrance of furan substituents.



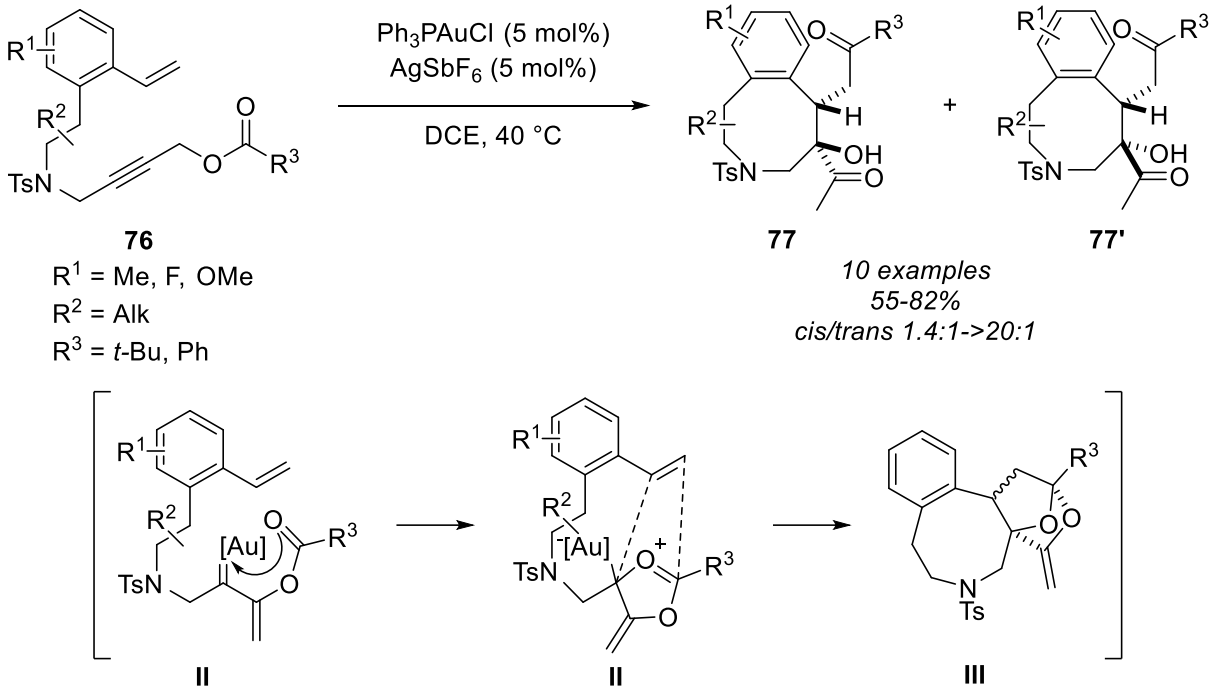
Scheme 2.29

Moreover, in 2016 Shi and co-workers proposed an interesting gold(I) catalyzed intramolecular cyclization for the synthesis of polycyclic indoline derivatives **74** and **75** bearing four contiguous stereocenters with high stereoselectivity starting from indolyl propargylic esters **73** (scheme 2.30).[113] In this transformation, the key gold(I) carbene intermediate evolves into the 1,3-dipole intermediate **II** that undergoes a [3+2] cycloaddition with the C2–C3 bond of the indole moiety to afford the final product **74**. The same reaction conducted under hydrolytic conditions (water) resulted in the ring opening rearrangement of the ketale moiety to afford ketone **75**.



Scheme 2.30

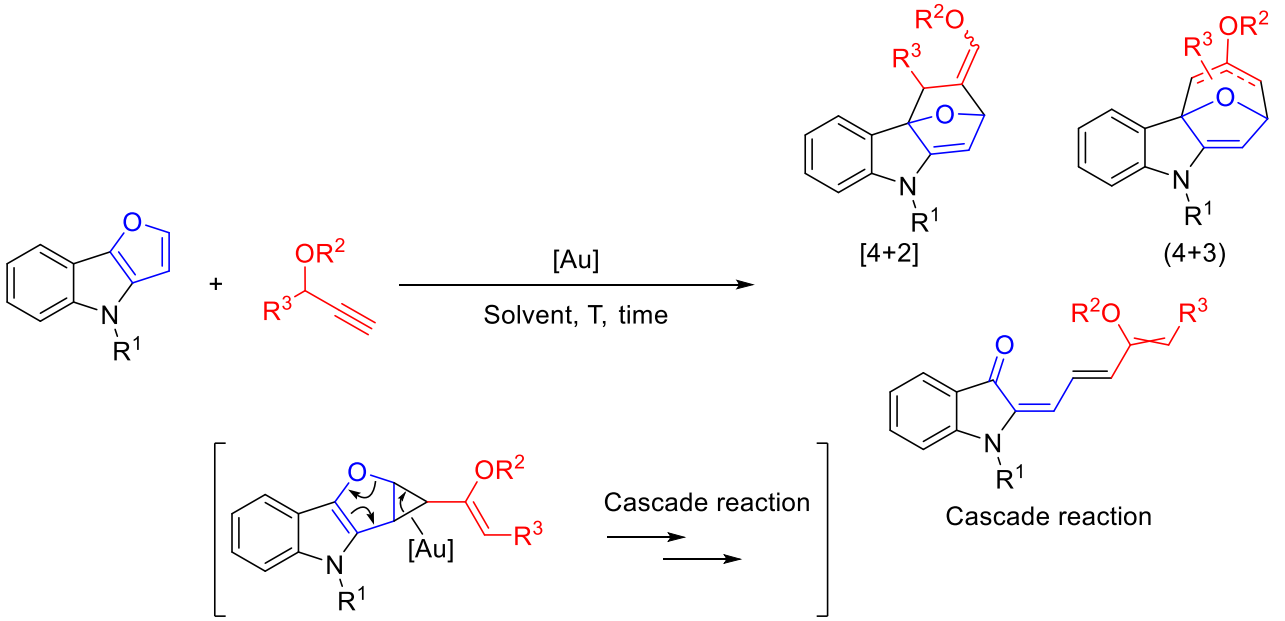
In the same year, She and co-workers proposed another transformation that included the gold(I)-catalyzed tandem 1,2-acyloxy shift/[3+2] cycloaddition of terminal 1,9-enynyl esters **76** for the synthesis of complex 8 member-fused rings **77** and **77'** (benzazocines, scheme 2.31).[114] Also in this case the key step of the transformation is the generation of a 1,3 dipole from the gold carbene that undergoes a [3+2] cyclization followed by water induced hydrolysis.


Ph3PAuCl (5 mol%)
AgSbF6 (5 mol%)
DCE, 40 °C
76
R1 = Me, F, OMe
R2 = Alk
R3 = t-Bu, Ph
77
77'
10 examples
55-82%
cis/trans 1.4:1->20:1
[Au]
II
II
III

Scheme 2.31

2.3.2 Objectives

On the basis of our previous work on the gold catalyzed synthesis of tetrahydrocarbazoles from 2-vinylindoles and propargyl esters[109] and on the previously described work on the reactivity of 4*H*-furo[3,2-*b*]indoles with *N*-allenamides, we became interested in the study of the reactions between 4*H*-furo[3,2-*b*]indoles and propargyl esters. As reported before, propargyl esters can be activated by gold(I) catalysts and upon the substituents array on the propargylic moiety, they can rearrange to activated gold-allenes or gold-carbenes. In particular, we decided to test the reactivity of 4*H*-furo[3,2-*b*]indoles in the presence of suitable propargyl esters able to generate, under gold catalysis, a gold carbene intermediate. Gold-carbenes arising from 1,2-migration of propargyl esters can be seen as pure carbenes or oxyallylcations and their reactions with furoindoles could in principle occur with different mechanisms, i.e. [4+2], (4+3) cycloadditions or cyclopropanation, possibly followed by furan ring rearrangement (scheme 2.32).



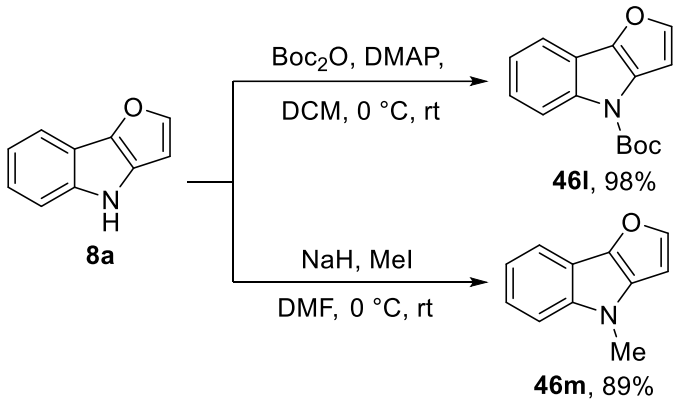
Scheme 2.32

2.3.3 Synthesis of starting materials

In this work of thesis, *N*-functionalized 4*H*-furo[3,2-*b*]indoles **46a,g,l-n**, as well as propargyl esters **6a-h**, both bearing different functional groups, have been synthetized and used.

2.3.3.1 Synthesis of 4H-furo[3,2-b]indoles ***46l-n***

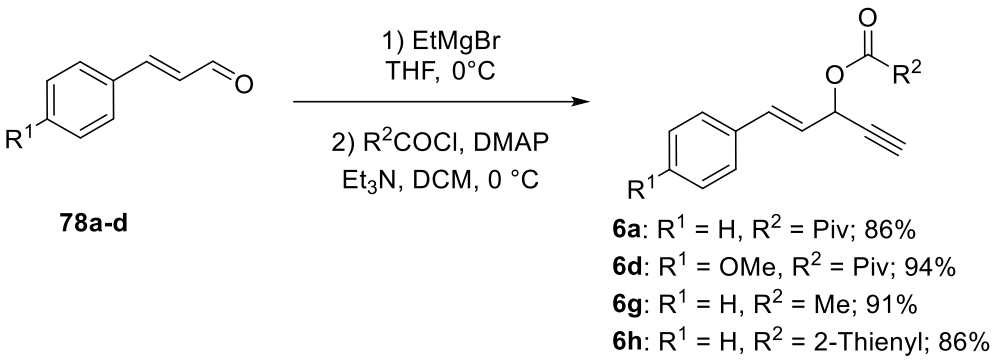
Ehyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a,g,n** were prepared according to the procedure described in section 2.2.4.1. Nitrogen protected 4*H*-furo[3,2-*b*]indoles **46l-m** were prepared starting from unprotected 4*H*-furo[3,2-*b*]indole **8a** as reported in the same section. For the synthesis of **46l,** 4*H*-furo[3,2-*b*]indole **8a** was treated with di-*tert*-butyl dicarbonate in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) at 0 °C in DCM (scheme 2.33). While the synthesis of 4-methyl-4*H*-furo[3,2-*b*]indole **46m** started from **8a** *via* deprotonation in the presence of NaH in DMF and subsequent methylation with MeI (scheme 2.33).



Scheme 2.33

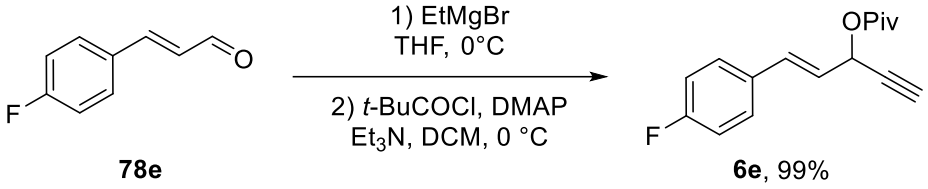
2.3.3.2 Synthesis of propargyl esters ***6a-f***

Propargyl esters **6a-d**,**g-h** are known compounds and were prepared following literature procedures.[115–118] Propargyl esters **6a,d,g,h** were synthetized in two steps starting from the corresponding *trans*-cinnamaldehydes **78a-d**. The first step was the synthesis of the corresponding propargyl alcohol by treatment with ethynylmagnesiumbromide in THF. Then, the crude was converted into the corresponding propargyl esters **6** employing the suitable acyl chloride in DCM under basic conditions. The synthetized propargyl esters were obtained in good overall yields (scheme 2.34).[115,116]



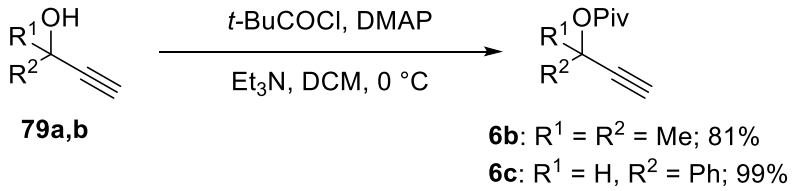
Scheme 2.34

The same procedure was followed for the unknown (*E*)-1-(4-fluorophenyl)pent-1-en-4-yn-3-yl pivalate **6e** obtained in excellent 99% yield (scheme 2.35).



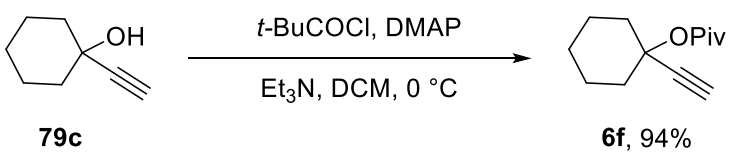
Scheme 2.35

The synthesis of propargyl esters **6b-c** was realized *via* acylation of 2-methylbut-3-yn-2-ol **79a** and 1-phenyl-2-propyn-1-ol **79b**, respectively, with pivaloyl chloride in DCM in the presence of DMAP and triethylamine (scheme 2.36).[117,118]



Scheme 2.36

The unknown compound 1-ethynylcyclohexyl pivalate **6f** was synthetized following the same procedure reported for compounds **6b-c** and **6f** and was obtained in 94% yield (scheme 2.37).

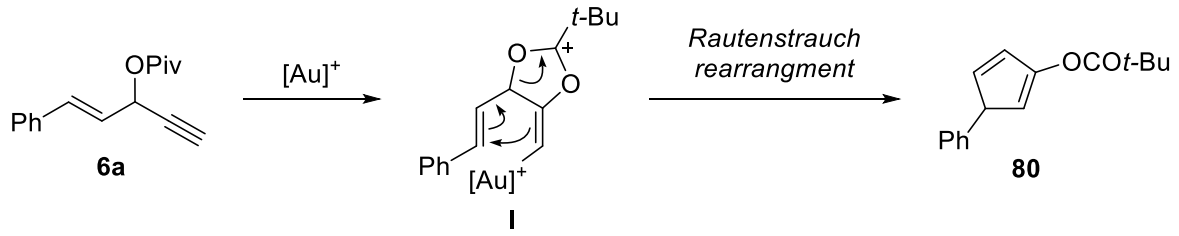


Scheme 2.37

2.3.4 Gold catalyzed cascade reactions between propargyl esters and 4*H*-furo[3,2-*b*]indoles

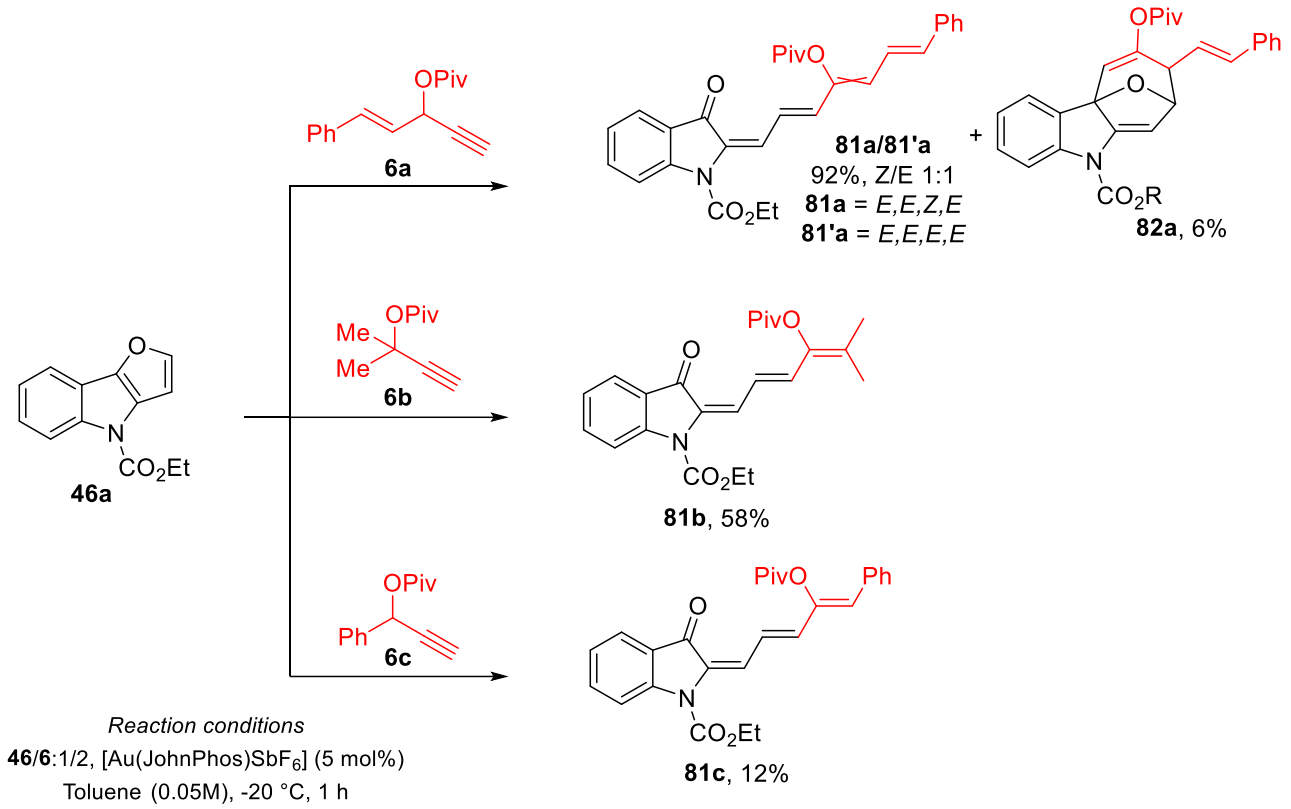
2.3.4.1 Initial studies

At the beginning, 4*H*-furo[3,2-*b*]indole **46a** was chosen as model compound for the gold catalyzed reactions with propargyl esters **6a-c** bearing different substituents in α-position (scheme 2.40). As reported in scheme 2.32, propargyl esters, upon activation by a gold catalyst, are able to form carbene-oxyallyl cation species that in principle can react with 4*H*-furo[3,2-*b*]indole **46a** following different reaction pathways. Moreover, using propargyl ester **46a** the competitive Rautenstrauch rearrangement[116,119–121], affording the cycloadduct **80** (scheme 2.38), could suppress the reaction with 4*H*-furo[3,2-*b*]indoles.



Scheme 2.38

Fortunately, performing the reaction between **46a** and **6a** in the presence of JohnPhosAuSbF$_6$ as catalyst in anhydrous toluene at -20 °C, after 1 hour it was possible to isolate a separable mixture of *Z/E* isomeric 2-(hepta-2,4,6-trien-1-ylidene)-3-oxoindolines **81a** and **81'a** in excellent overall yield besides a small amount of (4+3) cycloaddition compound **82a**. Performing the reaction in the presence of the dimethyl substituted propargyl ester **6b**, the corresponding oxoindoline **81b** was isolated although in low yield. While using phenyl substituted propargyl ester **6c**, the isolation of the corresponding product **81c** occurred in poor 12% yield besides unreacted **46a** and several unidentified by-products (scheme 2.39).



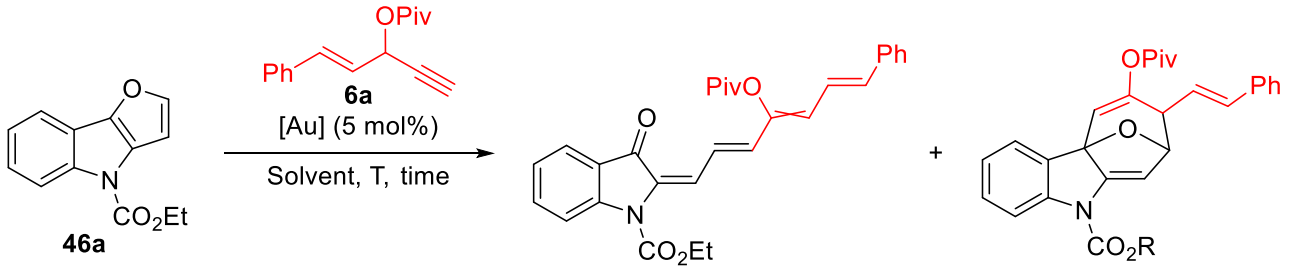
Scheme 2.39

The exact structures of compounds **81a**/**81'a** were determined based on analytical and spectral data, using both 1D and 2D NMR. To assign the geometry around the double bond, 2D NOESY NMR and ^{3}J *Z/E* coupling constants were examined. Moreover, starting from these results, we decided to investigate this transformation by studying the reactivity of α-styryl substituted propargyl esters with furoindoles in different reaction conditions.

*2.3.4.2 Screening of the reaction condition for the synthesis of compound **81a***

For the evaluation of the influence of gold(I) catalysts, counterions, solvents, stoichiometries and temperatures, 4*H*-furo[3,2-*b*]indole **46a** and propargyl ester **6a** were chosen as model compounds. The results of the screening for the best reaction conditions are reported in Table 2.5

*Table 2.5 Optimization of the reaction condition for the synthesis of compound **81a** and **81'a***



81a = *E,E,Z,E*
81'a = *E,E,E,E*

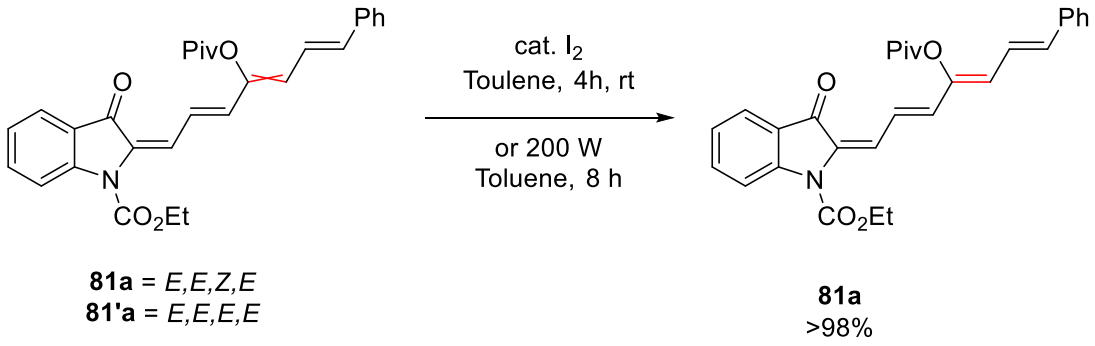
82a

Entry	46a/6a	[Au]	Solvent	Temp, °C	Time, h	81a[b] %	81'a[b] %	82a[b] %
1	1/2	JohnPhosAuSbF$_6$	Toluene	- 20	1	45	47	6
2[c]	1/2	IPrAuNTf$_2$	Toluene	- 20	43	15	6	6
3	1/2	(ArO)$_3$PAuSbF$_6$	Toluene	- 20	1	36	12	28
4[c]	1/2	Ph$_3$PAuNTf$_2$	Toluene	- 20	1	25	/	21
5	1/2	JohnPhosAuNTf$_2$	Toluene	- 20	1	40	41	7
6	1/2	JohnPhosAuSbF$_6$	TFE	- 20	1	38	43	/
7	1/2	JohnPhosAuSbF$_6$	DCM	- 20	1	47	46	4
8	1/1.2	JohnPhosAuSbF$_6$	Toluene	- 20	1	58	36	6
9	1/1.2	JohnPhosAuSbF$_6$	Toluene	- 35	10	/	/	/
10	1/1.2	JohnPhosAuSbF$_6$	Toluene	rt	1	14	6	/

[a]All reactions were carried out using **46a** (0.2 mmol) and **6a** (0.24-0.4 mmol, manual dropwise addition) in the stated solvent (0.05 M). [b]Isolated yield. [c]Some decomposition products were observed beside starting **46a**.[d]Ar = 2,4-di-t-butylphenyl. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. JohnPhos = (2-Biphenyl)di-tert-butylphosphine.

Entry 1 reports the results obtained in the preliminary test shown in scheme 2.40. Then the less electrophilic catalyst IPrAuNTf$_2$ was employed in toluene at -20 °C, giving rise to compounds **81a** and **81'a** in poorer reaction yields (Table 2.5, entry 2). Successively, more electrophilic gold catalysts (ArO)$_3$PAuSbF$_6$ and Ph$_3$PAuNTf$_2$ were employed resulting in the isolation of **81a** and **81'a** in good overall yields, however the selectivity decreased and the reaction afforded, beside the desired compounds, the cycloadduct **82a** in 28% and 22% yield, respectively (entries 3 and 4). Thus, the best choice in term of ligand for the gold(I) catalyst was JohnPhos. Changing the counterion from SbF_6^- into NTf_2^- did not result in significant variation in both yield and selectivity (entry 5). Thus, JohnPhosAuSbF$_6$, was selected as catalyst of choice to achieve the desired transformation. Then, different solvents were tested and negligible variations were observed using trifluoroethanol (TFE)

and DCM (entries 6 and 7). Thus, toluene was chosen as solvent because it is less expensive than TFE and it better solubilizes products **81a** and **81'a**. Decreasing the equivalent of the propargyl ester **6a**, the product **81a** and **81'a** were obtained in comparable excellent yields (entry 8 versus entry 1). The influence of the temperature was finally investigated. When the temperature was lowered to -35 °C the reaction did not occur, and the starting materials were recovered unreacted after 10 hours (entry 9). Moreover, performing the reaction at room temperature, the overall isolated yield of **81a** and **81'a** was poor and the reaction crude contained a complex mixture of unidentified products (entry 10). Finally, during the screening for the best reaction conditions, we observed that the isomer *E*,*E*,*E*,*E* **81'a** partially converted into the isomer *E*,*E*,*Z*,*E* **81a** under visible light. This is in agreement with literature reports on the light[122] or iodine[123] induced isomerization of polyene compounds. Thus, in order to obtain a single isomer, at the end of the reaction, the mixtures were quenched with 15 mol% of triphenylphosphine and treated with iodine for 4 hours or irradiated with a 200 W lamp for 8 hours. In both cases, the conversion reached successfully to the completeness (yield of **81a** >98%, scheme 2.40). Treatment with iodine was chosen as the best method for the conversion because the reaction required less time.

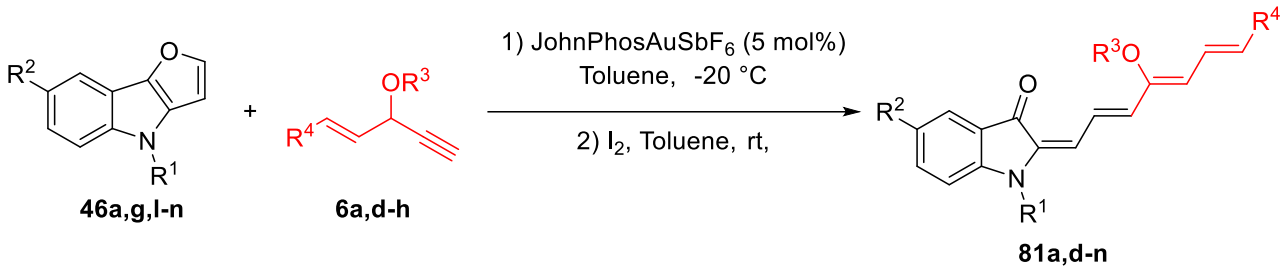


Scheme 2.40

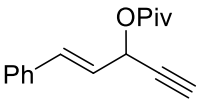
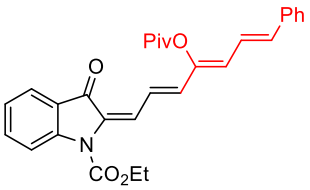
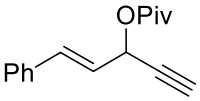
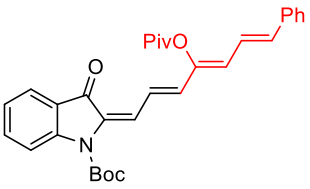
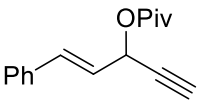
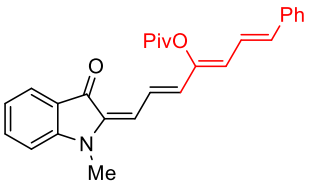
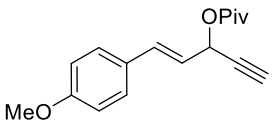
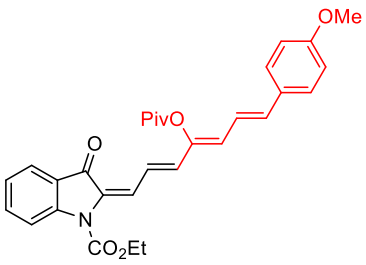
*2.3.4.3 Scope for the synthesis of 2-alkenylidene-3-oxoindoles **81***

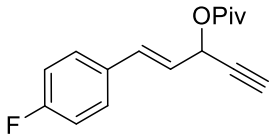
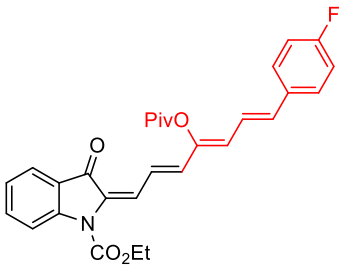
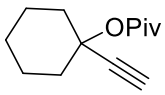
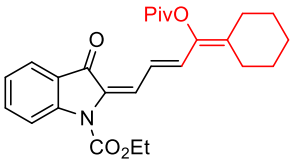
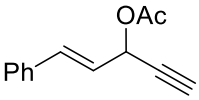
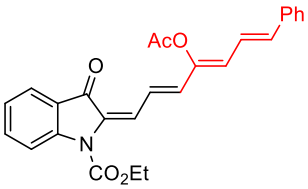
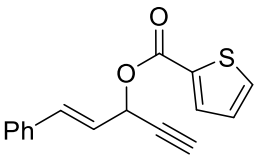
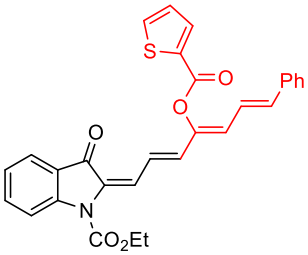
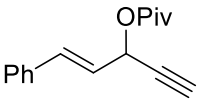
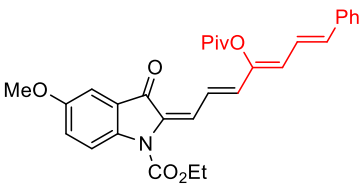
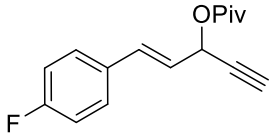
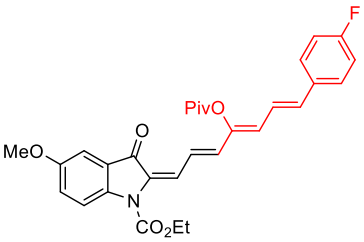
Having the best reaction conditions in hands (Table 2.5, entry 8), the scope and the limitation for this reaction were investigated using 4*H*-furo[3,2-*b*]indoles **46a,g,l-n** and propargyl esters **6a,d-h** both bearing substituents with different electronic properties. As reported before, each reaction was treated with iodine before the purification in order to obtain the single isomers **81a,d-n**. The results are summarized in table 2.6.

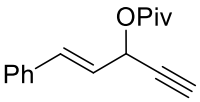
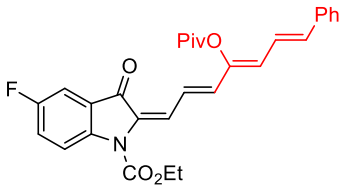
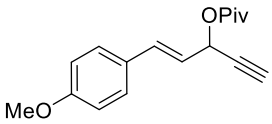
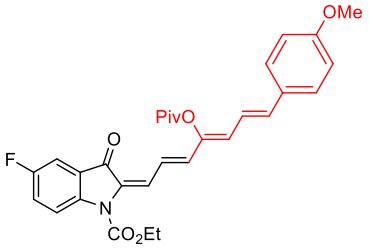
*Table 2.6 scope for the synthesis of compound **81a,d-n***



46a,g,l-n + **6a,d-h** → **81a,d-n**

Entry	46	R^1	R^2	6	Product	Yield,[b] %
1	**46a**	CO_2Et	H	 **6a**	 **81a**	94
2	**46l**	Boc	H	 **6a**	 **81d**	75
3	**46m**	Me	H	 **6a**	 **81e**	40
4	**46a**	CO_2Et	H	 **6d**	 **81f**	89

5	**46a**	CO_2Et	H	 **6e**	 **81g**	55
6	**46a**	CO_2Et	H	 **6f**	 **81h**	36
7	**46a**	CO_2Et	H	 **6g**	 **81i**	56
8	**46a**	CO_2Et	H	 **6h**	 **81j**	98
9	**46n**	CO_2Et	OMe	 **6a**	 **81k**	75
10	**46n**	CO_2Et	OMe	 **6e**	 **81l**	67

11	**46g**	CO_2Et	F	 **6a**	 **81m**	84
12	**46g**	CO_2Et	F	 **6d**	 **81n**	98

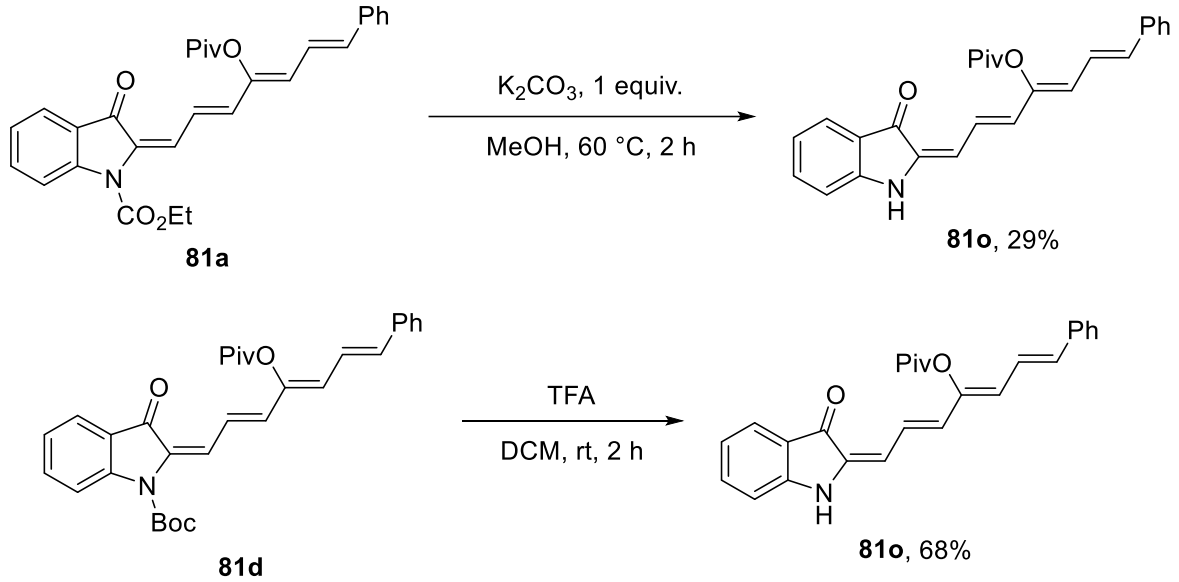
[a]All reactions were carried out using **46** (0.2 mmol), **6** (0.24 mmol), JohnPhosAuSbF$_6$ (5 mol%) in toluene (0.05 M), -20 °C, 1 h. [b]Isolated yields.

Firstly, the reaction between **46a** and **6a** was performed as reported in the screening and the crude mixture isomerized to give **81a** in excellent 94% yield (table 2.6, entry 1). Successively, we examined the influence of different nitrogen protecting groups on the outcome of the reaction. Therefore, 4*H*-furo[3,2-*b*]indoles **46l** and **46m**, bearing respectively Boc and Me groups, were reacted with propargyl ester **6a**. In the first case, the electron-withdrawing bulkier Boc substituent gave rise to a lower but satisfying 75% yield for **81d** (entry 2), while the electron-donating methyl group was less tolerated, and the corresponding oxoindole **81e** was isolated in 40% yield (entry 3). Successively, we moved on the investigation of the behavior of propargyl esters **6** introducing both electron-donating and withdrawing groups on the styryl moiety. The use of (*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-yl pivalate **6d** with **46a** resulted in the isolation of the corresponding product **81f** in excellent yield (entry 4). A similar trend was observed also by reacting **6d** with 7-fluorine-substituted furoindole **46g** (entry 12)**.** In contrast, employing propargyl ester **6e** bearing an electron-withdrawing fluorine atom on the styryl moiety, the isolation of the corresponding product with furoindoles **46a** and **46n** occurred in moderate yields (55% and 67%, respectively, entries 5 and 10), showing a negative effect of the fluorine group. Another α,α-disubstituted propargyl ester **6f** was thus tested instead of styryl propargyl esters, however the isolation of the desired compound was accomplished in only 36% yield (entry 6). The investigation on the propargyl esters continued focusing on the modification of the OR^3 group. The use of less hindered acetate group in **6g** resulted in a decrease of the yield (entry 7), while the more electron-withdrawing thienyl substituent in **6h** caused an increase in the yield affording the corresponding compound **81j** in 98% (entry 8). Then, we tried to rationalize the influence of different

substituents at the C7 position of the 4*H*-furo[3,2-*b*]indoles. Firstly, furoindole **46n** bearing an electron-donating methoxy derivative was employed with the model propargyl ester **6a** giving rise to a slightly decreased but good 75% yield (entry 9). In addition, as reported before, the reaction with fluorine substituted propargyl ester **6e** allowed isolating compound **81l** in good yield (entry 10). Then, employing furoindole **46g** bearing a fluorine C7 substituent, the reaction yields were enhanced with both standard propargyl ester **6a** and with methoxy derivative **6d**, and compound **81m** and **81n** were isolated in 84% and 98% yields, respectively (entries 11 and 12). In addition, most reactions showed the presence of traces of tetracyclic product **82**, as revealed by ^{1}H-NMR analysis.

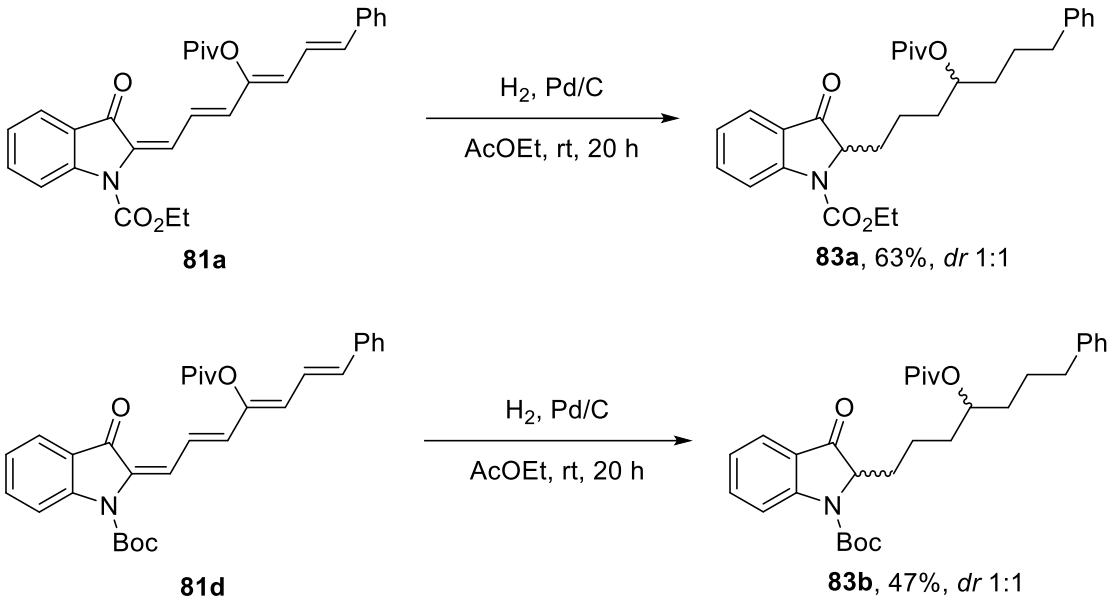
*2.3.4.4 Synthetic elaboration of 2-alkenylidene-3-oxoindoles **81***

In order to verify the stability and the reactivity of this class of compounds, we attempted some simple synthetic elaborations. In particular, compounds **81a** and **81d** were chosen as substrates. With both compounds, the first reaction tested was the hydrolysis of the protecting group on nitrogen atom. Compound **81a** was treated in methanol with K_2CO_3 as base giving rise to 2-alkylydene-3-oxoindole **81o** in moderate 29% yield, while compound **3d** treated with TFA allowed to isolate the same compound **81o** in good 68% yield (scheme 2.41).



Scheme 2.41

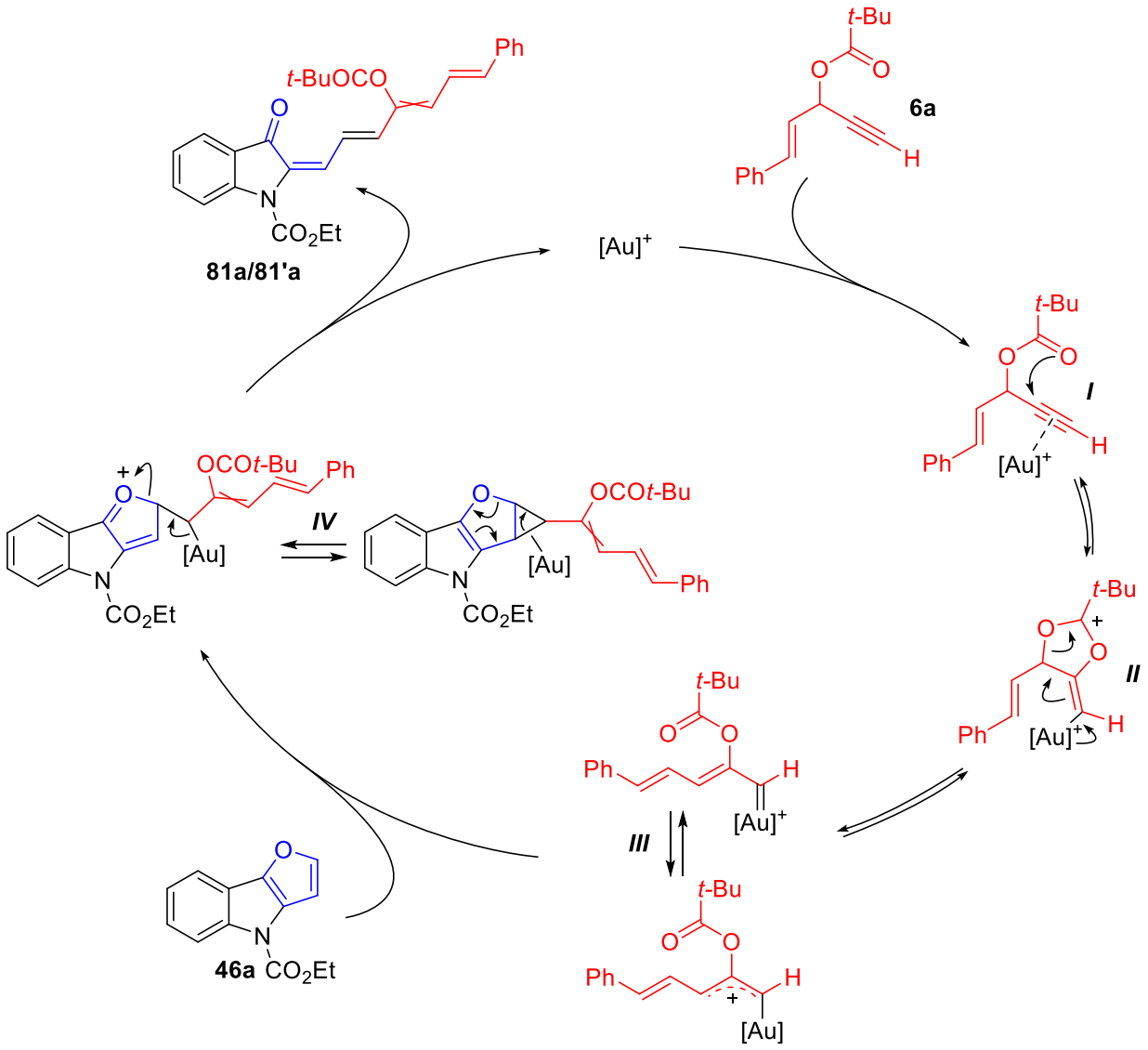
Finally, **81a** and **81d** were hydrogenated under catalytic condition using Pd/C in ethyl acetate. In both cases, the entire trienylidene moiety was fully reduced, resulting in a mixture of diastereoisomeric compounds **83a** and **83b** in 1:1 ratio and in 63 and 47% yields, respectively (scheme 2.42).



Scheme 2.42

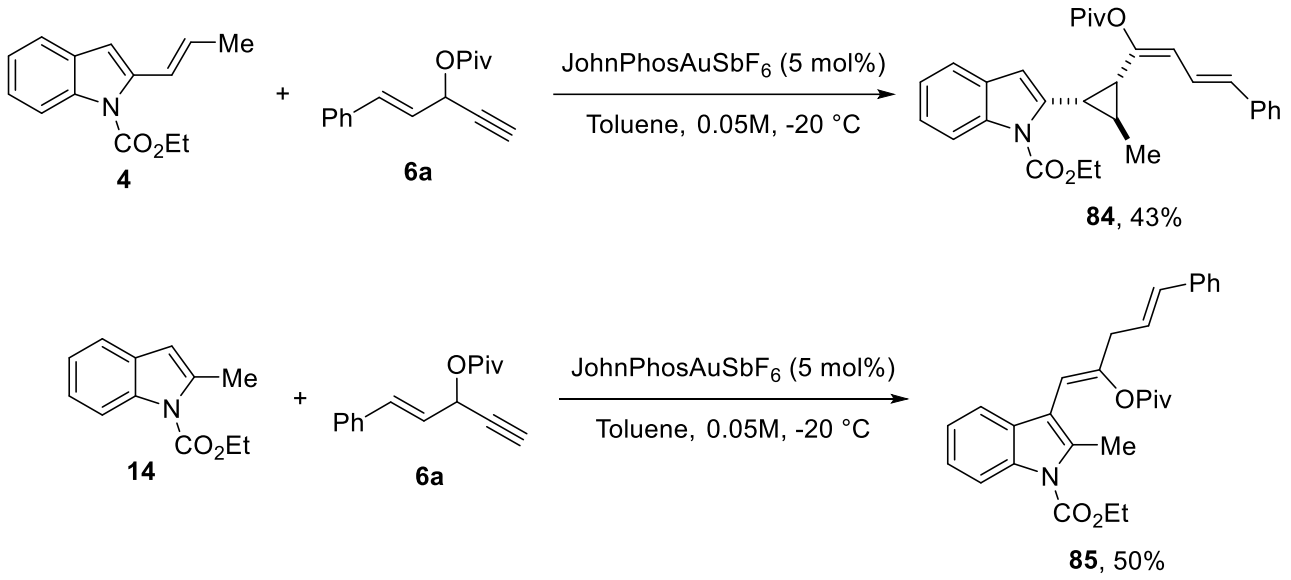
2.3.4.5 Proposed mechanism

The proposed mechanism for the synthesis of compounds **81** starts with the activation of the triple bond of the propargyl ester **6** by the gold(I) complex followed by the 1,2-acyloxy migration. The formed intermediate **III** can be described as a gold-carbene or as an oxyallyl cation. Both species react with the nucleophilic furoindole giving rise to intermediate **IV** described as a cyclopropanation product, formed *via* gold-carbene mediated cyclopropanation of C2-C3 furan carbons, in equilibrium with a linear intermediate, formed by the nucleophilic attack of the C2 furan carbon on the oxyallyl cation. From both species **IV**, the formation of the 2-alkenylidene-3-oxoindoles **81/81'** is due to furan ring opening accompanied by the regeneration of the catalyst. Ring opening rearrangements of furans in the presence of carbene species has been widely reported in the literature.[89,112,124–126] Probably, the double nature of the intermediate **III** induces the formation of the two isomers **81** and **81'** observed as reaction products. Thus, intermediate **III** possesses a fixed geometry only in the carbenic form as dictated by the mechanism of 1,2-migration. In addition, as reported before, the Rautenstrauch rearrangement product was not detected in any reaction, this means that the addition of furoindole **46** to the gold(I)-carbene intermediate **III** (derived from 1,2-acyloxymigration) is faster than the Rautenstrauch rearrangement (scheme 2.43).



Scheme 2.43

In order to support the proposed mechanism, we performed some additional experiments. Firstly, 2-vinylindole **4** was employed as substrate instead of furoindole **46**. The reaction resulted in the isolation in good yield of a new compound **84** arising from the regioselective cyclopropanation reaction at the exocyclic double bond, as already reported for the reaction of 2-vinylindoles and carbenes generated from diazocompounds under metal catalysis.[30] Successively, 2-methylindole **14** was treated with propargyl ester **6a** under gold catalysis and the isolation of the hydroarylated product **85** was achieved in 50% yield (scheme 2.44).



Scheme 2.44

The obtained results are in agreement with the proposed existence of intermediate **III** as two species in equilibrium, the carbene and the oxyallyl cation. The carbene is responsible for the formation of compound **84** *via* cyclopropanation reaction, whereas **85** arises from the nucleophilic attack of C2 of the indole nucleus over the external carbon atom of the oxyallyl cation.

2.3.4.6 Spectroscopic characterization of 2-alkenylidene-3-oxoindoles derivatives

The correct structures of compound **81a** and **81'a** were assigned based on analytical and spectral data. In particular, 1D-NMR (^{1}H and APT) and 2D-NMR (COSY, HSQC, HMBC) were used for the assignment of the chemical shifts of all carbon and proton atoms and for determining the H-H coupling constants. Figure 2.12 shows the chemical shift attribution to significant hydrogens of compounds **81a** and **81'a** using 1D- and 2D-NMR. The spectra were performed using CD_2Cl_2 as solvent at 300 MHz.

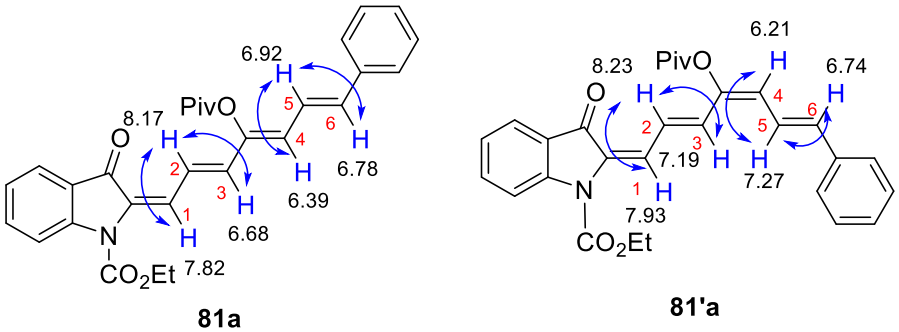


Figure 2.12

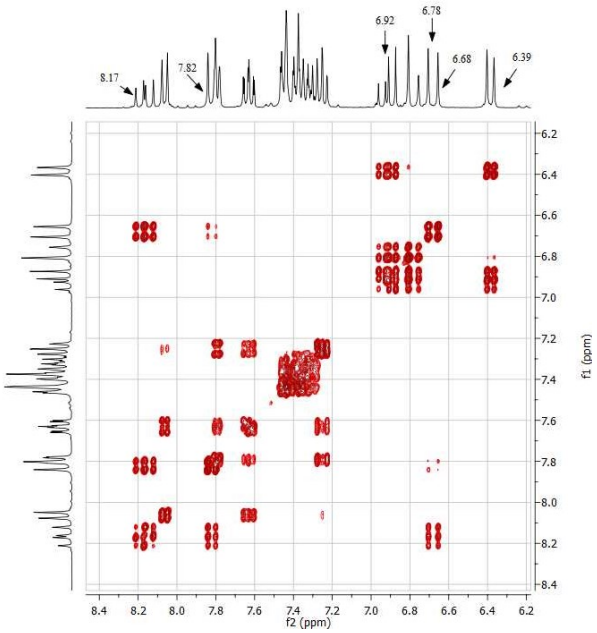
Moreover, from the ^{1}H-NMR it was possible to determine the coupling constants between the hydrogens on the lateral chain. The calculation of the constants allowed to confirm that all protons were in *trans* positions each other in the two different spin systems (Table 2.7).

*Table 2.7 J constants for compound **81a** and **81'a***

H	81a	81'a
H 2	^{3}J H^{1}-H^{2}: 12.0 Hz	^{3}J H^{1}-H^{2}: 12.1 Hz
	^{3}J H^{2}-H^{3}: 15.1 Hz	^{3}J H^{2}-H^{3}: 14.8 Hz
H 5	^{3}J H^{4}-H^{5}: 10.8 Hz	^{3}J H^{4}-H^{5}: 11.9 Hz
	^{3}J H^{5}-H^{6}: 15.6 Hz	^{3}J H^{5}-H^{6}: 15.3 Hz

The COSY 2D analysis confirmed the right attribution of the proton chemical shifts. Figure a) 2.13 reports the aromatic region of the spectrum for compound **81a**, while figure b) 2.13 reports the same region of the spectrum for compound **81'a**.

a)



b)

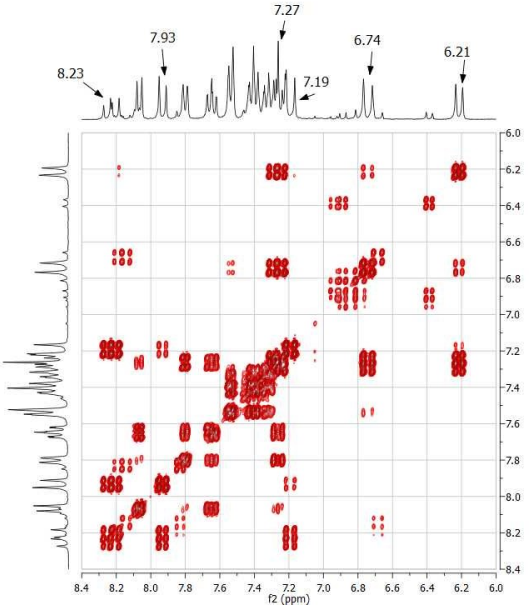


Figure 2.13

In the spectrum of compound **81'a**, it was evident the presence of traces of compound **81a** due to the conversion of the less stable isomer **81'a** into the more stable compound **81a** during the analysis.
The attribution of the protons on the lateral chain was confirmed by 2D NOESY NMR, showing the spatial interactions between protons. In fact, the interaction between the *ortho* aromatic hydrogens of the phenyl ring and the hydrogen of the chain allowed to attribute the proton at the terminal carbon atom of the lateral chain and in combination with the coupling constant values and the COSY interactions also the other protons of the system (figure 2.14)

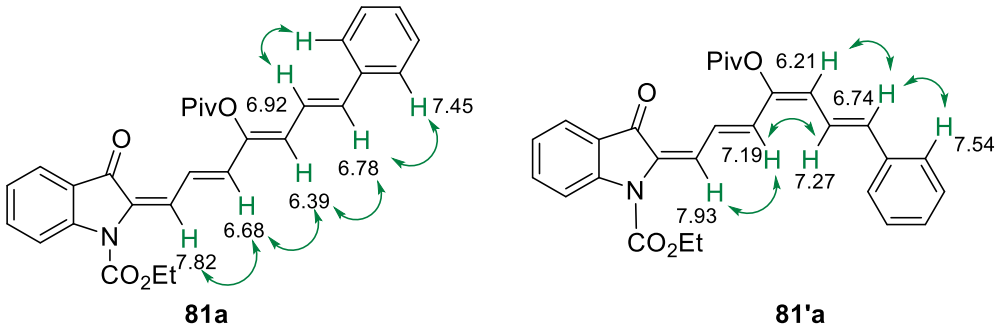


Figure 2.14

In particular, for compound **81a** the aromatic hydrogens of the phenyl moiety show a signal at 7.45 ppm that coupled spatially with the two protons at 6.92 and 6.78 ppm (figure a) 2.15). While in compound **81'a** the coupling between proton of the chain at 6.74 and protons of the phenyl group at 7.54 supports the assignments (figure b) 2.15).

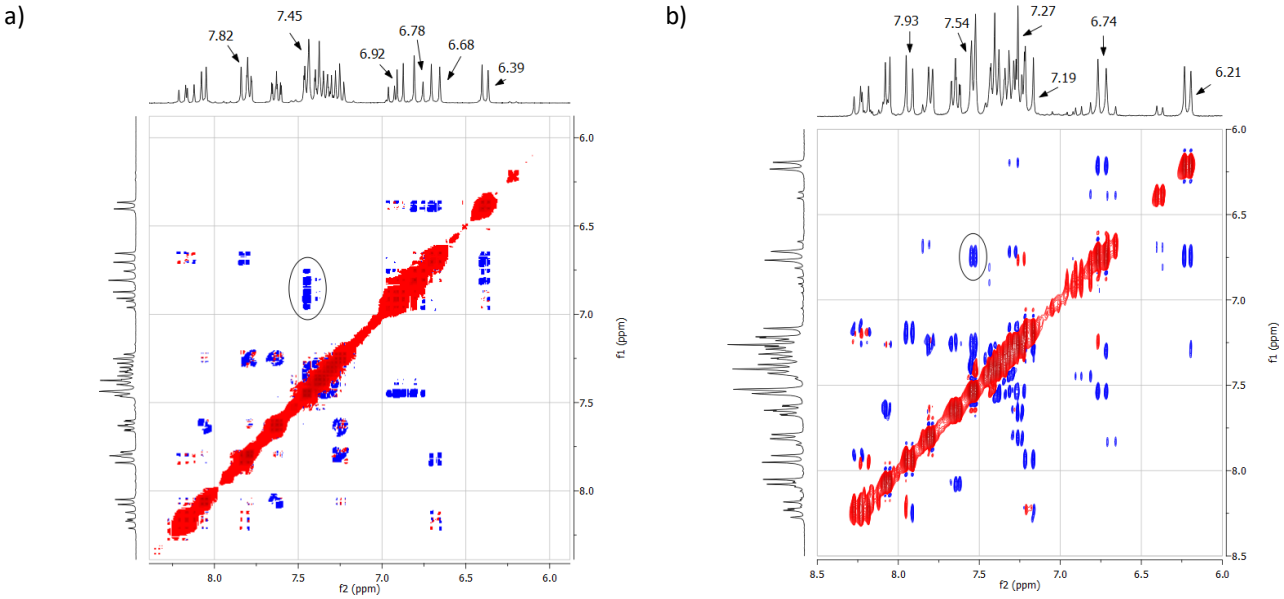
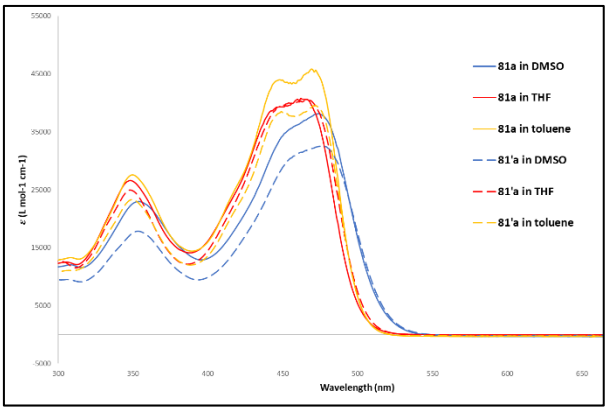


Figure 2.15

2.3.4.7 UV characterization for compound

2-alkenylidene-3-oxindolines **81a-n** presented an intense coloration (from yellow to purple) thanks to the extended conjugated π-system among the molecules. Thus, preliminary photophysical properties were investigated on compounds **81a** and **81d** and on their isomers **81'a** and **81'd**, respectively. For each compound, the UV/Vis spectra were recorded in three different solvents of increasing polarity, toluene, THF and DMSO. Then, from the absorbance values, the molar extinction coefficients (ε) were determined using the linear regression method. Each compound present two peaks of maximum at about 350 and 470 nm (figure 2.16).

a)



b)

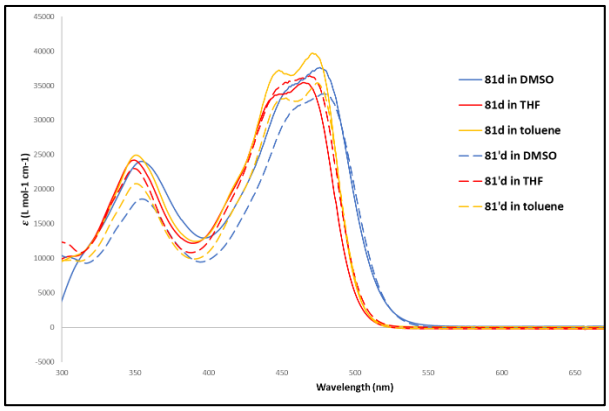


Figure 2.16

Compounds **81a** and **81d** present similar values of absorption wavelengths while the main difference with the corresponding isomers is the values of absorbance and therefore of the extinction coefficient. Molar extinction coefficients for the four compounds are summarized in table 2.8.

*Table 2.8 Extinction coefficients for compound **81a/81'a** and **81d/81'd** measured in different solvents.*

	DMSO		THF		Toluene	
Compound	ε (L mol^{-1} cm^{-1})		ε (L mol^{-1} cm^{-1})		ε (L mol^{-1} cm^{-1})	
81'a	ε_{353} 17873	ε_{474} 32504	ε_{348} 24985	ε_{468} 40446	ε_{349} 23324	ε_{472} 39580
81a	ε_{354} 22988	ε_{474} 38170	ε_{348} 26630	ε_{466} 40636	ε_{350} 27593	ε_{470} 45751
81'd	ε_{355} 18604	ε_{479} 33831	ε_{349} 22986	ε_{466} 36935	ε_{350} 20826	ε_{474} 35413
81d	ε_{354} 24052	ε_{476} 37628	ε_{349} 24209	ε_{465} 35417	ε_{351} 24945	ε_{471} 39690

The results reported that the ε for both the *Z* isomers were higher than for *E* isomers, exception made for **81d** that presented a red-shifted peak in THF. Unfortunately, the solvatochromism was not relevant for this class of compounds and the change in the solvent polarity caused only an extinction variation and not an absorption variation. However, in compound **81'a** the larger extinction variations were observed switching from DMSO to THF.

Successively the isomerization of pure compound **81'a** and **81'd** was followed through UV-Vis measurements irradiating a solution of the compounds in DMSO (2 x 10^{-5}) with a 200 W lamp until the complete conversion to **81a** and **81d**. For this experiment, a rotaflo-equipped cuvette was employed in order to avoid the variation of the concentration for solvent evaporation. The monitoring of the conversion was executed every 20 minutes and an increase of the extinction coefficient was reported. For the two compounds the equilibrium was reached in 2 hours and a prolonged irradiation (until 6 hours) demonstrated a slightly decomposition of the products. Figure 2.17 reports the rate of

the conversion by plotting the intensity of the peaks at 354 nm vs time and the maximum represents the total conversion.

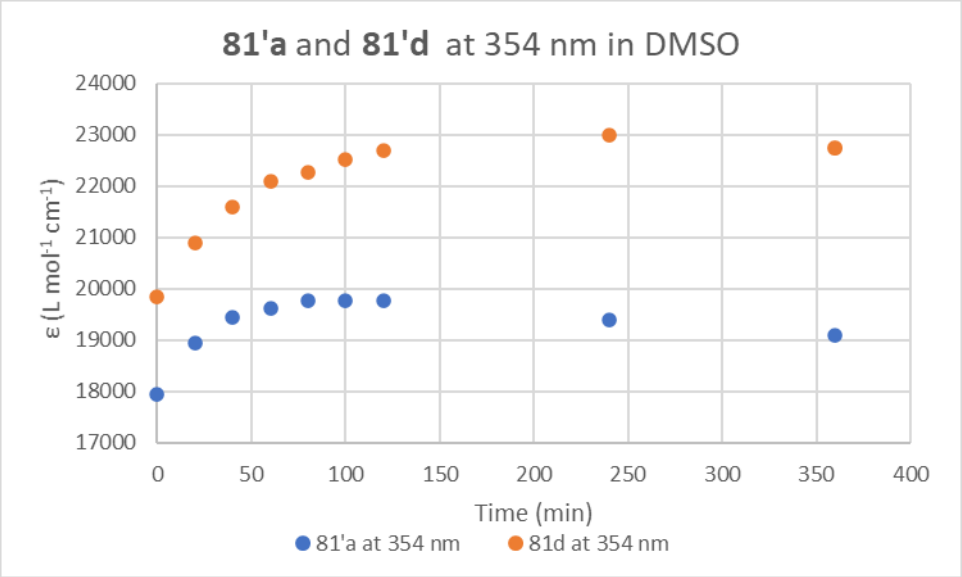


Figure 2.17

2.3.5 Experimental data

2.3.5.1 Preface

2.3.5.1.1 General methods

All the reactions that involve the use of reagents sensitive to oxygen or hydrolysis were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

2.3.5.1.2 Reagents

This study was carried out using 4*H*-furo[3,2-*b*]indoles **46a,g,n** which syntheses have already been described in section 2.2.4.1, while **46l-m**, were prepared following the procedure described in section 2.3.3.1.

Propargyl esters **6a-h** are known compounds and were prepared following the procedure 2.3.3.2 according to literature procedure.[115–118]

Indole **4** and **14** are known compound and were prepared according to literature procedures.[127,128]

PPh_3PAuCl, JohnPhosAuSbF_6 $AgNTf_2$ and $AgSbF_6$ were purchased from commercial suppliers and used as received; the rest of the gold catalysts were prepared following literature procedure.[41–43,100]

2.3.5.1.3 Solvents

Solvents, used for reactions sensitive to oxygen and hydrolysis, were purchased from commercial suppliers.

2.3.5.1.4 Immersion cooler

The immersion cooler *Julabo FT 402* was used for reactions carried out at -20 °C or -35 °C.

2.3.5.1.5 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade* 9385 60Å (230-400 mesh).

For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm).

2.3.5.1.6 NMR spectroscopy

^{1}H-NMR analyses were performed with a *Varian-Gemini 300* or with *Brucker 300, 500, 600 Avance* spectrometers at room temperature, respectively at 300, 500 or 600 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shift (δ) in ppm. The multiplicities of the proton spectra were described by following abbre*via*tions: s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double dublet).
^{13}C-NMR analyses were performed with the same instruments at 75.45, 125.75 MHz; APT sequences were used to distinguish the methane and methyl carbon signals from those arising from methylene and quaternary carbon atoms.
Two-dimensional NMR techniques (COSY, HSQC, HMBC, NOESY) were performed, where appropriate, to aid the correct assignment of structures.

2.3.5.1.7 Mass Spectroscopy

Low resolution MS spectra were recorded with *a FISONS MD 800* spectrometer with electron impact source and a *Thermo-Finnigan LCQ-advantage AP* electron spray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown
in brackets.

2.3.5.1.8 Melting points

The melting points of the solid products were measured in capillary tube with the device *StuarScientific* SMP3.

2.3.5.1.9 Syringe pump

Slow additions were performed using NE-1000 Programmable Single Syringe Pump of the New Era Pump Systems Inc.

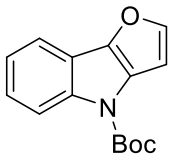
2.3.5.1.10 UV Spectroscopy

UV spectra were measured in solution using an Agilent 1453E instrument and an open top UV quartz cell, 10 mm, 3.0 ml vol.

2.3.5.2 Experimental data

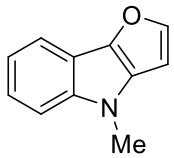
2.3.5.2.1 Procedures for the synthesis of 4*H*-furo[3,2-*b*]indole 46l-n

tert-butyl 4*H*-furo[3,2-*b*]indole-4-carboxylate (46l)



To a N_2-flushed solution of 4*H*-furo[3,2-*b*]indole **8a** (157 mg, 1 mmol) in dichloromethane (5 mL), Boc_2O (659 mg, 3 mmol) and DMAP (12 mg, 0.1 mmol) were added at 0 °C. The mixture was warmed up to room temperature and stirred for 2.5 h. Then the solvent was evaporated, and the crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield **46l** (252 mg, 98%) as white solid (m.p. 82.4-84.6 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.32 (bs, 1H), 7.66 (ddd, *J* = 6.7, 3.3, 2.1 Hz, 1H), 7.56 (t, *J* = 16.1 Hz, 1H), 7.38 – 7.19 (m, 2H), 6.79 (bs, 1H), 1.71 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 149.77 (C), 145.59 (CH), 143.24 (C), 138.80 (C), 129.67 (C), 123.74 (CH), 123.03 (CH), 117.88 (C), 116.33 (CH), 116.23 (CH), 103.07 (CH), 83.42 (C), 28.25 (3xCH_3). **ESI(+)-MS**: m/z(%) = 258 (100) $[M+H]^+$; Anal. Calcd. for $C_{15}H_{15}NO_3$ [257.29]: C, 70.02; H, 5.88; N, 5.44; found C, 70.15; H, 5.86, N 5.46.

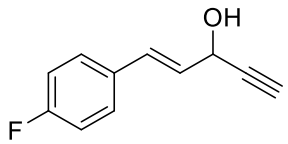
4-methyl-4*H*-furo[3,2-*b*]indole (46m)



To a N_2-flushed solution of NaH (28 mg, 1.1 mmol) in DMF (6 ml) 4*H*-furo[3,2-*b*]indole **8a** (157 mg, 1 mmol) was added in small portions at 0 °C and the mixture was stirred for 30 min at 0 °C. Then MeI (156 mg, 1.1 mmol) was added and the reaction was warmed to room temperature and stirred for 1 h before being quenched with water. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and the solvent concentrated under reduced pression. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield **46m** (153 mg, 89%) as pink oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.75 (dd, *J* = 7.1, 0.8 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.09 (m, 2H), 6.61 (d, *J* = 2.1 Hz, 1H), 3.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 145.69 (CH), 140.82 (C), 140.44 (C), 133.10 (C), 121.15 (CH), 118.94 (CH), 116.25 (CH), 113.96 (C), 109.63 (CH), 98.18 (CH), 31.21 (CH_3). **ESI(+)-MS**: m/z(%) = 172 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_9NO$ [171.20]: C, 77.17; H, 5.30; N, 8.18; found C, 76.89; H, 5.33; N, 8.15.

2.3.5.2.2 Procedures for the synthesis of propargylic esters 6e,f

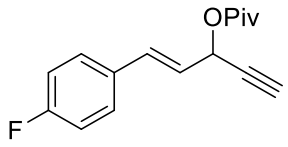
(*E*)-1-(4-fluorophenyl)pent-1-en-4-yn-3-ol



To a N_2-flushed solution of (*E*)-3-(4-fluorophenyl)acrylaldehyde **78e** (753 mg, 5 mmol) in tetrahydrofuran (10 mL), a solution of ethynylmagnesium bromide (0.5 M in tetrahydrofuran, 12 mL, 6 mmol) was added dropwise at

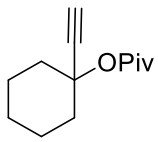
0 °C. The mixture was warmed up to room temperature and stirred for 1h before of being quenched with ammonium chloride saturated solution. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and the solvent concentrated under vacuum. The crude was used directly for the next step, quantitative yield.

(*E*)-1-(4-fluorophenyl)pent-1-en-4-yn-3-yl pivalate (6e)



To a solution of (*E*)-1-(4-fluorophenyl)pent-1-en-4-yn-3-ol (889 mg, 5 mmol), triethylamine (1.52 g, 15 mmol), DMAP (61 mg, 0.5 mmol) in dichloromethane (21.5 mL), pivaloyl chloride (720 mg, 6 mmol) was added at 0 °C. The mixture was warmed up to room temperature and stirred for 2h before of being quenched with ammonium chloride saturated solution. The organic layer was extracted with dichloromethane, washed with brine, dried over Na_2SO_4 and the solvent concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2) to yield **6e** (1.3 g, quantitative) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.49 – 7.27 (m, 2H), 7.06 – 6.98 (m, 2H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.14 (dd, *J* = 15.7, 6.3 Hz, 1H), 6.01 (ddd, *J* = 6.3, 2.2, 1.2 Hz, 1H), 2.61 (d, *J* = 2.2 Hz, 1H), 1.24 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 177.08 (C), 162.78 (d, *J* = 248.1 Hz, C), 133.18 (CH), 131.87 (d, *J* = 3.4 Hz, C), 128.51 (d, *J* = 8.2 Hz, 2xCH), 123.39 (d, *J* = 2.2 Hz, CH), 115.57 (d, *J* = 21.6 Hz, 2xCH), 79.48 (C), 74.99 (CH), 63.69 (CH), 38.76 (C), 26.98 (3xCH_3). **ESI(-)-MS**: m/z(%) = 520 (100) [dimer]$^-$; Anal. Calcd. for $C_{16}H_{17}FO_2$ [260.30]: C, 73.83; H, 6.58; found C, 73.57; H, 6.60.

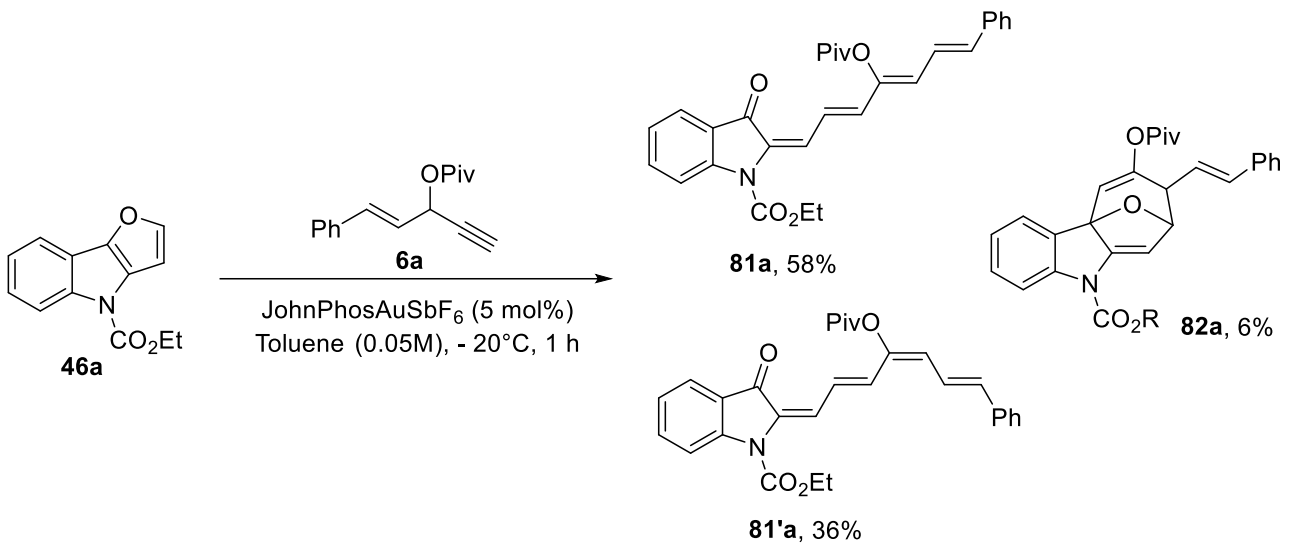
1-ethynylcyclohexyl pivalate (6f)



1-Ethynylcyclohexanol **79c** (500 mg, 4 mmol) and pivalic anhydride (815 mg, 4.4 mmol) were stirred at 80 °C for 1h in presence of magnesium perchlorate (9 mg, 0.04 mmol). The mixture was diluted with water, saturated solution of $NaHCO_3$ and extracted with Et_2O. the organic layers were washed with saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4 and the solvent concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 99:1 to 98:2) to yield **6f** (781 g, 94%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 2.54 (s, 1H), 2.06 – 1.90 (m, 4H), 1.66 – 1.52 (m, 4H), 1.51 – 1.34 (m, 2H), 1.19 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 176.43 (C), 84.08 (C), 74.15 (C), 73.44 (CH), 39.16 (C), 36.75 (2xCH_2), 27.08 (3xCH_3), 25.08(CH_2), 22.16 (2xCH_2). **ESI(+)-MS**: m/z(%) = 209 (100) $[M+H]^+$; Anal. Calcd. for $C_{13}H_{20}O_2$ [208.30]: C, 74.96; H, 9.68; found C, 75.23; H, 9.64.

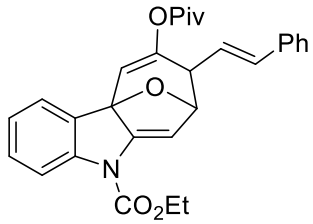
2.3.5.2.3 Preliminary reactions between 1a and 2a-c

Reaction between 46a and 6a



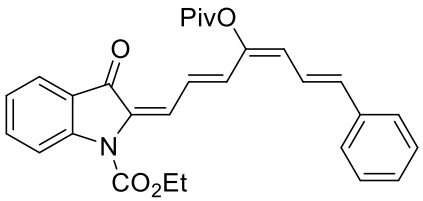
To a N_2-flushed solution of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol) and JohnPhosAuSbF$_6$ (5 mol%) in anhydrous toluene (2 mL), a solution of (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (58 mg, 0.24 mmol) in toluene (2 mL, final concentration 0.05 M) was added dropwise at -20 °C. The reaction mixture was stirred for 1 h at -20 °C and then quenched with PPh_3 (15 mol%). Purification by flash chromatography (SiO_2, toluene/ethyl acetate 99:1) yielded progressively **82a** (6 mg, 6%) as pale oil, **81'a** (34 mg, 36%) as a red solid (m.p. 174.2-176.3 °C) and **81a** (55 mg, 58%) as a red solid (m.p. 171.3-173.6 °C).

(*E*)-ethyl 9-(pivaloyloxy)-8-styryl-7,8-dihydro-5*H*-7,10a-epoxycyclohepta[*b*]indole-5-carboxylate (82a)



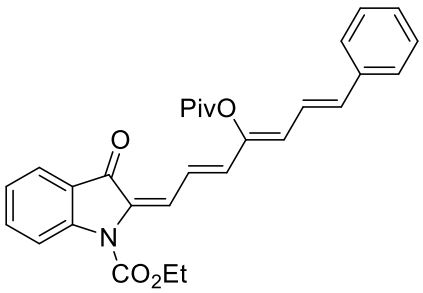
^{1}H NMR (300 MHz, $CDCl_3$): 7.92 (bs, 1H), 7.51 (d, *J* = 6.7 Hz, 1H), 7.44 – 7.20 (m, 6H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.44 (dd, *J* = 15.8, 8.8 Hz, 1H), 5.89 (d, *J* = 1.1 Hz, 1H), 5.68 (bs, 1H), 5.15 (d, *J* = 2.6 Hz, 1H), 4.58 – 4.21 (m, 2H), 3.29 (d, *J* = 9.0 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.14 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 176.43 (C), 156.41 (C), 151.50 (C), 146.87 (C), 146.03 (C), 136.84 (C), 133.13 (CH), 130.40 (CH), 128.81 (CH), 128.53 (2xCH), 128.45 (C), 127.54 (CH), 126.35 (2xCH), 124.86 (CH), 124.37 (CH), 120.74 (CH), 115.82 (CH), 104.10 (CH), 89.27 (CH), 62.75 (CH_2), 45.48 (CH), 39.05 (C), 29.66 (C), 26.99 (3xCH_3), 14.39 (CH_3). **ESI(+)-MS**: m/z(%) = 472 (100) $[M+H]^+$; Anal. Calcd. for $C_{29}H_{29}NO_5$ [471.54]: C, 73.87; H, 6.20; N, 2.97; found C, 73.76; H, 6.17; N, 2.98.

(*E*)-ethyl 3-oxo-2-((2*E*,4*E*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81'a)



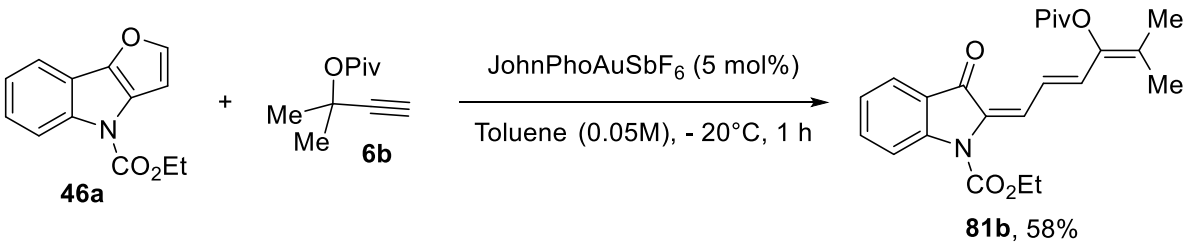
^{1}H NMR (300 MHz, CD_2Cl_2): 8.23 (dd, *J* = 14.8, 12.1 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 12.1 Hz, 1H), 7.80 (m, 1H), 7.65 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.45 – 7.36 (m, 2) 7.35 – 7.14 (m, 4H), 6.74 (d, *J* = 15.3 Hz, 1H), 6.21 (d, *J* = 11.9 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H), 1.50 (s, 9H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 184.10 (C), 176.76 (C), 151.75 (C), 146.88 (C), 146.85 (C), 136.95 (C), 135.53 (CH), 135.49 (CH), 132.57 (C), 130.62 (CH), 128.72 (2xCH), 128.23 (CH), 126.98 (CH), 126.71 (2xCH), 125.19 (CH), 125.07 (CH), 124.18 (CH), 123.87 (C), 123.58 (CH), 122.01 (CH), 117.28 (CH), 63.27 (CH_2), 39.11 (C), 27.07 (3xCH_3), 14.23 (CH_3). **ESI(+)-MS**: m/z(%) = 472 (100) $[M+H]^+$; Anal. Calcd. for $C_{29}H_{29}NO_5$ [471.54]: C, 73.87; H, 6.20; N, 32.97; found C, 74.15; H, 6.22; N, 2.96.

(*E*)-ethyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81a)



^{1}H NMR (300 MHz, CD_2Cl_2): 8.17 (dd, *J* = 15.1, 12.0 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.88 – 7.74 (m, 2H), 7.63 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.52 – 7.14 (m, 6H), 6.92 (dd, *J* = 15.6, 10.9 Hz, 1H) 6.78 (d, *J* = 15.6 Hz, 1H), 6.68 (d, *J* = 15.1 Hz, 1H), 6.39 (d, *J* = 10.8 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.60 (s, 9H), 1.52 (d, *J* = 7.1, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 184.03 (C), 175.86 (C), 151.69 (C), 146.99 (C), 146.86 (C), 136.87 (C), 135.84 (CH), 135.78 (CH), 135.43 (CH), 132.15 (C), 128.73 (2xCH), 128.38 (CH), 127.11 (2xCH), 126.71 (CH), 124.87 (CH), 124.58 (CH), 124.22 (C), 123.81 (CH), 123.50 (CH), 121.79 (CH), 117.25 (CH), 63.21 (CH_2), 39.38 (C), 27.20 (3xCH_3), 14.16 (CH_3). **ESI(+)-MS**: m/z(%) = 472 (100) $[M+H]^+$; Anal. Calcd. for $C_{29}H_{29}NO_5$ [471.54]: C, 73.87; H, 6.20; N, 32.97; found C, 73.67; H, 6.18; N, 2.96.

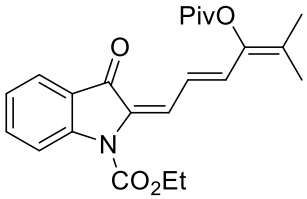
Reaction between 46a and 6b



To a N_2-flushed solution of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol) and JohnPhosAuSbF$_6$ (5 mol%) in anhydrous toluene (2 mL), a solution of 2-methylbut-3-yn-2-yl pivalate **6b** (67 mg, 0.4 mmol) in toluene (2 mL, final concentration 0.05 M) was added dropwise at -20 °C. The reaction mixture was stirred for 1 h at -20 °C and then quenched with PPh_3 (15 mol%).

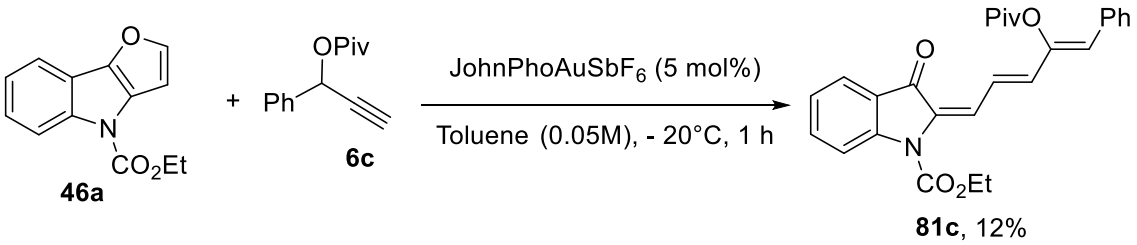
Purification by flash chromatography (SiO_2, hexane/ ethyl acetate 95:5 to 9:1) yielded **81b** (46 mg, 58%) as a yellow solid (138.4 °C dec.).

(*E*)-ethyl 2-((*E*)-5-methyl-4-(pivaloyloxy)hexa-2,4-dien-1-ylidene)-3-oxoindoline-1-carboxylate (81b)



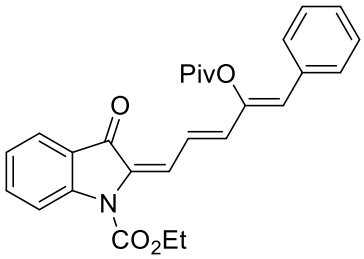
^{1}H NMR (300 MHz, $CDCl_3$): 8.06 – 7.93 (m, 2H), 7.90 – 7.74 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 14.7 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.99 (s, 3H), 1.75 (s, 3H), 1.61 – 1.42 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.00 (C), 176.23 (C), 151.81 (C), 146.64 (C), 141.46 (C), 135.23 (CH), 133.11 (CH), 131.56 (C), 129.80 (C), 128.86 (CH), 124.45 (C), 123.79 (CH), 123.72 (CH), 122.36 (CH), 117.19 (CH), 62.98 (CH_2), 39.20 (C), 27.42 (3xCH_3), 19.27 (CH_3), 18.98 (CH_3), 14.41 (CH_3). **ESI(+)-MS**: m/z(%) = 420 (100) $[M+Na]^+$; Anal. Calcd. for $C_{23}H_{27}NO_5$ [397.46]: C, 69.50; H, 6.85; N, 3.52; found C, 69.36; H, 6.87; N, 3.54.

Reaction between 46a and 6c



To a N_2-flushed solution of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol) and JohnPhosAuSbF$_6$ (5 mol%) in anhydrous toluene (2 mL), a solution of 1-phenylprop-2-yn-1-yl pivalate **6c** (86 mg, 0.4 mmol) in toluene (2 mL, final concentration 0.05 M) was added dropwise at -20 °C. The reaction mixture was stirred for 1 h at -20 °C and then quenched with PPh_3 (15 mol%). Purification by flash chromatography (SiO_2, hexane/ ethyl acetate 95:5 to 9:1) yielded **81c** (11 mg, 12%) as a yellow oil.

(*E*)-ethyl 3-oxo-2-((2*E*,4*Z*)-5-phenyl-4-(pivaloyloxy)penta-2,4-dien-1-ylidene)indoline-1-carboxylate (81c)



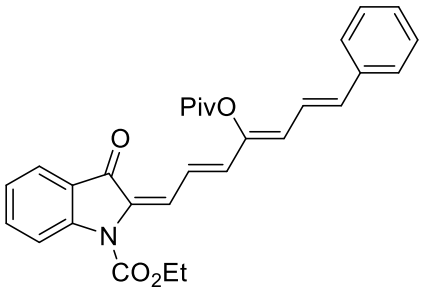
^{1}H NMR (300 MHz, $CDCl_3$): 8.15 (dd, *J* = 15.0, 11.8 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.81 (m, 2H), 7.58 (ddd, *J* = 8.6, 7.3, 1.4 Hz, H), 7.49 (m, 2H), 7.37 – 7.27 (m, 3H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.66 (s, 1H), 6.46 (s, 1H), 4.49 (q, *J* = 7.1 Hz, 3H), 1.58 – 1.41 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.17 (C), 175.53 (C), 151.76 (C), 146.83 (C), 146.49 (C), 137.64 (CH), 135.48 (CH), 134.04 (C), 132.08 (C), 129.13 (2xCH), 128.38 (2xCH), 128.25 (CH), 127.64 (CH), 124.61 (CH), 124.37 (CH), 124.29 (C), 123.89 (CH), 117.24 (CH), 63.12

(CH_2), 39.30 (C), 27.47 (3xCH_3), 14.42 (CH_3). One CH is missing, probably overlapping. **ESI(+)-MS**: m/z(%) = 468 (100) $[M+Na]^+$; Anal. Calcd. for $C_{27}H_{27}NO_5$ [445.51]: C, 72.79; H, 6.11; N, 3.14; found 73.08; H, 6.09; N, 3.15.

2.3.5.2.4 Preparation and characterization data for products 81a-n

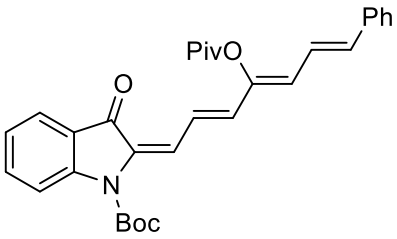
To a N_2-flushed solution of *N* protected 4*H*-furo[3,2-*b*]indole **46a,g,l-n** (1 equiv.) and JohnPhosAuSbF$_6$ (5 mol%) in anhydrous toluene (2 mL), a solution of propargylic ester **6a-h** (1.2 or 2 equiv.) in toluene (2 mL, final concentration 0.05 M) was added dropwise at -20 °C. The reaction mixture was stirred for the stated time at -20 °C and then quenched with PPh_3 (15 mol%). Then the reaction mixture was warmed to room temperature and further stirred for 4 h in the presence of one crystal of I_2. The solvent was removed under reduced pression and the crude residue was purified by flash column chromatography to yield the desired product **81a-n**.

(*E*)-ethyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81a)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (58 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, toluene/ethyl acetate 99:1) yielded **81a** (89 mg, 98%). Data analysis are reported previously.

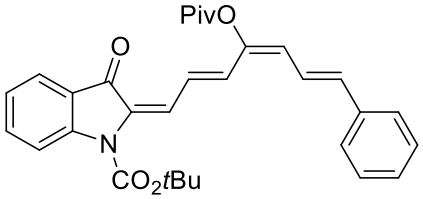
(*E*)-tert-butyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81d)



General procedure was followed using *tert*-butyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46l** (52 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (58 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2,toluene to toluene/ethyl acetate 98:2) yielded **81d** (75 mg, 75%) as a red solid (170.2 °C, dec). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.15 (dd, *J* = 14.9, 12.1 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.68 (m, 2H), 7.56 (m, 1H), 7.44 – 7.06 (m, 6H), 6.85 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.71 (d, *J* = 15.7 Hz, 1H), 6.60 (d, *J* = 15.1 Hz, 1H), 6.31 (d, *J* = 11.0 Hz, 1H), 1.68 (s, 9H), 1.57 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.31 (C), 176.03 (C), 150.41 (C), 147.09 (C), 146.89 (C), 136.94

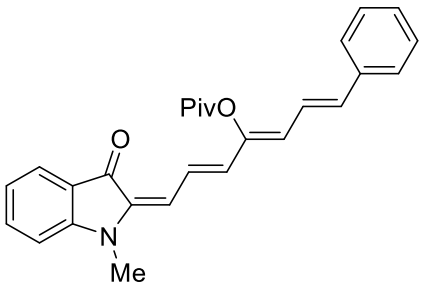
(C), 135.83 (CH), 135.75 (CH), 135.30 (CH), 132.32 (C), 128.74 (2xCH), 128.32 (CH), 127.54 (CH), 126.70 (2xCH), 124.88 (CH), 124.79 (CH), 124.19 (C), 123.80 (CH), 123.56 (CH), 121.89 (CH), 117.16 (CH), 84.21 (C), 39.50 (C), 28.32 (3xCH_3), 27.46 (3xCH_3). **ESI(+)-MS**: m/z(%) = 500 (100) $[M+H]^+$; Anal. Calcd. for $C_{31}H_{33}NO_5$ [499.60]: C, 74.53; H, 6.66; N, 2.80; found C, 74.78; H, 6.64; N, 2.79.

(*E*)-tert-butyl 3-oxo-2-((2*E*,4*E*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81'd)



General procedure was followed using *tert*-butyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46l** (52 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (58 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, avoiding the isomerization step with I_2. Purification by flash chromatography (SiO_2, toluene to toluene/ethyl acetate 98:2) yielded progressively **81'd** (35 mg, 35%) as red solid (177.3 °C, dec.) and **3d** (48 mg, 48%). **^{1}H NMR** (500 MHz, $CDCl_3$): 8.24 (dd, *J* = 14.9, 12.1 Hz, 1H), 7.96 (dd, *J* = 22.2, 10.2 Hz, 2H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.59 (m, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.31 (m, 1H), 7.26 – 7.15 (m, 2H), 7.12 (d, *J* = 14.9 Hz, 1H), 6.70 (d, *J* = 15.3 Hz, 1H), 6.19 (d, *J* = 11.7 Hz, 1H), 1.74 (s, 9H), 1.51 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): 184.35 (C), 177.00 (C), 150.50 (C), 147.05 (C), 146.76 (C), 137.00 (C), 135.52 (CH), 135.39 (CH), 132.77 (C), 130.72 (CH), 128.76 (2xCH), 128.20 (CH), 127.51 (CH), 126.74 (2xCH), 125.34 (CH), 125.20 (CH), 124.20 (C), 123.93 (CH), 123.65 (CH), 122.10 (CH), 117.18 (CH), 84.33 (C), 39.28 (C), 28.38 (3xCH_3), 27.37 (3xCH_3). **ESI(+)-MS**: m/z(%) = 500 (100) $[M+H]^+$; Anal. Calcd. for $C_{31}H_{33}NO_5$ [499.60]: C, 74.53; H, 6.66; N, 2.80; found C, 74.73; H, 6.68; N, 2.81.

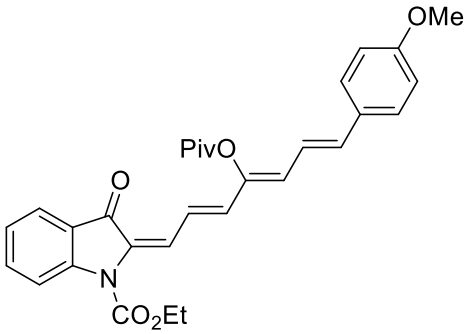
(1*E*,3*Z*,5*E*,7*E*)-7-(1-methyl-3-oxoindolin-2-ylidene)-1-phenylhepta-1,3,5-trien-4-yl pivalate (81e)



General procedure was followed using 4-methyl-4*H*-furo[3,2-*b*]indole **46m** (34 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (58 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, toluene/ethyl acetate 99:1 to 98:2) yielded **81e** (33 mg, 40%) as a purple solid (m.p. 189.8-191.2 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.99 (dd, *J* = 15.0, 12.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.13 (m, 6H), 6.99 – 6.77 (m, 3H), 6.67 (d, *J* = 15.6 Hz, 1H), 6.46 (d, *J* = 15.1 Hz, 1H), 6.25 (d, *J* = 11.2 Hz, 1H), 6.09 (d, *J* = 11.9 Hz, 1H), 3.22 (s,

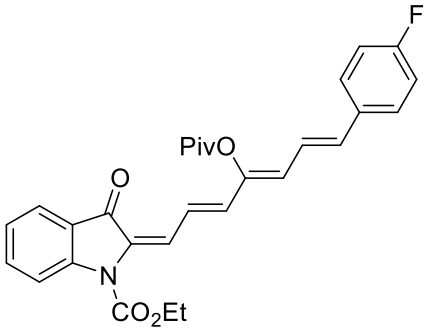
3H), 1.60 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 185.44 (C), 176.22 (C), 151.90 (C), 147.32 (C), 137.17 (C), 136.45 (C), 135.40 (CH), 134.61 (CH), 131.23 (CH), 128.75 (2xCH), 128.09 (CH), 126.60 (2xCH), 124.92 (CH), 124.47 (CH), 122.99 (CH), 122.12 (CH), 121.34 (C), 119.19 (CH), 115.14 (CH), 108.58 (CH), 39.53 (C), 28.53 (CH_3), 27.52 (3xCH_3). **ESI(+)-MS**: m/z(%) = 414 (100) $[M+H]^+$; Anal. Calcd. for $C_{27}H_{27}NO_3$ [413.51]: C, 78.42; H, 6.58; N, 3.39; found C, 78.35; H, 6.61; N, 3.38.

(*E*)-ethyl 2-((2*E*,4*Z*,6*E*)-7-(4-methoxyphenyl)-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)-3-oxoindoline-1-carboxylate (81f)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol), (*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-yl pivalate **6d** (109 mg, 0.4 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **81f** (89 mg, 89%) as a red solid (m.p. 154.3-156.8 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.11 (dd, *J* = 14.9, 11.9 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.78 (m, 1H), 7.57 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.19 (m, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 15.0 Hz, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.57 (s, 9H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.01 (C), 176.01 (C), 159.95 (C), 151.75 (C), 146.65 (C), 146.05 (C), 136.40 (CH), 135.68 (CH), 135.28 (CH), 131.81 (C), 129.83 (C), 128.10 (2xCH), 127.97 (CH), 125.49 (CH), 124.40 (C), 124.09 (CH), 123.80 (2xCH), 119.90 (CH), 117.21 (CH), 114.28 (2xCH), 63.06 (CH_2), 55.30 (CH_3), 39.48 (C), 27.46 (3xCH_3), 14.40 (CH_3). **ESI(+)-MS**: m/z(%) = 502 (100) $[M+H]^+$; Anal. Calcd. for $C_{30}H_{31}NO_6$ [501.57]: C, 71.84; H, 6.23; N, 2.79; found C, 72.10; H, 6.25; N, 2.80.

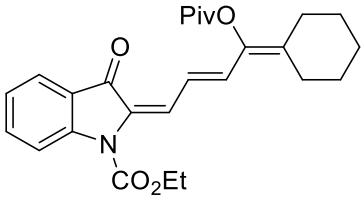
(*E*)-ethyl 2-((2*E*,4*Z*,6*E*)-7-(4-fluorophenyl)-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)-3-oxoindoline-1-carboxylate (81g)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol), (*E*)-1-(4-fluorophenyl)pent-1-en-4-yn-3-yl pivalate **6e** (62 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2,

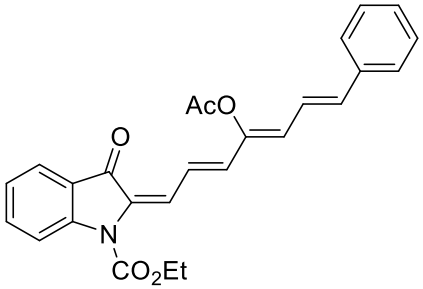
toluene/ethyl acetate 99:1) yielded **81g** (54 mg, 55%) as a red solid (m.p. 162.2-164.3 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.16 (dd, *J* = 14.9, 12.1 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.88 – 7.73 (m, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H),7.03 (t, *J* = 8.6 Hz, 2H), 6.85 – 6.56 (m, 3H), 6.32 (d, *J* = 10.3 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.59 (s, 9H), 1.51 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.14 (C), 176.09 (C), 162.69 (d, *J* = 249.1 Hz, C), 151.75 (C), 146.83 (d, *J* = 1.1 Hz, C),146.68 (C), 136.13 (CH), 135.46 (CH), 134.55 (CH), 133.15 (d, *J* = 3.4 Hz, C), 132.03 (C), 128.28 (d, *J* = 8.0 Hz, 2xCH), 127.72 (CH), 124.87 (CH), 124.71 (CH), 124.30 (C), 123.90 (CH), 123.87 (CH), 121.57 (d, *J* = 2.3 Hz, CH), 117.26 (CH), 115.83 (d, *J* = 21.9 Hz, 2xCH), 63.15 (CH_2), 39.53 (C), 27.47 (3xCH_3), 14.43 (CH_3). **ESI(+)-MS**: m/z(%) = 490 (100) $[M+H]^+$; Anal. Calcd. for $C_{29}H_{28}FNO_5$ [489.53]: C, 71.15; H, 5.77; N, 2.86; found C, 71.37; H, 5.79; N, 2.86.

(*E*)-ethyl 2-((*E*)-4-cyclohexylidene-4-(pivaloyloxy)but-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (81h)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **1a** (46 mg, 0.2 mmol), 1-ethynylcyclohexyl acetate **6f** (83 mg, 0.4 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 22 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5 to 9:1) yielded **81h** (32 mg, 36%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 8.06 – 7.94 (m, 2H), 7.86 – 7.72 (m, 2H), 7.56 (m, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 14.8 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.58 – 2.34 (m, 2H), 2.16 (d, *J* = 6.6 Hz, 2H), 1.77 – 1.01 (m, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.00 (C), 176.48 (C), 151.82 (C), 146.64 (C), 138.65 (C), 137.83 (C), 135.21 (CH), 132.88 (CH), 131.44 (C), 129.06 (CH), 124.47 (C), 123.79 (CH), 123.71 (CH), 122.64 (CH), 117.20 (CH), 62.98 (CH_2), 39.19 (C), 29.76 (CH_2), 28.89 (CH_2), 27.76 (CH_2), 27.46 (3xCH_3), 27.07 (CH_2), 26.29 (CH_2), 14.43 (CH_3). **ESI(+)-MS**: m/z(%) = 438 (100) $[M+H]^+$; Anal. Calcd. for $C_{26}H_{31}NO_5$ [437.53]: C, 71.37; H, 7.14; N, 3.20; found C, 71.18; H, 7.11; N, 3.22.

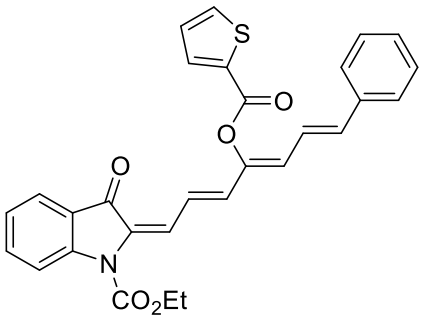
(*E*)-ethyl 2-((2*E*,4*Z*,6*E*)-4-acetoxy-7-phenylhepta-2,4,6-trien-1-ylidene)-3-oxoindoline-1-carboxylate (81i)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl acetate **6g** (48 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 2 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, hexane/ethyl

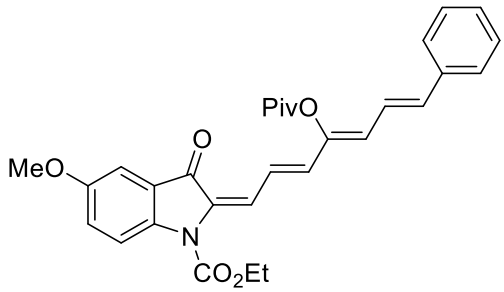
acetate 9:1 to 8:2) yielded **81i** (48 mg, 56%) as a red solid (m.p. 88.2-90.1 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.21 (dd, *J* = 15.0, 12.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.61 (m, 1H), 7.53 – 7.41 (m, 2H), 7.37 – 7.17 (m, 4H), 6.87 (d, *J* = 10.9 Hz, 1H), 6.75 (d, *J* = 15.8 Hz, 1H), 6.62 (d, *J* = 15.0 Hz, 1H), 6.35 (d, *J* = 10.9 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 1.51 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.37 (C), 168.72 (C), 151.73 (C), 146.73 (C), 146.59 (C), 136.81 (C), 136.43 (CH), 135.79 (CH), 135.57 (CH), 132.08 (C), 128.72 (2xCH), 128.47 (CH), 127.74 (CH), 126.94 (2xCH), 125.39 (CH), 124.81 (CH), 124.31 (C), 123.99 (CH), 123.76 (CH), 121.92 (CH), 117.31 (CH), 63.18 (CH_2), (CH_3), 14.42 (CH_3). **ESI(+)-MS**: m/z(%) = 452 (100) $[M+Na]^+$; $C_{26}H_{23}NO_5$ [429.46].

(*E*)-ethyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-((thiophene-2-carbonyl)oxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81j)



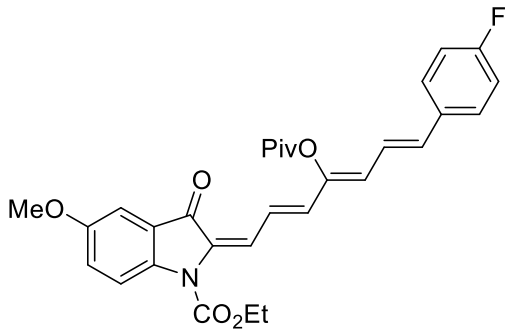
General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46 mg, 0.2 mmol (*E*)-1-phenylpent-1-en-4-yn-3-yl thiophene-2-carboxylate **6h** (65 mg, 0.24 mmol) and JohnPhosSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 22 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1+1% dichloromethane) yielded **81j** (98 mg, 98%) as a red solid (m.p. 172.3-174.5 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.29 (dd, *J* = 15.0, 12.0 Hz, 1H), 8.14 (dd, *J* = 3.7, 1.1 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 12.0 Hz, 1H), 7.79 – 7.70 (m, 2H), 7.56 (m, 1H), 7.43 – 7.36 (m, 2H), 7.34 – 7.14 (m, 5H), 6.95 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.78 (d, *J* = 15.7 Hz, 1H), 6.71 (d, *J* = 15.1 Hz, 1H), 6.46 (d, *J* = 11.0 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.56 (C), 160.12 (C), 152.13 (C), 147.13 (C), 146.59 (C), 137.16 (C), 137.02 (CH), 136.58 (CH), 135.83 (CH), 135.61 (CH), 134.34 (CH), 132.45 (C), 132.40 (C), 129.06 (2xCH), 128.84 (CH), 128.71 (CH), 128.19 (CH), 127.38 (2xCH), 126.04 (CH), 125.39 (CH), 124.67 (C), 124.29 (CH), 124.22 (CH), 122.41 (CH), 117.65 (CH), 63.55 (CH_2), 14.81 (CH_3). **ESI(+)-MS**: m/z(%) = 520 (100) $[M+Na]^+$; $C_{29}H_{23}NO_5S$ [497.56].

(*E*)-ethyl 5-methoxy-3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81k)



General procedure was followed using ethyl 7-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46n** (52 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (58 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 2 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, toluene/ethyl acetate 99:1 to 98:2) yielded **81k** (77 mg, 75%) as a red solid (m.p. 164.2-166.5 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.12 (dd, *J* = 14.9, 12.1 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 12.2 Hz, 1H), 7.45 – 7.08 (m, 7H), 6.85 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.76 – 6.56 (m, 2H), 6.32 (d, *J* = 10.8 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.58 (s, 9H), 1.48 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 183.92 (C), 175.96 (C), 156.43 (C), 151.60 (C), 146.85 (C), 141.25 (C), 136.93 (C), 136.20 (CH), 135.90 (CH), 132.52 (C), 128.73 (2xCH), 128.33 (CH), 127.92 (CH), 126.71 (2xCH), 125.05 (CH), 124.68 (CH), 124.13 (CH), 121.87 (CH), 118.40 (CH), 105.09 (CH), 62.92 (CH_2), 55.77 (CH_3), 39.49 (C), 27.46 (3xCH_3), 14.41 (CH_3), one quaternary carbon is missing, probably overlapping. **ESI(+)-MS**: m/z(%) = 502 (100) $[M+H]^+$; Anal. Calcd. for $C_{30}H_{31}NO_6$ [501.57]: C, 71.84; H, 6.23; N, 2.79; found C, 71.62; H, 6.20; N, 2.80.

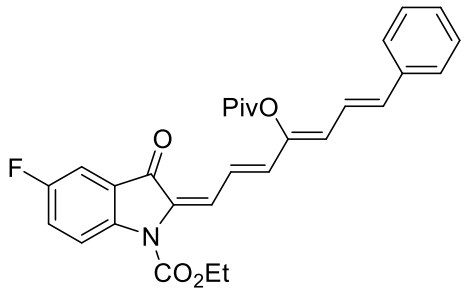
(*E*)-ethyl 2-((2*E*,4*Z*,6*E*)-7-(4-fluorophenyl)-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)-5-methoxy-3-oxoindoline-1-carboxylate (81l)



General procedure was followed using ethyl 7-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46n** (52 mg, 0.2 mmol), (*E*)-1-(4-fluorophenyl)pent-1-en-4-yn-3-yl pivalate **6e** (62 mg, 0.24 mmol) and JohnPhosAuSbF$_6$ (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 2 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5 to 91) yielded **81l** (70 mg, 67%) as a red solid (m.p. 161.5-163.7 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.12 (dd, *J* = 15.0, 12.1 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 1H), 7.79 (d, *J* = 12.1 Hz, 1H), 7.33 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.22 (d, *J* = 2.7 Hz, 1H), 7.15 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.76 – 6.55 (m, 3H), 6.29 (d, *J* = 10.2 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.57 (s, 9H), 1.48 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 183.95 (C), 175.96 (C), 162.69 (d, *J* = 249.1 Hz, C), 156.45 (C), 151.61 (C), 146.86 (C), 141.26 (C), 136.07 (CH), 134.48 (CH), 133.18 (d, *J* = 3.4 Hz, C), 132.57 (C), 128.24 (d, *J* = 8.0 Hz, 2xCH), 127.85 (CH), 125.05 (C), 124.78 (CH),124.75 (CH), 124.17 (CH), 121.63 (CH), 118.41 (CH), 115.79 (d, *J* = 21.9 Hz, 2xCH), 105.10

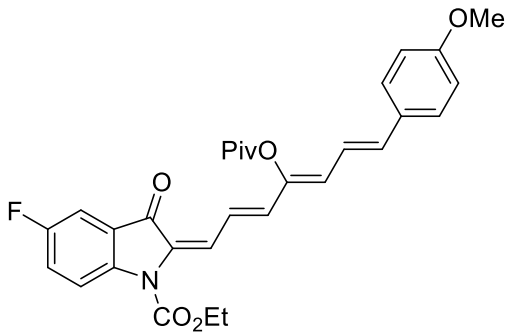
(CH), 62.93 (CH_2), 55.77 (CH_3), 39.49 (C), 27.45 (3xCH_3), 14.41 (CH_3). **ESI(+)-MS**: m/z(%) = 520 (100) $[M+H]^+$; Anal. Calcd. for $C_{30}H_{30}FNO_6$ [519.56]: C, 69.35; H, 5.82; N, 2.70; found C, 69.13; H, 5.84; N, 2.69

(*E*)-ethyl 5-fluoro-3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate (81m)



General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46g** (49 mg, 0.2 mmol), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (97 mg, 0.4 mmol) and [Au(JohnPhos)SbF_6] (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5 to 9:1) yielded **81m** (82 mg, 84%) as a red solid (m.p.144.6-146.1 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.10 (dd, *J* = 14.9, 12.2 Hz, 1H), 7.98 (dd, *J* = 9.0, 3.9 Hz, 1H), 7.78 (d, *J* = 12.1 Hz, 1H), 7.44 (dd, *J* = 6.8, 2.7 Hz, 1H), 7.40 – 7.22 (m, 6H), 6.85 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.76 – 6.59 (m, 2H), 6.33 (d, *J* = 10.9 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.57 (s, 9H), 1.48 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 183.00 (C), 175.98 (C), 159.27 (d, *J* = 245.6 Hz, C), 151.50 (C), 146.77 (C), 142.82 (C), 136.86 (C), 136.83 (CH), 136.20 (CH), 132.15 (C), 128.74 (2xCH), 128.58 (CH), 128.42 (CH), 126.74 (2xCH), 125.49 (d, *J* = 7.7 Hz, C), 125.50 (CH), 124.46 (CH), 122.46 (d, *J* = 24.3 Hz, CH), 121.81 (CH), 118.76 (d, *J* = 7.4 Hz, CH), 109.47 (d, *J* = 23.4 Hz, CH), 63.21 (CH_2), 39.50 (C), 27.43 (3xCH_3), 14.38 (CH_3). **ESI(+)-MS**: m/z(%) = 490 (100) $[M+H]^+$; Anal. Calcd. for $C_{29}H_{28}FNO_5$ [489.53]: C, 71.15; H, 5.77; N, 2.86; found C, 71.43; H, 5.75; N, 2.85.

(*E*)-ethyl 5-fluoro-2-((2*E*,4*Z*,6*E*)-7-(4-methoxyphenyl)-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)-3-oxoindoline-1-carboxylate (81n)

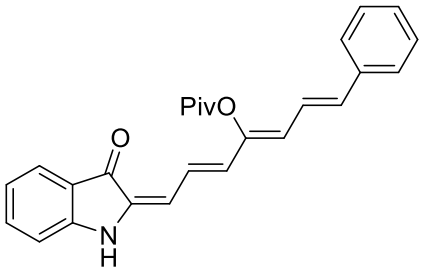


General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46g** (49 mg, 0.2 mmol), (*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-yl pivalate **6d** (109 mg, 0.4 mmol) and JohnPhosAuSbF_6 (7.7 mg, 0.01 mmol) in anhydrous toluene (2+2 mL) at -20 °C for 1 h, followed by isomerization with I_2 for 4 h at rt. Purification by flash chromatography (SiO_2, dichloromethane/hexane 95:5) yielded **81n** (102 mg, 98%) as a red solid (m.p. 175.9-177.6 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.22 – 7.94 (m, 2H), 7.77 (d, *J* = 12.1 Hz, 1H), 7.43 (dd, *J* = 6.9, 2.7 Hz, 1H), 7.36 – 7.24 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.76 – 6.55 (m, 3H), 6.31 (d, *J* = 9.3 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.81

(s, 3H), 1.57 (s, 9H), 1.48 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 182.94 (C), 176.00 (C), 160.01 (C), 159.25 (d, J = 245.5 Hz, C), 151.49 (C), 145.98 (C), 142.74 (C), 137.10 (CH), 136.03 (CH), 131.92 (C), 129.75 (C), 128.86 (CH), 128.15 (2xCH), 126.05 (CH), 125.55 (d, J = 7.6 Hz, C), 123.87 (CH), 122.35 (d, J = 24.2 Hz, CH), 119.82 (CH), 118.73 (d, J = 7.4 Hz, CH), 114.28 (2xCH), 109.40 (d, J = 23.3 Hz, CH), 63.17 (CH_2), 55.28 (CH_3), 39.48 (C), 27.45 (3xCH_3), 14.38 (CH_3). **ESI(+)-MS**: m/z(%) = 542 (100) $[M+Na]^+$; Anal. Calcd. for $C_{30}H_{30}FNO_6$ [519.56]: C, 69.35; H, 5.82; N, 2.70; found C, 69.64; H, 5.80; N, 2.69.

2.3.5.2.5 Preparation of products 81o, 83a-b, 84 and 85

(1*E*,3*Z*,5*E*,7*E*)-7-(3-oxoindolin-2-ylidene)-1-phenylhepta-1,3,5-trien-4-yl pivalate (81o)

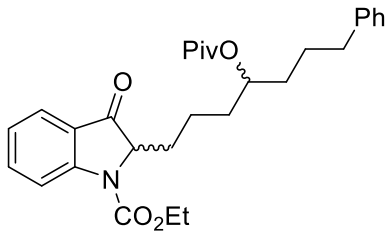


To a solution of (*E*)-tert-butyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate **81d** (57 mg, 0.11 mmol) in dichloromethane (1 ml), trifluoroacetic acid (0.1 mL) was added. The mixture was stirred at room temperature for 2 h, then the reaction was quenched with 1 N sodium hydroxide aqueous solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 3:1) to yield (1*E*,3*Z*,5*E*,7*E*)-7-(3-oxoindolin-2-ylidene)-1-phenylhepta-1,3,5-trien-4-yl pivalate **81o** (30 mg, 68%) as a red solid (m.p. 198.2-200.1 °C).

Alternatively, **81o** was prepared from **81a** according to the following procedure. To a solution of (*E*)-ethyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate **81a** (35 mg, 0.07 mmol) in methanol (0.7 ml), K_2CO_3 (10 mg, 0.07 mmol) was added. The mixture was stirred at 60 °C for 2 h, then the reaction extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 3:1) to yield (1*E*,3*Z*,5*E*,7*E*)-7-(3-oxoindolin-2-ylidene)-1-phenylhepta-1,3,5-trien-4-yl pivalate **81o** (8 mg, 29%). **^{1}H NMR** (300 MHz, DMSO): 10.06 (s, 1H), 7.63 – 7.23 (m, 7H), 7.06 (d, J = 8.0 Hz, 1H),6.94 – 6.65 (m, 4H), 6.64 – 6.52 (m, 1H), 6.51 – 6.42 (m, 2H), 1.43 (d, J = 24.0 Hz, 9H). **^{13}C NMR** (75 MHz, DMSO): 185.70 (C), 175.93 (C), 152.89 (C), 146.98 (C), 136.99 (C), 136.49 (CH), 136.41 (C), 135.80 (CH), 133.25 (CH), 129.43 (2xCH), 128.92 (CH), 126.99 (2xCH), 124.47 (CH), 124.07 (CH), 123.09 (CH), 121.95 (CH), 121.16 (C), 120.00 (CH), 112.49 (CH), 110.94 (CH), 139.50 (C) 27.57

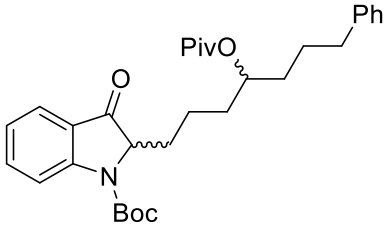
(3xCH$_3$). **ESI(+)-MS**: m/z(%) = 400 (100) $[M+H]^+$; Anal. Calcd. for $C_{26}H_{25}NO_3$ [399.48]: C, 78.17; H, 6.31; N, 3.51; found C, 77.95; H, 6.30; N, 3.53.

Ethyl 3-oxo-2-(7-phenyl-4-(pivaloyloxy)heptyl)indoline-1-carboxylate (83a)



To a solution of (*E*)-ethyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate **3a** (70 mg, 0.15 mmol) in ethyl acetate, Pd/C (7 mg, 10% wt) was added. The reaction mixture was stirred under H_2 at room temperature overnight, then was filtered over a pad of celite and the solvent was evaporated under reduce pression. The crude residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1) to yield ethyl 3-oxo-2-(7-phenyl-4-(pivaloyloxy)heptyl)indoline-1-carboxylate **5a** as a mixture of two diastereoisomers (45 mg, 63%, 1:1) as a pale oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 8.14 (s, 2H), 7.71 (dd, *J* = 7.7, 3.5 Hz, 2H), 7.68 – 7.58 (m, 2H), 7.33 – 7.22 (m, 4H), 7.22 – 7.08 (m, 8H), 4.86 – 4.74 (m, 2H), 4.44 – 4.22 (m, 6H), 2.67 – 2.49 (m, 4H), 2.32 – 1.96 (m, 4H), 1.66 – 1.45 (m, 12H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.30 – 1.17 (m, 4H), 1.14 (s, 9H), 1.11 (s, 9H). Most signals are overlapped for two diastereoisomers. **^{13}C NMR** (75 MHz, $CDCl_3$): 199.57 (C), 199.39 (C), 178.41 (2xC), 152.42 (2xC), 142.48 (4xC), 137.46 (CH), 137.34 (CH), 128.70 (3xCH), 128.67 (3xCH), 126.13 (4xCH), 124.63 (2xC) 124.15 (CH), 124.03 (CH), 123.71 (CH), 123.64 (CH), 117.28 (CH), 117.24 (CH), 73.24 (CH), 72.93 (CH), 65.54 (2xCH), 62.80 (CH_2), 62.76 (CH_2), 39.16 (C), 39.14 (C), 35.97 (2x CH_2), 34.40 (CH_2), 34.30 (CH_2), 34.13 (CH_2), 33.98 (CH_2), 31.14 (CH_2), 30.98 (CH_2), 27.52 (3xCH_3), 27.50 (3xCH_3), 27.32 (CH_2), 27.28 (CH_2), 19.29 (CH_2), 19.02 (CH_2), 14.92 (CH_3), 14.90 (CH_3). **ESI(+)-MS**: m/z(%) = 502 (100) $[M+Na]^+$; $C_{29}H_{37}NO_5$ [479.27].

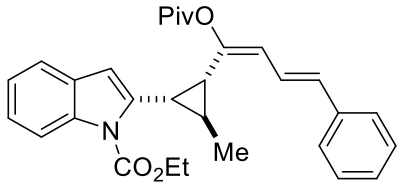
***Tert*-butyl 3-oxo-2-(7-phenyl-4-(pivaloyloxy)heptyl)indoline-1-carboxylate (83b)**



To a solution of (*E*)-tert-butyl 3-oxo-2-((2*E*,4*Z*,6*E*)-7-phenyl-4-(pivaloyloxy)hepta-2,4,6-trien-1-ylidene)indoline-1-carboxylate **3d** (88 mg, 0.17 mmol) in ethyl acetate, Pd/C (9 mg, 10% wt) was added. The reaction mixture was stirred under H_2 at room temperature overnight, then was filtered over a pad of celite and the solvent was evaporated under reduce pression. The crude residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) to yield **5b** as a mixture of two diastereoisomers (41 mg, 47%, 1:1) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 8.09 (bs, 2H), 7.71 – 7.64 (m, 2H), 7.60 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 2H), 7.30 – 7.21 (m, 4H), 7.19 – 7.04 (m, 8H), 4.85 – 4.72 (m, 2H), 4.23 (bs, 2H), 2.60 – 2.51 (m, 4H), 2.16 – 2.00 (m, 4H), 1.64 – 1.43 (m, 34H), 1.11 (s, 9H), 1.08 (s, 9 H). Most

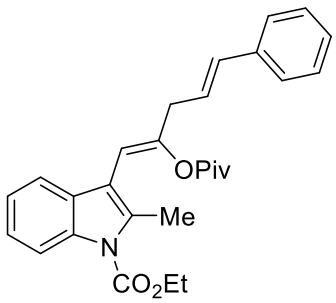
signals are overlapped for two diastereoisomers. **^{13}C NMR** (75 MHz, $CDCl_3$): 199.28 (2xC), 177.98 (2xC), 150.88 (2xC), 142.08 (2xC), 136.93 (2xCH), 128.29 (3xCH), 128.25 (3xCH), 125.70 (4xCH), 124.16 (2xC), 123.67 (CH), 123.58 (CH), 122.95 (CH), 122.89 (CH), 116.85 (CH), 116.75 (CH), 82.42 (2xC), 72.90 (CH), 72.82 (CH), 65.21 (2xCH), 38.74 (2xC), 35.58 (2xCH_2), 34.09 (CH_2), 34.02 (CH_2), 33.57 (2xCH_2), 30.84 (2xCH_2), 28.32 (6xCH_3), 27.11 (3xCH_3), 27.08 (3xCH_3), 26.86 (2xCH_2), 18.92 (CH_2), 18.82(CH_2). 2 quaternary carbons are missing, probably overlapped. **ESI(+)-MS**: m/z(%) = 530 (100) $[M+Na]^+$; $C_{31}H_{41}NO_5$ [507.66].

Ethyl 2-(2-methyl-3-((1*Z*,3*E*)-4-phenyl-1-(pivaloyloxy)buta-1,3-dien-1-yl)cyclopropyl)-1*H*-indole-1-carboxylate (84)



To a N_2-flushed solution of (*E*)-ethyl 2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4** (46 mg, 0.2 mmol) and JohnPhosAuSbF_6 (5 mol%) in anhydrous toluene (2 mL), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (97 mg, 0.4 mmol) in toluene (2 mL, final concentration 0.05 M) was added dropwise at -20 °C. The reaction mixture was stirred for 1 h at -20 °C and then quenched with PPh_3 (15 mol%). Purification by flash chromatography (SiO_2, hexane/ ethyl acetate 98:2) yielded **84** (41 mg, 43%) as a yellow oil. **^{1}H NMR** (300 MHz, CD_2Cl_2): 7.99 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.44 (m, 3H), 7.42 – 7.34 (m, 2H), 7.31 – 7.10 (m, 4H), 6.46 (d, *J* = 15.6 Hz, 1H), 6.37 (s, 1H), 5.89 (d, *J* = 11.3 Hz, 1H), 4.43 – 4.18 (m, 2H), 2.89 (dd, *J* = 8.1, 6.4 Hz, 1H), 2.35 (dd, *J* = 8.6, 5.6 Hz, 1H), 1.77 (m, 1H), 1.46 – 1.27 (m, 6H), 1.12 (s, 9H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 176.28(C), 151.80 (C), 148.19 (C), 139.13 (C), 137.63 (C), 136.42 (C), 131.81 (CH), 129.09 (C),128.55 (2xCH), 127.35 (CH), 126.27 (2xCH), 123.41 (CH), 123.24 (CH), 122.61 (CH), 120.37 (CH), 119.79 (CH), 115.42 (CH), 107.60 (CH), 63.06 (CH_2), 38.68 (C), 29.00 (CH), 27.95 (CH), 26.70 (3xCH_3), 19.65 (CH), 17.74 (CH_3), 13.99 (CH_3). **ESI(+)-MS**: m/z(%) = 494 (100) $[M+Na]^+$; Anal. Calcd. for $C_{30}H_{33}NO_4$ [471.59]: C, 76.41; H, 7.05; N, 2.97; found C, 76.25; H, 7.02; N, 2.98

Ethyl 2-methyl-3-((1*Z*,4*E*)-5-phenyl-2-(pivaloyloxy)penta-1,4-dien-1-yl)-1*H*-indole-1-carboxylate (85)



To a N_2-flushed solution of (*E*)-ethyl 2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate**14** (46 mg, 0.2 mmol) and [Au(JohnPhos)SbF_6] (5 mol%) in anhydrous toluene (2 mL), (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate **6a** (97 mg, 0.4 mmol) in toluene (2 mL, final concentration 0.05 M) was added dropwise at -20 °C. The reaction mixture was stirred for 1 h at -20 °C and then quenched with PPh_3 (15 mol%). Purification by flash chromatography (SiO_2, hexane/ ethyl acetate 98:2) yielded **85** (44 mg, 50%) as a yellow oil. **^{1}H NMR**

(300 MHz, C_6D_6): 8.52 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.81 (dd, *J* = 6.5, 2.2 Hz, 1H), 7.53 – 6.90 (m, 7H), 6.58 (d, *J* = 15.7 Hz, 1H), 6.35 (dt, *J* = 15.8, 7.0 Hz, 1H), 6.09 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.47 (d, *J* = 7.0 Hz, 2H), 2.65 (s, 3H), 1.16 – 0.88 (m, 12H). **^{13}C NMR** (75 MHz, C_6D_6): 175.46 (C), 151.78 (C), 151.07 (C), 137.39 (C), 136.09 (C), 134.69 (C), 133.53 (CH), 129.47 (C),128.64 (3xCH), 126.37 (2xCH), 125.15 (CH), 123.84 (CH), 122.90 (CH), 119.99 (CH), 115.72 (CH), 114.21 (C), 108.30 (CH), 62.47 (CH_2), 38.68 (C), 37.62 (CH_2), 26.75 (3xCH_3), 14.90 (CH_3), 13.75 (CH_3). **ESI(+)-MS**: m/z(%) = 446 (100) $[M+H]^+$; $C_{28}H_{31}NO_4$ [445.55].

2.3.5.2.6 UV analysis for compound 81a, 81'a, 81d and 81'd

The determination of UV-Vis spectra was made for compounds **81a**, **81'a**, **81d** and **81'd**. In order to obtain the UV-Vis spectra, standard solution with 2.35 mg of **81a** and **81'a** in 10 mL volumetric flask and 1.25 mg of **81d** and **81'd** in 5 mL volumetric flask were prepared in toluene, tetrahydrofuran and dimethylsulfoxide. The standard solutions were used for the preparation of 10^{-4}-10^{-5} solutions of each compound. The extinction coefficients were determined using *Lambert-Beer* law after the determination of UV-Vis spectra using Agilnt 1453E and open top UV quartz cell, 10 mm, 3.0 ml vol.

In the conversion experiments two solutions of pure **81'a** and **81'd** at the concentration of $2 \cdot 10^{-5}$ in dimethylsulfoxide were prepared. Experiments were conducted in a rotaflo-equipped quartz cuvette and the cuvette was irradiated with a 200 W lamp for a period of 6h. Measurements have been taken every 20 minutes to monitor the isomerization. Relative concentrations of *E* and *Z* isomers in the reaction mixture were calculated using *Lambert-Beer* law by the following equation (1):

$$[E]_t = \frac{A_t - \varepsilon_Z C_0}{\varepsilon_E - \varepsilon_Z}$$

Where:

$[E]_t$ = concentration of the *E* isomer at time t;

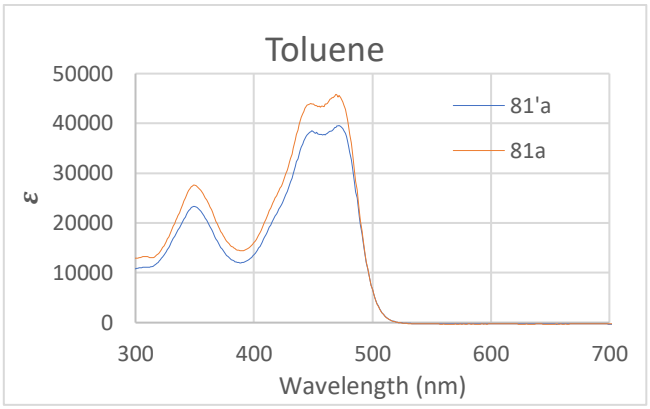
A_t = Absorbance at time t at 354 nm;

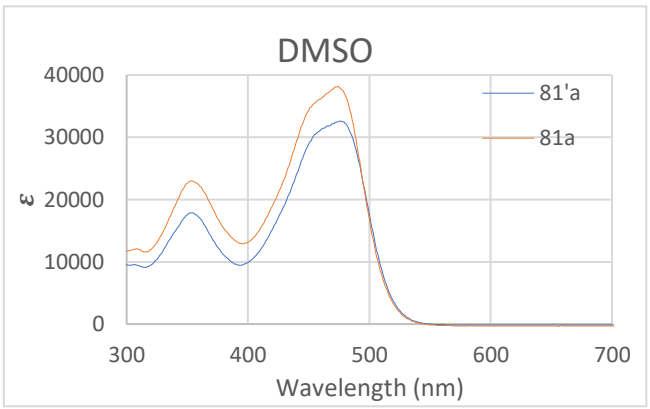
ε_Z = molar extinction coefficient for the isomer *Z* at 354 nm;

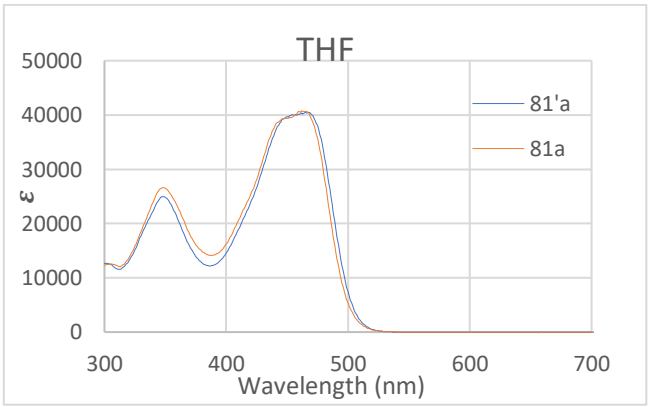
ε_E = molar extinction coefficient for the isomer *E* at 354 nm;

C_0 = starting concentration of **81'a** or **81'd**, respectively

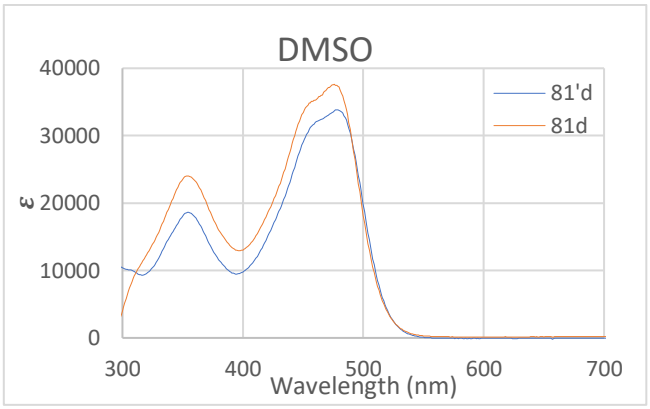
The following diagrams represent the molar extinction coefficient for **81a** and **81'a** in toluene, DMSO and THF obtained with linear regression method.

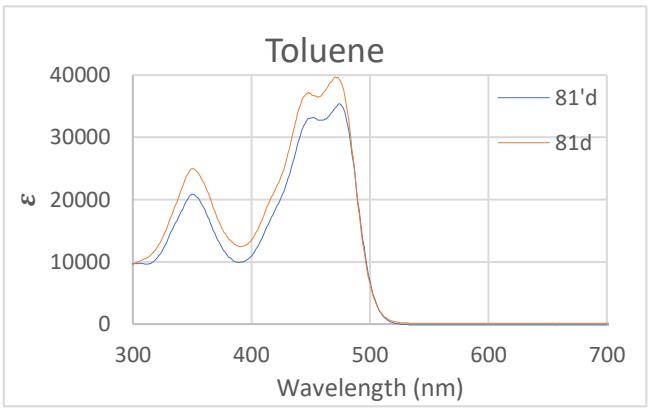


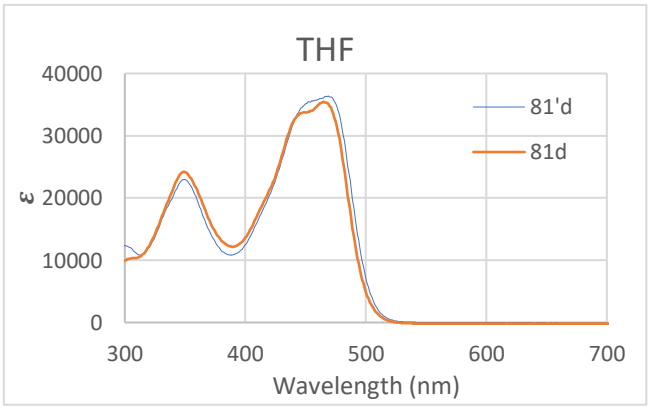




The following diagrams represent the molar extinction coefficient for **81d** and **81'd** in toluene, DMSO and THF obtained with linear regression method.


DMSO
40000
30000
20000
10000
0
ε
300
400
500
600
700
Wavelength (nm)
81'd
81d


Toluene
40000
30000
20000
10000
0
ε
300
400
500
600
700
Wavelength (nm)
81'd
81d


THF
40000
30000
20000
10000
0
ε
300
400
500
600
700
Wavelength (nm)
81'd
81d

Chapter 3. Copper catalyzed synthesis of complex indole derivatives from 4*H*-furo[3,2-*b*]indoles

The work described in this chapter has been published in *ChemCatChem,* **2020**, *12*, 5250-5255 as "Synthesis of 2-alkenylidene-3-oxoindolines: cascade reactions of 4*H*-furo[3,2-*b*]indoles with diazoacetates catalyzed by a Cu(I) macrocyclic pyridine-containing ligand (PcL) complex".

3.1 Homogeneous copper catalysis for the generation of copper carbenes

Homogeneous copper catalysis is known from long time as a powerful tool in organic synthesis.[129–131] Unlike gold, for copper the relativistic effects on the properties of the metal and its salts are negligible. The main consequence is the possibility of interaction with the substrate as a Lewis acid or with π-coordination chemistry, leading to the development of a rich chemistry and to a lot of different transformations.[132]

The electronic properties of copper atom and copper catalysts

Copper is a metal atom that pertains to the 11 group and period 4 of the periodic table with an electronical configuration [Ar]$3d^{10}4s^{1}$ (figure 3.1).

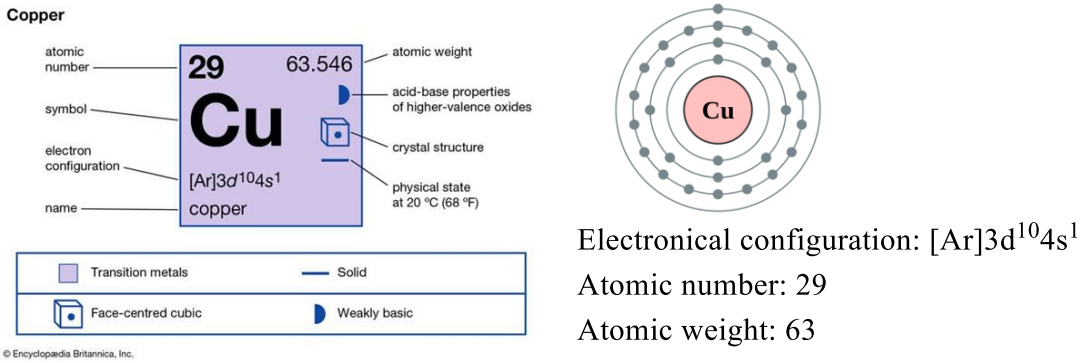


Figure 3.1

Copper presents four different oxidation states: Cu(0), Cu(I), Cu(II) and copper(III). These different oxidation states allow copper to take part in one-electron or two-electron processes. Thus, the organocopper intermediates can follow radical or two-electron bond-forming pathways. Recently copper zero-valent nanoparticles has been employed in catalysis thanks to their relatively low cost, low environmental impact, good performance and high selectivity.[133] Copper(III) represent a high valent copper intermediate with an important role in copper catalyzed cross-coupling and organocuprate reactions. However, the isolation of copper(III) intermediates is not easy and the study of transformations that involve this high valent catalyst is difficult and only few examples are reported in the literature.[134] The most employed copper catalysts are Cu(I) and Cu(II) that catalyze a series of different reactions such as all the variants of Ullmann coupling, cross-coupling reactions for the formation of both carbon–carbon and carbon–heteroatom bonds, additions to multiple bonds and nucleophilic substitutions, selective oxidations, cyclopropanations, cycloadditions and

aziridinations.[129–131,135] The following paragraph deals with the application of copper(I) carbene complexes in synthetic organic chemistry.

3.1.1 Copper carbene complexes from diazo compounds

Transition metal carbene complexes are organometallic compounds possessing a M=CR^2 double bond and represent a class of compounds of increasing significance in organic synthesis. Two types of transition metal carbene complexes can be identified and distinguished: Fischer carbene complexes and Schrock carbene complexes.[136–139] They present a different electronic distribution of the electrons in the bond of the CR^2 group to the metal. In the free form, a carbene carbon atom has two distinct spin isomers: singlet and triplet with different electronic distribution between the orbitals of the C*sp2* carbon atom. In the singlet state two electrons are paired in the *sp2* orbital leaving the p_z orbital unoccupied whereas in the triplet state both the *sp2* and *p* orbitals are singly occupied, (figure 3.2)

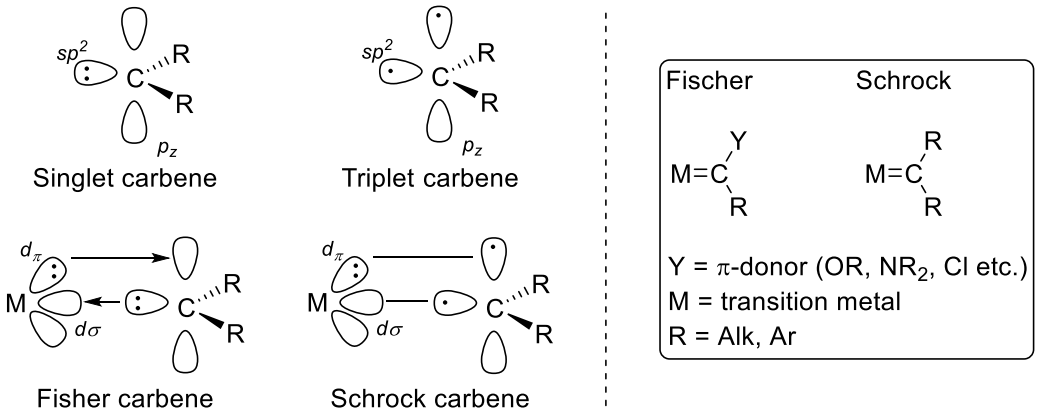


Figure 3.2

Therefore, when a metal is bound to a carbene two different situations can occur. In the Fischer case, direct carbon to metal donation predominates and the carbon tends to be positively charged. In the Schrock case, two covalent bonds are formed, each polarized toward the carbon giving it a negative polarization and a nucleophilic character. Typical substituent arrangements of both Fischer and Schrock carbenes are reported in figure 3.2. When copper is involved as a metal the corresponding copper carbene complexes are classified as Fischer-type metal carbenes. The σ lone pair of the carbene donates to the vacant *d* orbital of the metal, and simultaneously π-back-donation occurs from the metal *d* orbital to the unoccupied carbene *p*-orbital, which together form the metal-carbon bond in the Fischer-type metal carbene complex.[140,141] Fischer-type carbene complexes are generally formed with transition metals with low oxidation states, and presents heteroatom (π-donor) substituents on carbene center (normally alkoxy or amino groups) in order to stabilize the complex. The carbene center in Fischer-type carbene complexes is electrophilic reacting with nucleophiles.

Apart from stabilizing donor substituents, the reactivity of Fisher carbenes can be modulated by different substituents on the carbenic carbon atom. Depending on the nature of the substituents they are classified as acceptor, acceptor/acceptor and donor/acceptor species (figure 3.3). The presence of electron-acceptor groups (EAG) induces an increase in the reactivity in nucleophilic addition, causing a loss in selectivity.

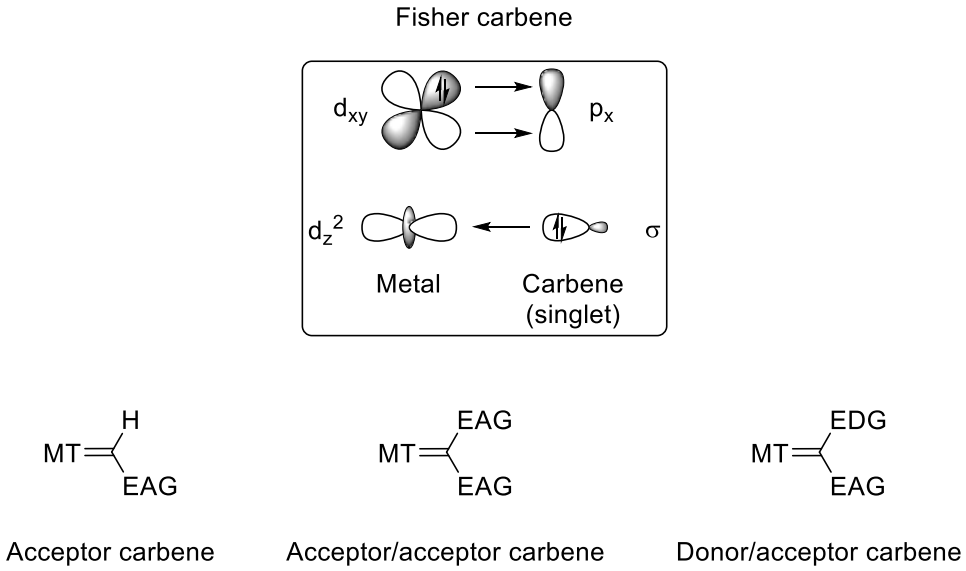
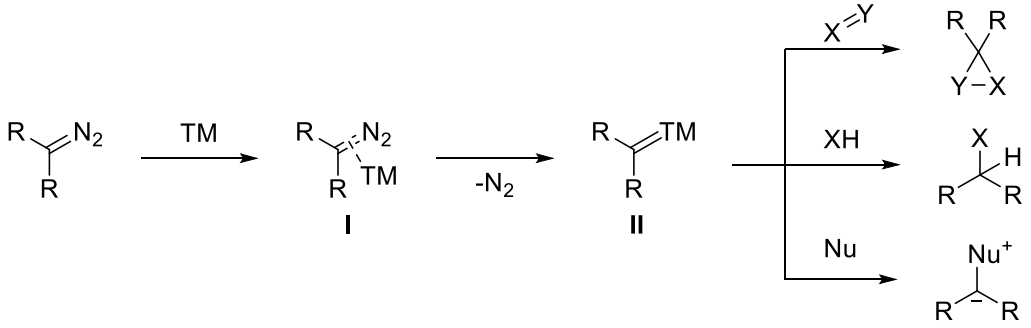


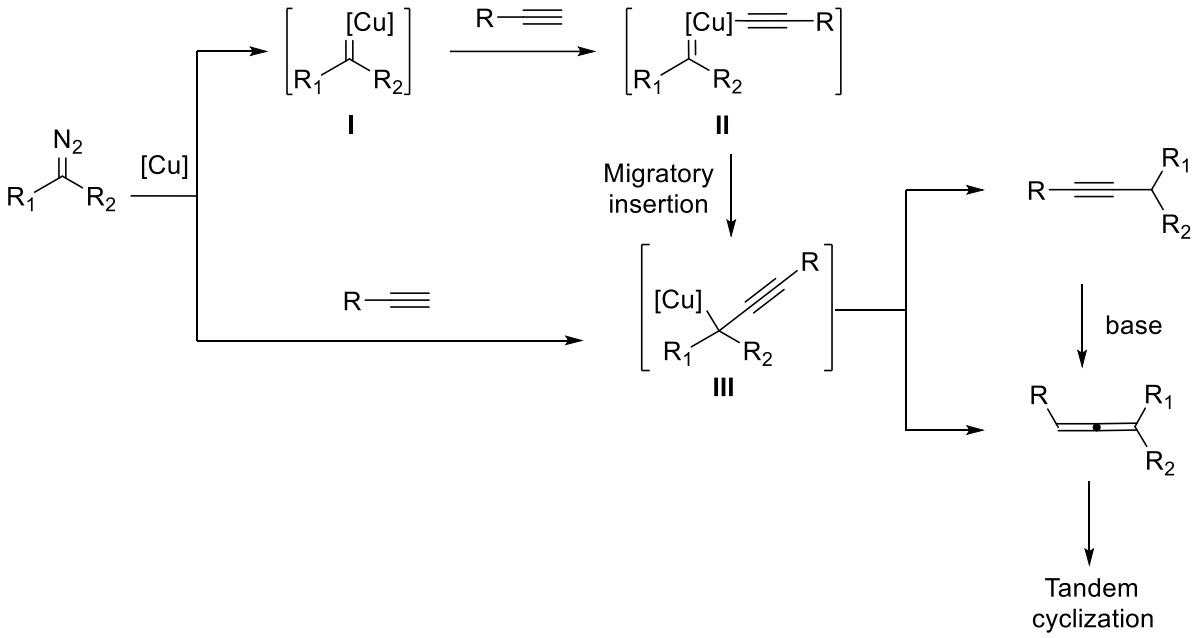
Figure 3.3

The easiest way to generate carbenes is from the decomposition of diazo compounds in the presence of a transition metal able to generate a metal-stabilized carbene. Depending on the type of metal involved, the carbene intermediate can react with alkenes, alkynes, arenes or imines giving rise to three-membered rings. Moreover, it can take part in reaction of X-H insertion, with C-H, SiH, O-H or N-H. Furthermore, the electrophilic carbene after a nucleophilic attack by a generic nucleophile Nu, can generate ylide species, conceivably involved in subsequent transformations (scheme 3.1).[142]



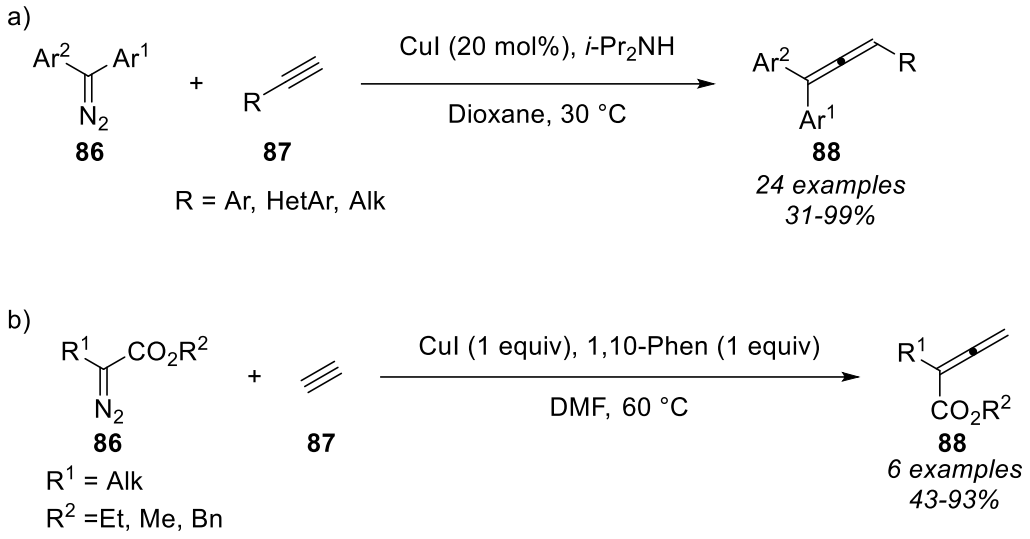
Scheme 3.1

The copper carbenes have been employed in a huge number of cross-coupling synthesis of allene derivatives from diazocompounds and terminals alkynes.[143,144] The copper-catalyzed cross-coupling of diazo compounds with terminal alkynes affords copper-carbene intermediate **II** from the direct attack of the terminal alkyne on the copper carbene **I** from diazo compound. Successively, the formation of intermediate **III** is obtained by the migratory insertion. The same intermediate **III** can be obtained from the copper acetylide reaction with copper carbene **I**. Thus, intermediate **III** undergoes protonation that allows for the generation of the C-C bond giving rise to the alkyne product or the isomerized allene (scheme 3.2). Moreover, the allene product can undergo tandem cyclization reaction to afford hetero- and carbocycle compounds in the presence of suitable reaction partners.



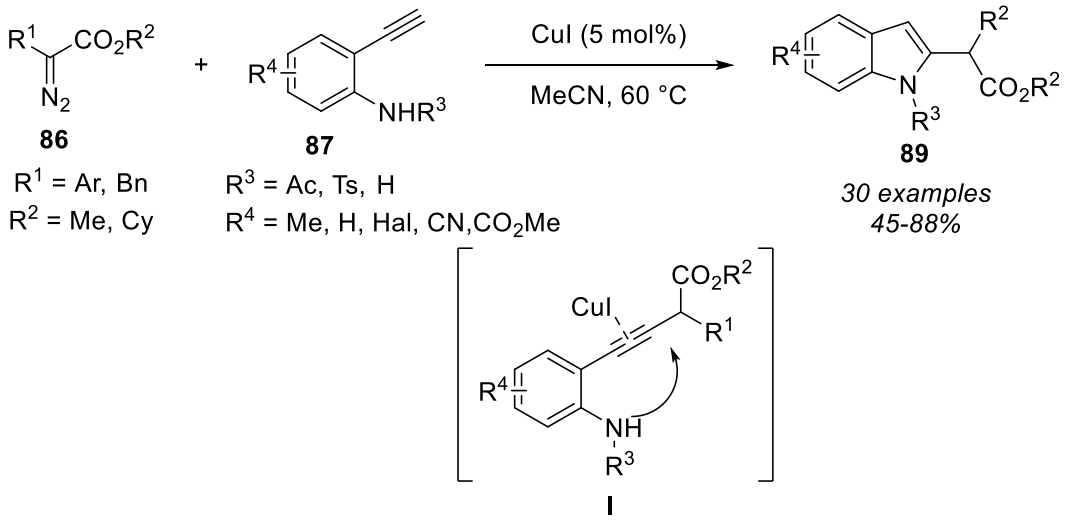
Scheme 3.2

In 2015 the research group of Wang reported the synthesis of tri-aryl-substituted allenes **88** under CuI catalysis from diazocompounds **86** and alkynes **87**.[145] This transformation represented an easy way for the synthesis of allenes because of the employment of ligand free and cheap CuI catalyst. In addition, the reaction presented a wide substrate scope at relatively low temperature, resulting in an atom economy process (molar ratio 1:1 between the starting materials, scheme a) 3.3). Successively, the same group showed a more challenging synthesis of terminal allenes always under CuI catalysis with the addition of the 1,10-phenantroline ligand (scheme b) 3.3).[146]



Scheme 3.3

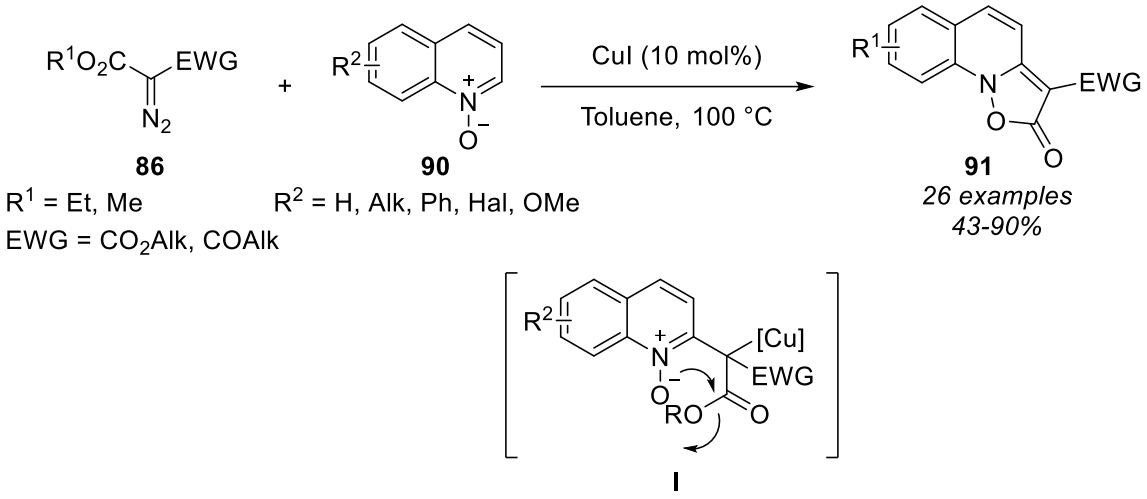
In 2014 Sun and co-workers reported the tandem cross-coupling/cyclization reaction of diazo esters **86** and 2-ethynylanilines **87** for the synthesis of C2-functionalized indoles **89** with good functional group tolerance in moderate to good yields (scheme 3.4).[147] In this transformation, the presence of a strong base was not required, preserving sensitive substrates. In addition, the formation of the indole derivative occurred through the copper-activation of the alkyne moiety, resulting from the migratory insertion of the carbene, by intramolecular cyclization with the nitrogen nucleophile.



Scheme 3.4

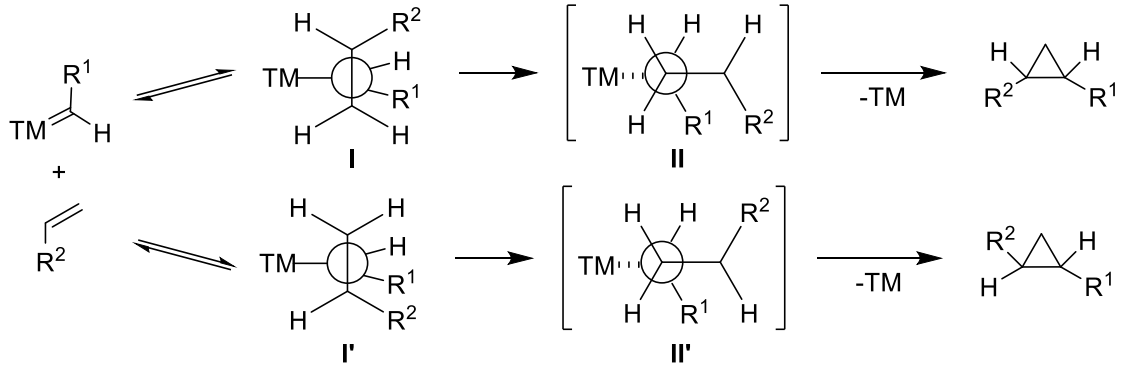
Copper carbenes are involved also in C-H activation reactions.[139] In particular, copper carbenes are employed with arenes, especially heteroarenes bearing soft acidic protons. A particular example was reported by Samanta and co-workers in 2016. They proposed a copper catalyzed reaction of quinoline

N-oxides **90** with diazo esters **86** for the synthesis of heteroarene-containing π-systems **91**.[148] This reaction proceeds starting from the formation of the C-H carbene coupling intermediate that undergoes the nucleophilic attack by the negative oxygen with release of a molecule of alcohol (scheme 3.5).



Scheme 3.5

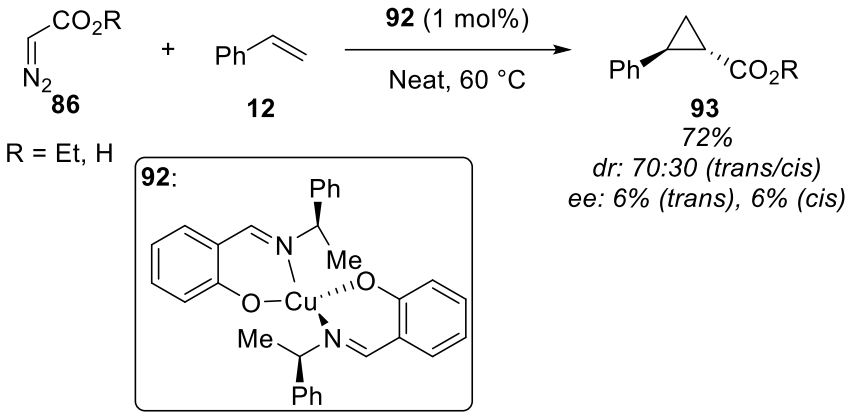
Furthermore, the reactivity of copper carbenes is exploited for the construction of cyclopropyl rings starting from alkenes.[136] The formation of the three-member cycle starts with interaction of the alkene π-bond with the electrophilic center of the metal-carbene complex allowing for the formation of intermediates **I** and **I'**. Next σ-bond formation is promoted by the backside displacement of the catalyst from intermediates **II** and **II'**. Thus, the steric and the electronic interactions between the π-system and the carbene intermediate influence the stereochemistry of the reaction (scheme. 3.6).



Scheme 3.6

One of the first examples of alkene cyclopropanation was proposed by Nozaki group in 1966. They reported on the cyclopropanation of styrene **12** using ethyl diazo acetate **86** and salicylaldimine–

copper complex **92** (scheme 3.7).[149] The transformation represents one of the first examples of asymmetric cyclization even if the enantiomeric excess was quite low.



Scheme 3.7

Some year later, Pfaltz proposed new chiral anionic ligands with a semicorrin scaffold that catalyzed the cyclopropanation of styrene inducing good enantioselectivities. Successively many others structurally different chiral ligands have been developed and tested in the cyclopopanation reaction of styrene. The main structures for these ligands are based on bis(oxazoline), bipyridine-derived or diamine derivatives (figure 3.4).[130]

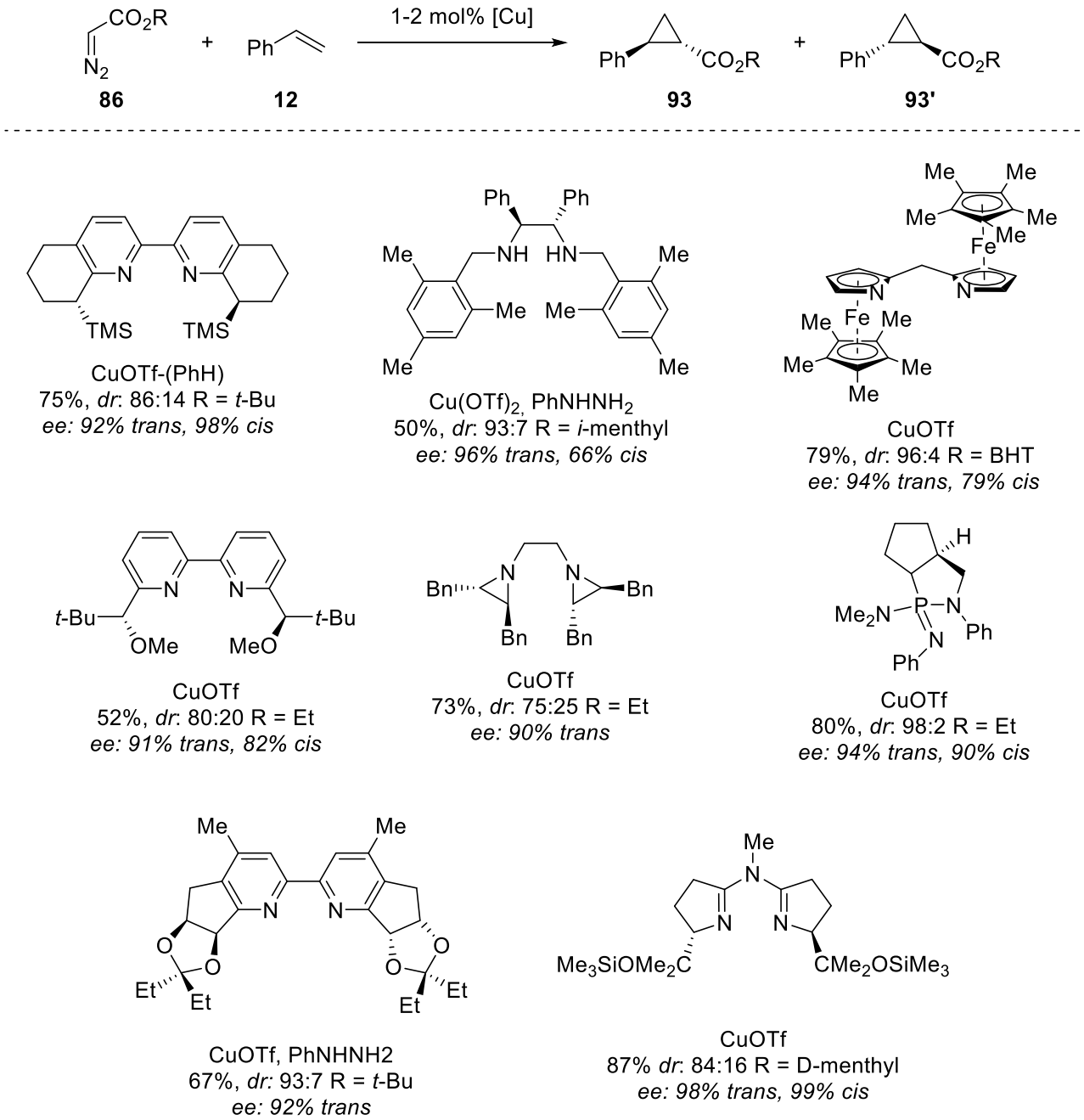
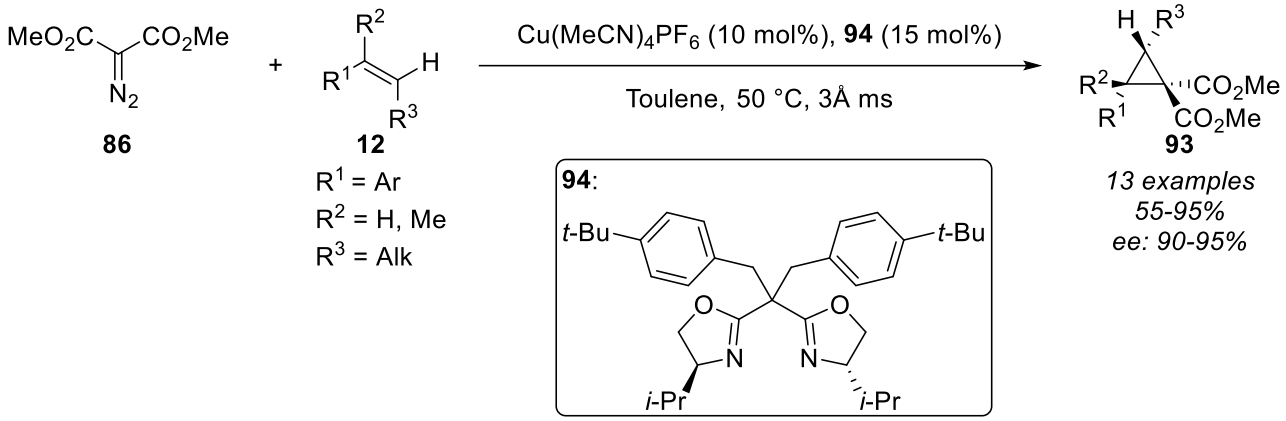


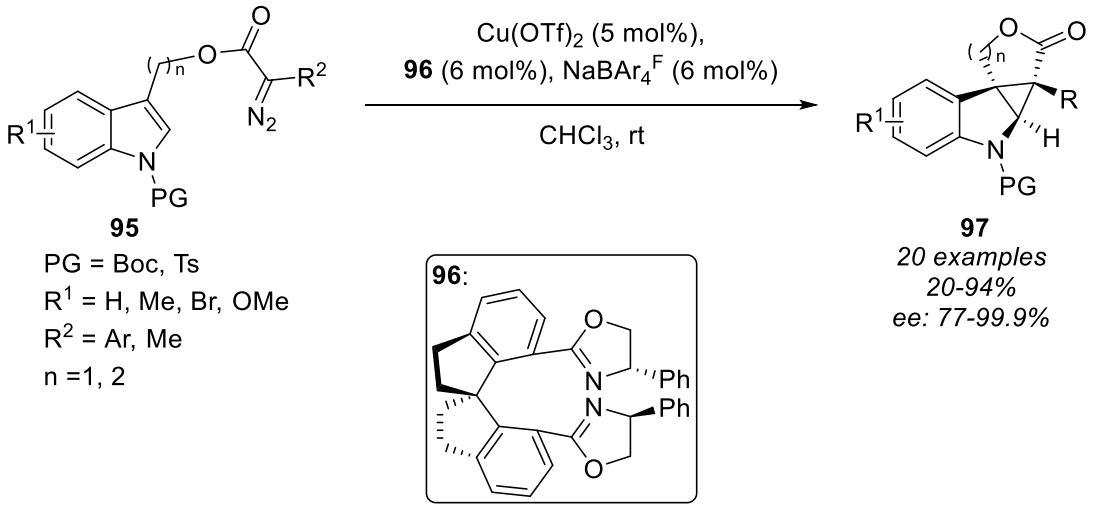
Figure 3.4

More recently, Zhang and co-workers realized the first enantioselective cyclopropanation of internal olefins **12** with diazomalonates **86**.[150] The research group underlined the excellent results in term of yield and scope and the high level of enantioselection achieved using a chiral bi-side arm bisoxazoline **94** as ligand for the copper(I) complex (scheme 3.8).



Scheme 3.8

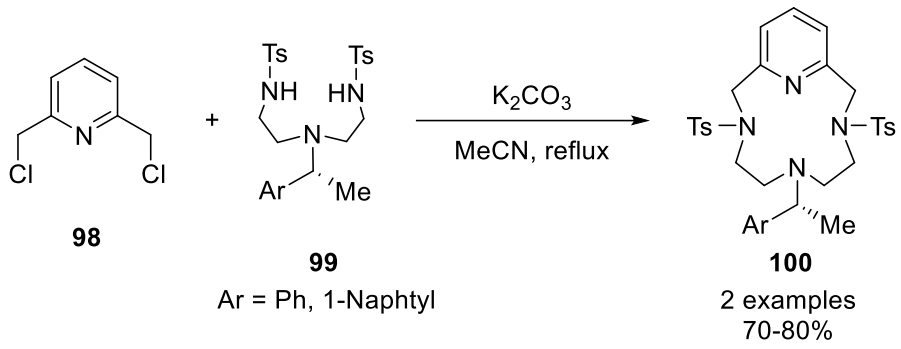
In 2017 Zhou and co-workers reported the first intramolecular enantioselective cyclopropanation of indoles **95**, proposing an efficient strategy for the construction of high complex polycyclic indole derivatives **97** bearing all-carbon quaternary stereogenic center at the indole skeleton (scheme 3.9).[151] Using the chiral bisoxazoline ligand **96** for copper, they were able to reach excellent enantiomeric excesses.



Scheme 3.9

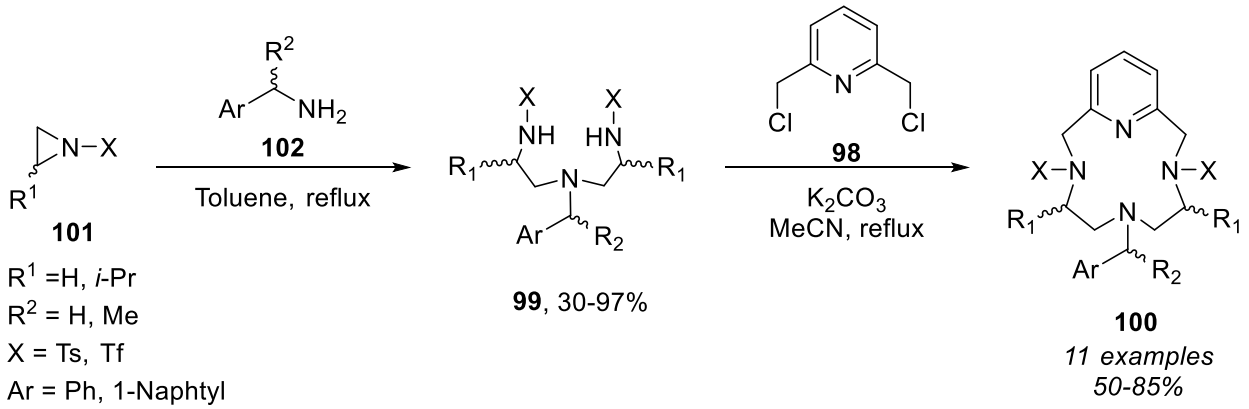
3.1.2 Pyridine-containing macrocycles copper(I) complexes in cyclopropanation reactions

In 2008 Caselli and co-workers reported the synthesis and the characterization of copper(I) complexes generated in the presence of a new class of 12-membered pyridine-containing tetraaza macrocyclic ligands **100** (PcL).[152] PcL ligands can be easily synthesized in few steps and starting from commercially available and cheap starting materials. The crucial key step is the formation of the 12-member ring realized by reaction between 2,6-bis(chloromethyl)pyridine **98** and bis(sulfonamide) **43** in anhydrous acetonitrile and in the presence of anhydrous potassium carbonate (scheme 3.10).



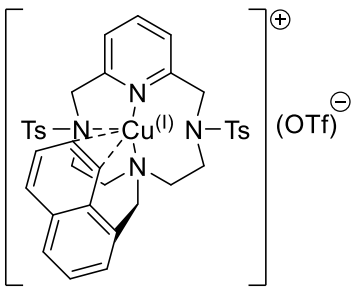
Scheme 3.10

Successively, in 2013, the same group realized the synthesis of different 12-member macrocycle ligands of increasing complexity.[153] The synthesis started with the formation of bis-sulfonamides **99** achieved in good yields by reaction of primary amines **102** with aziridines **101**. The heterogeneous reaction conditions led to the isolation of the cyclization products **100** up to 94% yield. Moreover, it was possible to obtain the macrocycles as enantiomerically pure compounds starting from chiral amines or chiral aziridines, leading to the final synthesis of optically pure ligands for enantioselective transformations (scheme 3.11).



Scheme 3.11

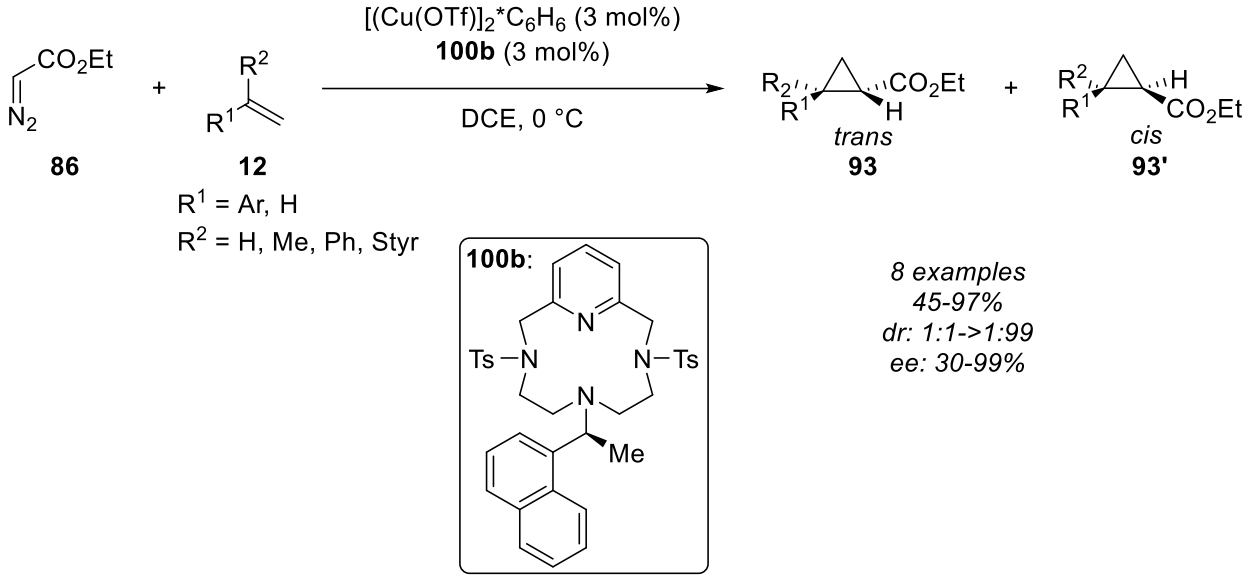
A peculiarity of these ligands is related to the presence of the tosyl group bounds to the nitrogen atom. In fact, it plays the double role of protecting group and electron-withdrawing center. Furthermore, the tosyl group induces a more flexible coordination sphere around metal because of the presence of two strongly coordinating nitrogen donor atoms and two less basic *N*-tosyl donor atoms. Several derivatives were also characterized by X-ray diffraction studies. For example, the naphtyl derivative **100a** in figure 3.5, presents tetracoordination geometry for the copper(I) atom which is placed into the cavity of the macrocyclic ligand. In principle, five potential coordination sites (the four nitrogens and the naphthyl moiety) are present in this complex. The favorite four coordination mode is due to steric reasons inducing a shift of the metal on one side of the macrocycle with consequent generation of a strongly distorted trigonal bipyramidal geometry in the complex structure. In addition, the presence of a naphtyl moiety adds another possible coordinating point that allowed a better stabilization of copper ion (figure 3.5).



$Cu^{(I)}$100a

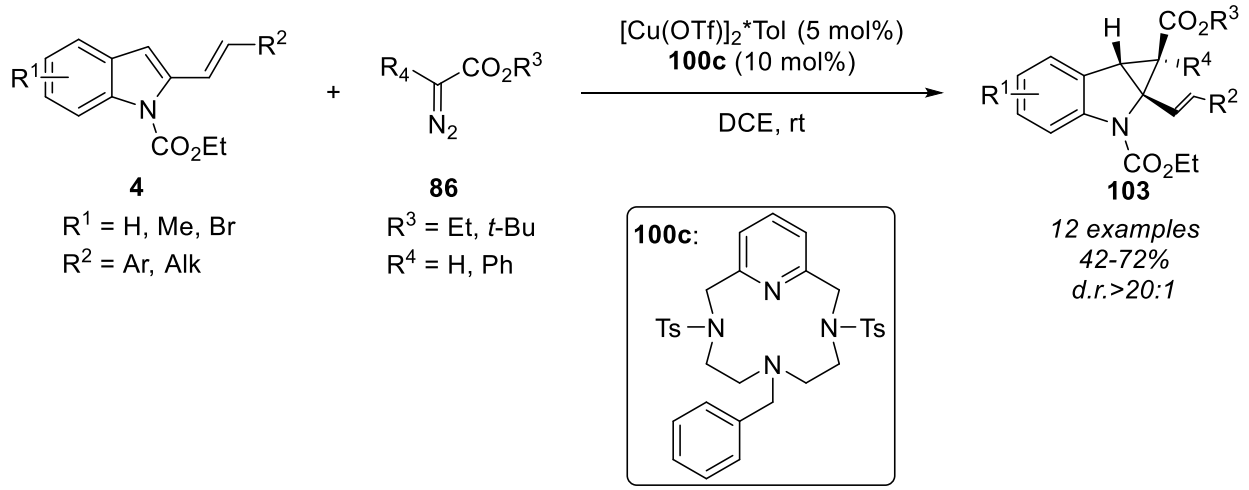
Figure 3.5

The catalytic system, copper(I)-**100b** complex, was tested for the enantioselective cyclopropanation of alkenes **12** with ethyl diazo acetate **86**. Even if the reached diastereoselectivity was modest, the cyclopropanated products **93** and **93'** were obtained in high yields with excellent enantiomeric excesses with both aliphatic and aromatic alkenes (scheme 3.12).



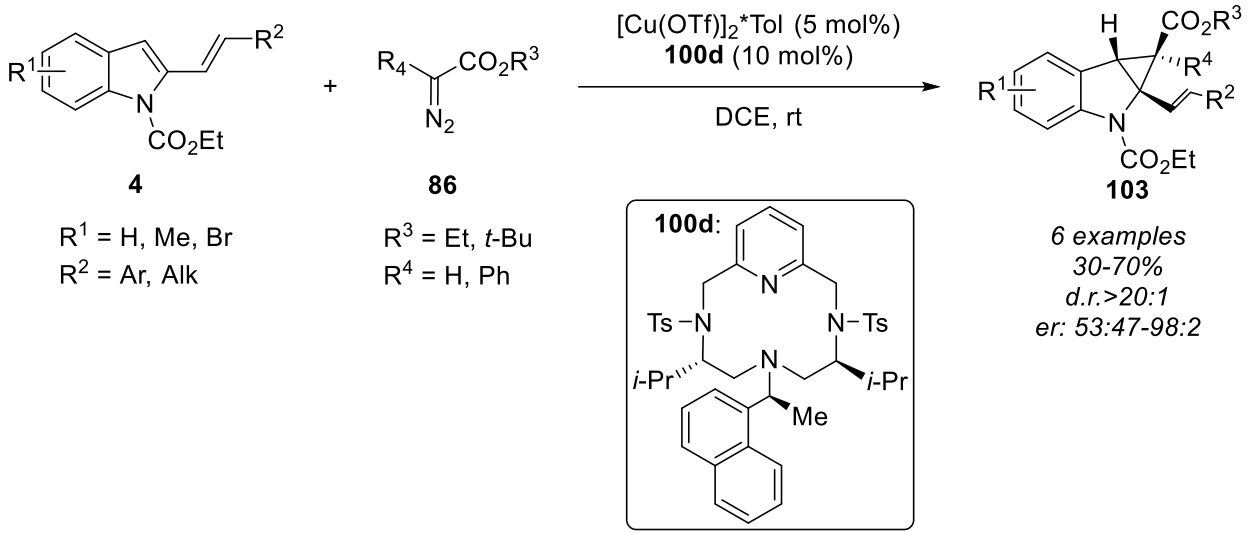
Scheme 3.12

Recently, our research group reported the cyclopropanation of 2-vinylindoles **4** using diazo compounds **86** and the previously reported copper(I)-**100c** complex (scheme 3.13).[30] The reaction was completely regioselective for the endo-cyclic double bond and completely diasteroselective leading to a new class of polycyclic indole derivatives **103**.



Scheme 3.13

In addition, as reported before, pyridine-containing ligands can be prepared in chiral form introducing different chiral groups on the macrocycle. Thus, performing the reaction using the chiral ligand **100d**, 2-cyclopropyl[*b*]indolines **103** could be also prepared with high degree of enantioselection (scheme 3.14).

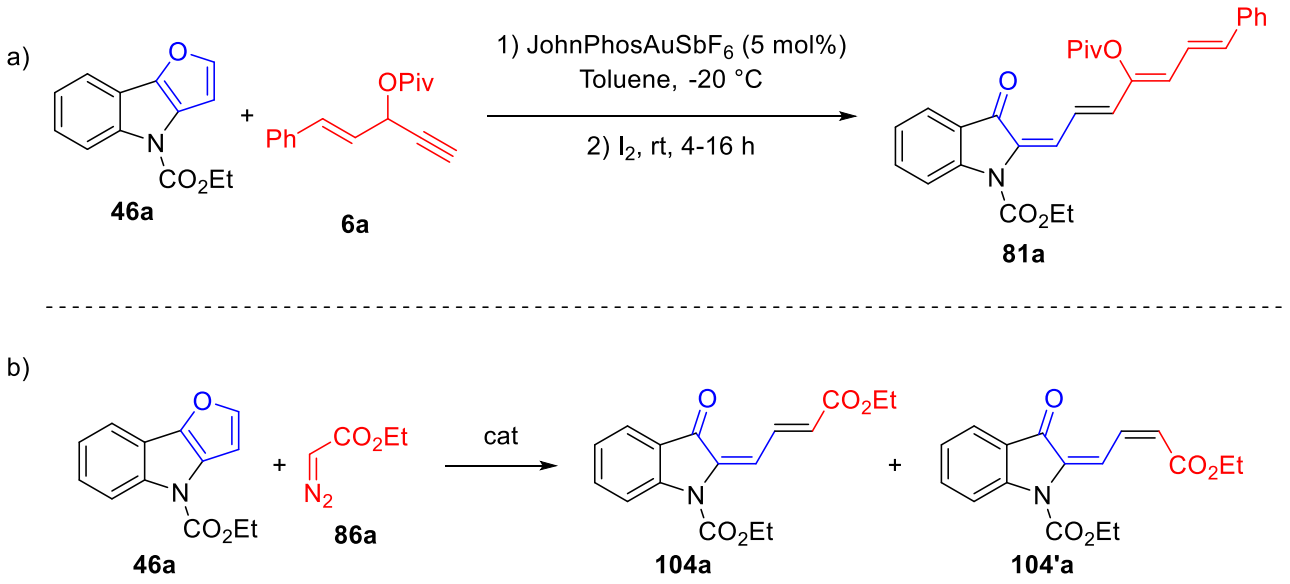

R1
R2
N
CO2Et
4
+
R4
CO2R3
N2
86
[Cu(OTf)]2*Tol (5 mol%)
100d (10 mol%)
DCE, rt
100d:
Ts
N
Ts
i-Pr
i-Pr
Me
H
CO2R3
R4
R1
R2
N
CO2Et
103
R1 = H, Me, Br
R2 = Ar, Alk
R3 = Et, t-Bu
R4 = H, Ph
6 examples
30-70%
d.r.>20:1
er: 53:47-98:2

Scheme 3.14

3.2 Synthesis of 2-alkenylidene-3-oxoindoles from diazo compounds and 4*H*-furo[3,2-*b*]indoles

3.2.1 Objectives

Taking into account the previously reported studies on the reactions of diazo compounds under copper catalysis and our recent interest in the cyclopropanation of 2-vinylindoles using Cu(I)-PcL complexes,[30] we decided to test the reactivity of 4*H*-furo[3,2-*b*]indoles in presence of diazo compounds under copper catalysis. In particular, in 2019 we reported the synthesis of 2-alkenylidene-3-oxoindoles **81** from 4*H*-furo[3,2-*b*]indoles **46** and gold(I) carbenes generated from propargyl esters **6**, see chapter 2 section 2.3.[154] These reactions furnished the desired compounds in excellent yields but are effective only when a styryl moiety was embedded in the starting propargyl ester (scheme 3.15a). Extending the reactivity of 4*H*-furo[3,2-*b*]indoles to copper carbene complexes could permit the synthesis of homologous compounds bearing a less extended conjugate system (scheme 3.15b).



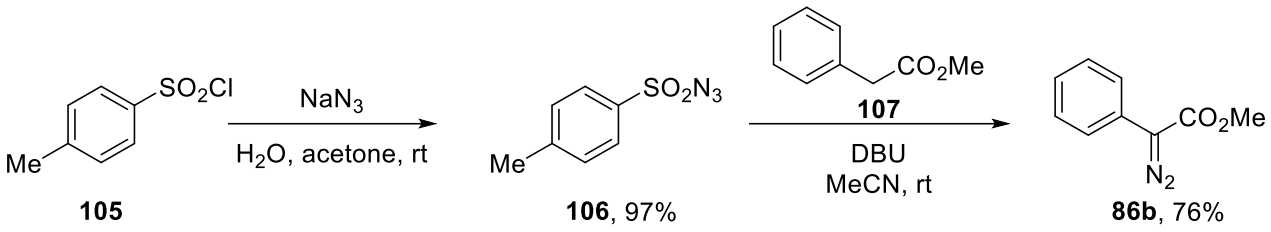
Scheme 3.15

3.2.2 Synthesis of starting materials

In this work of thesis, ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a,f,g,l-p**, as well as diazo compounds **86a,b**, both bearing groups with different electronic properties, have been synthetized and used. In addition, the copper(I) complex **100a** was synthesized.

*3.2.2.1 Synthesis of methyl 2-diazo-2-phenylacetate **86b***

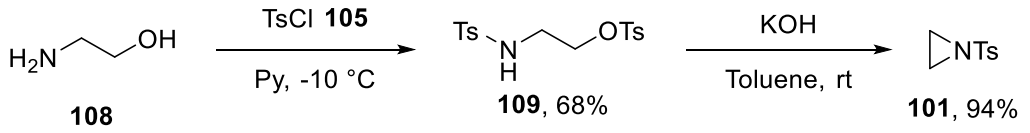
Methyl 2-diazo-2-phenylacetate **86b** is a known compound and was prepared according literature procedure.[155] The synthesis started with the preparation in excellent yield of tosyl azide **106** from tosyl chloride **105** and sodium azide. Sequentially, the azide **106** was converted in good yield into the methyl 2-diazo-2-phenylacetate **86b** using DBU and methyl 2-phenylacetate **107** (scheme 3.176.



Scheme 3.16

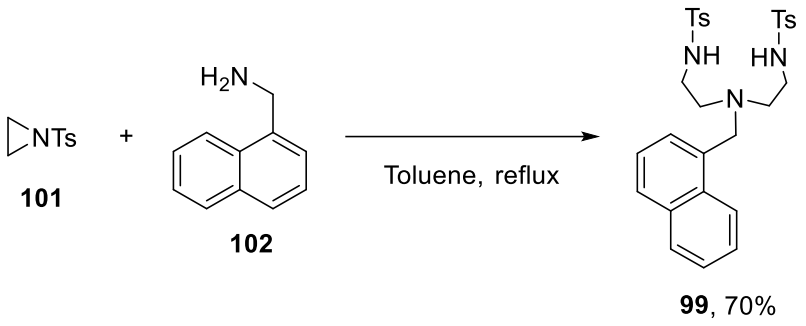
*3.2.2.2 Synthesis of copper complex Cu$^{(I)}$**100a***

The pyridine-containing macrocyclic ligand **100a** is a known compound and was prepared according to literature procedure.[153] The synthesis started with the preparation of the *N*-tosylaziridine **101** from ethanolamine **108** by double nitrogen and oxygen tosylation followed by base catalyzed intramolecular cyclization (scheme 3.17).



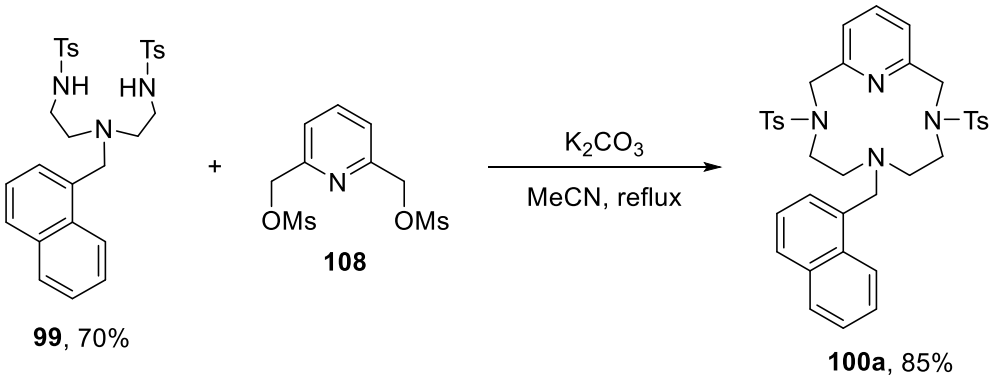
Scheme 3.17

Successively, two equivalents of aziridine **101** were reacted with the primary 1-naphthylmethylamine **102** in toluene. The reaction gave rise to the bis(sulfonamide) **99** in good yield (scheme 3.18)



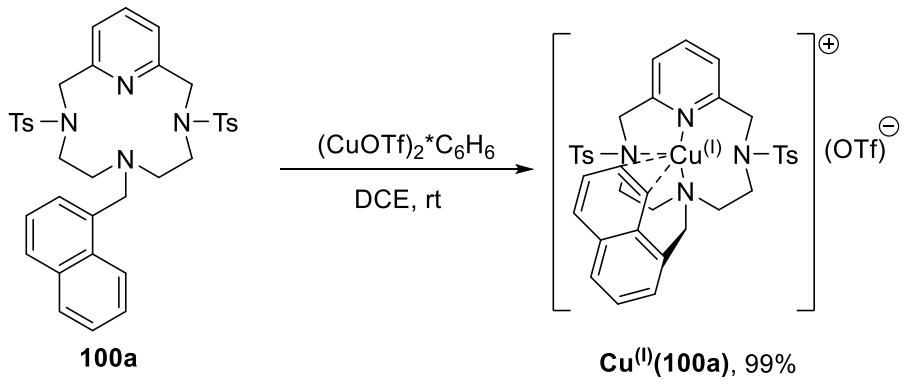
Scheme 3.18

Then, by reacting 2,6-bis(methanesulfonyloxymethyl)pyridine **108** with *bis*-sufonamide **99** in anhydrous acetonitrile and in the presence of anhydrous potassium carbonate, the macrocyclic derivative **100a**, was obtained in 85% yield (scheme 3.19).



Scheme 3.19

Finally, the synthesis of the copper complex Cu(I)(**100a**) was realized by treating the macrocyclic ligand **100a** with copper(I) triflate benzene complex in anhydrous DCE for one hour at room temperature. The isolated Cu(I)(**100a**), obtained in excellent 99% yield, is stable under controlled conditions and can easily undergo oxidation of the metal core if stored under air (scheme 3.20).



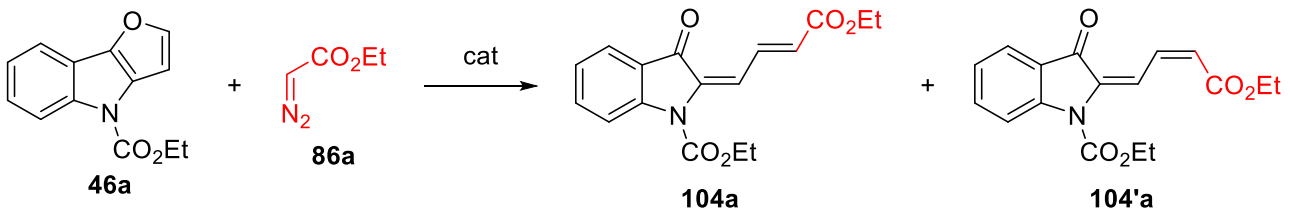
Scheme 3.20

3.2.3 Copper catalyzed reactions between diazo compounds and 4*H*-furo[3,2-*b*]indoles

*3.2.3.1 Initial studies and screening of the reaction conditions for the synthesis of compound **104a***

At the outset, furoindole **46a** and diazo compound **86a** were chosen as model compounds for the synthesis of 2-(penta-2,4-dien-1-ylidene) 3-oxoindoline derivatives **104a** and **104'a**. The decomposition of ethyldiazoacetate **86a** to the corresponding metal carbene was performed in the presence of different transition metals under different reaction conditions. The obtained results are summarized in Table 3.1.

*Table 3.1 Optimization of reaction conditions for the synthesis of **104a***

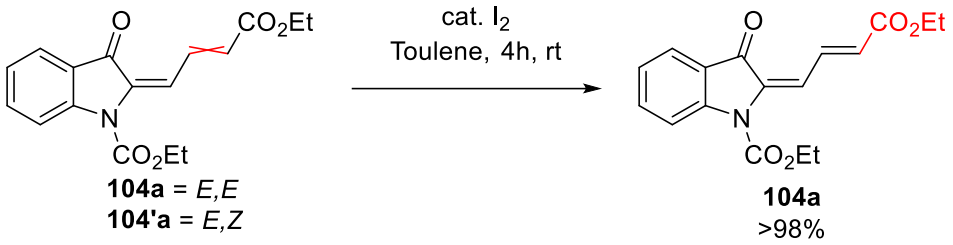


Entry	Catalyst	Solvent (M)	Equiv 86a	T (°C)	Time (h)	104a,[b] %	104',[b] %
1	$Rh_2(Oct)_4$ 2.5 mol%	DCM, 0.05	2[c]	rt	1.5	49	20
2	$Rh_2(Oct)_4$ 1 mol%	DCM, 0.05	2[c]	rt	1.5	41	17
3	JohnPhosAuSbF$_6$ 5 mol%	DCM, 0.05	2[c]	rt	1.5	/[d]	/
4	IPrAuCl 5 mol% $NaBAr_F$ 5 mol%	DCM, 0.1	2[e]	rt(2h) 40 (3h)	5	/[d]	/
5	$(ArO)_3PAuNTf_2$ 5 mol%	DCM, 0.1	2[e]	rt(2h) 40 (3h)	5	/[d]	/
6	$Cu(OTf)_2$ 15 mol% Ph-$NHNH_2$ 15 mol%	DCM, 0.05	2[c]	rt	1.5	29	12
7	$Cu(OTf)_2$ 8 mol%	DCE, 0.07	1.5[f]	rt	2	19	6
8	$(CuOTf)_2$*C_6H_6 (5 mol%) **100a** (10 mol%)	DCE, 0.07	2.5[f]	rt	1	75	12
9	$Cu^{(I)}$(**100a**) (8 mol%)	DCE, 0.07	1[f]	rt	1	30	6

10	$Cu^{(I)}$(**100a**) (8 mol%)	DCE, 0.07	1.5[g]	rt	2	74	25

[a]All reactions were carried out using **46a** (0.2 mmol) and **86a** (0.2-0.5 mmol) in the stated solvent (0.1-0.05 M) in the presence of 4 Å MS. [b]Isolated yield. [c]**86a** added with syringe pump in 1h in 1 ml of solvent. [d]**46a** and **86a** recovered unreacted at the end of the reactions. [e]**86a** added manually dropwise. [f]**86a** added with syringe pump in 1h in 2 ml of solvent. [g]**86a** added with syringe pump in 2h in 2 ml of solvent. [h]$Rh_2(Oct)_4$ = rhodium(II) octanoate dimer. JohnPhos = (2-Biphenyl)di-tert-butylphosphine IPr = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]. Ar = 2,4-di-t-butylphenyl.

At the beginning, classical dirhodium octanoate dimer complex was investigated for its well-known ability to induce the formation of Rh(II)-carbene intermediates from diazo compounds.[156] Thus, a solution of **86a** was slowly added to a solution of furoindole **46a** and rhodium complex, allowing for the isolation of a separable mixture of E/Z isomeric 2-(penta-2,4-dien-1-ylidene)-3-oxoindolines **104a** and **104'a** in a 2.5:1 ratio and in an overall 69% yield after 1.5 hours (entry 1). The structure of the two isomers was assigned by mono-dimensional NMR analysis. Successively, the catalyst loading was decreased resulting in a slight reduction of the total yield (entry 2). Next, different catalytic systems, based on cationic gold(I) complexes, were investigated.[157] Firstly, cationic JohnPhosAuSbf$_6$ was employed, resulting in the quantitative recovery of the starting materials (entry 3). Successively, other two cationic gold catalysts were tested, namely IPrAuBAr$_F$, and [(2,4-di-*t*-Bu-$C_6H_3O)_3$PAu]NTf$_2$. However, both catalysts were ineffective in promoting the desired transformation also after prolonged heating (entries 4 and 5). Shifting the catalytic system to copper, some improvements were obtained. Thus, copper(II) triflate was employed with and without the presence of a reducing agent. In both cases, the isolation of the two isomers **104a** and **104'a** was possible, but in unsatisfying low yields (entries 6 and 7). Then, the copper(I) triflate/**100a** complex, formed *in situ* from the corresponding copper(I) chloride/**100a** complex by chloride abstraction with silver triflate, was tested and fortunately the two isomers **104a** and **104'a** were isolated in overall 86% yield and in a diastereoisomeric ratio of 6.25:1 (entry 8). In order to optimize the equivalent of **86a** employed, the reaction was performed with the isolated copper(I) triflate/**100a** complex and by slow addition, *via* a syringe pump, of 1 or 1.5 equivalents of **86a** (entries 9 and 10). In the first case, the yield was reduced, while in the second case the reaction gave almost quantitative overall yield of **104a** and **104'a** in a diastereoisomeric ratio of 3:1. As reported for 3-oxo-2-(hepta-2,4,6-trien-1-yilidene)indolines **81** in chapter 2.3, it was possible to promote the transformation of the diastereoisomeric mixture of **104a** and **104'a** into pure **104a** isomer by treating the crude reaction mixture with iodine. The conversion reached the completeness in 4 hours (scheme 3.21).

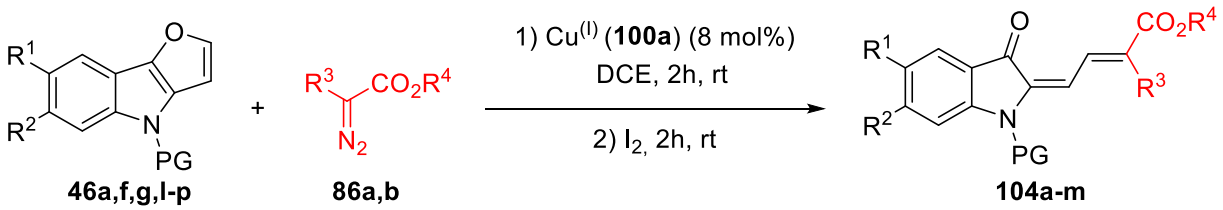


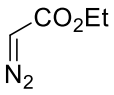
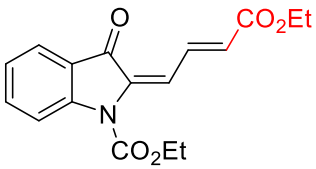
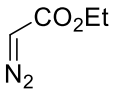
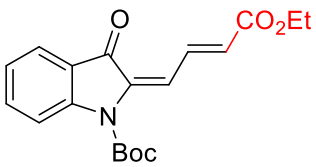
Scheme 3.21

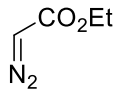
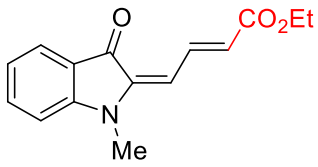
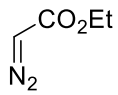
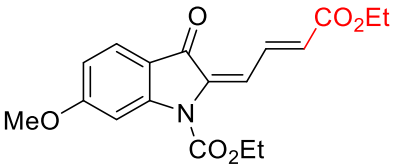
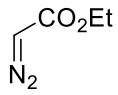
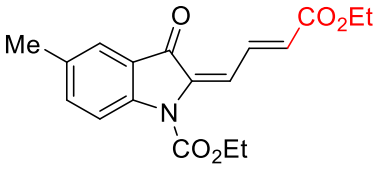
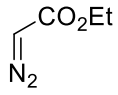
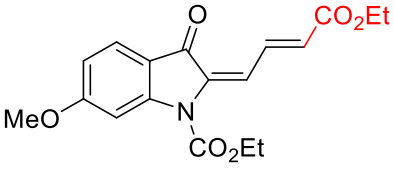
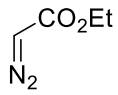
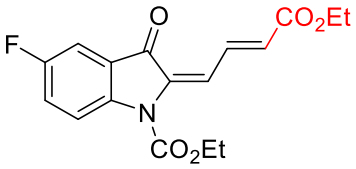
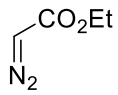
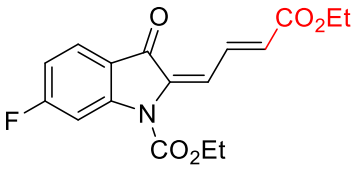
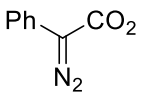
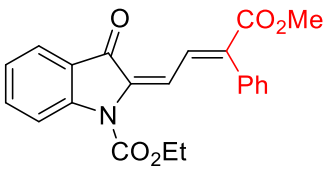
*3.2.3.2 Scope for the synthesis of 2-alkenylidene-3-oxoindoles **104***

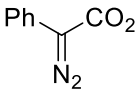
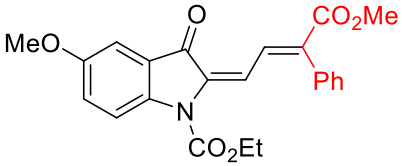
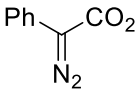
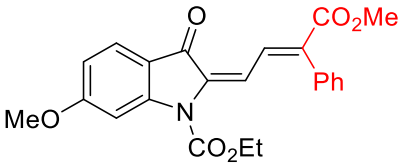
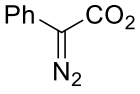
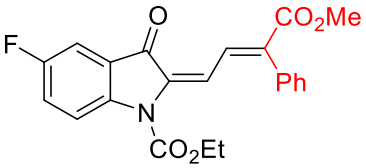
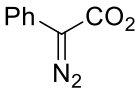
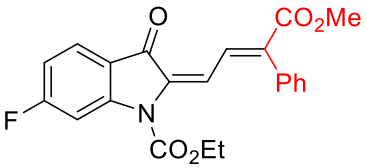
Having the best reaction conditions in hands (Table 3.1, entry 10), the scope and the limitations for this transformation were investigated using 4*H*-furo[3,2-*b*]indoles **46a,f,g,l-p**, bearing substituents with different electronic properties, and diazo compounds **86a-b**. As reported before, each reaction was treated with iodine before the purification in order to obtain the single isomers **104a-m**. The results are summarized in table 3.2

*Table 3.2 Scope for the synthesis of compound **104a-m***



Entry	1	PG	R^1	R^2	2	Product	Yield,[b] %
1	**46a**	CO_2Et	H	H	 **86a**	 **104a**	99
2	**46l**	Boc	H	H	 **86a**	 **104b**	68

3	**46m**	Me	H	H	 **86a**	 **104c**	77
4	**46n**	CO_2Et	OMe	H	 **86a**	 **104d**	73
5	**46f**	CO_2Et	Me	H	 **86a**	 **104e**	94
6	**46o**	CO_2Et	H	OMe	 **86a**	 **104f**	66
7	**46g**	CO_2Et	F	H	 **86a**	 **104g**	73
8	**46p**	CO_2Et	H	F	 **86a**	 **104h**	61
9	**46a**	CO_2Et	H	H	 **86b**	 **104i**	69[c]

10	**46n**	CO_2Et	OMe	H	 **86b**	 **104j**	93
11	**46o**	CO_2Et	H	OMe	 **86b**	 **104k**	95[d]
12	**46g**	CO_2Et	F	H	 **86b**	 **104l**	92[e]
13	**46p**	CO_2Et	H	F	 **86b**	 **104m**	80[f]

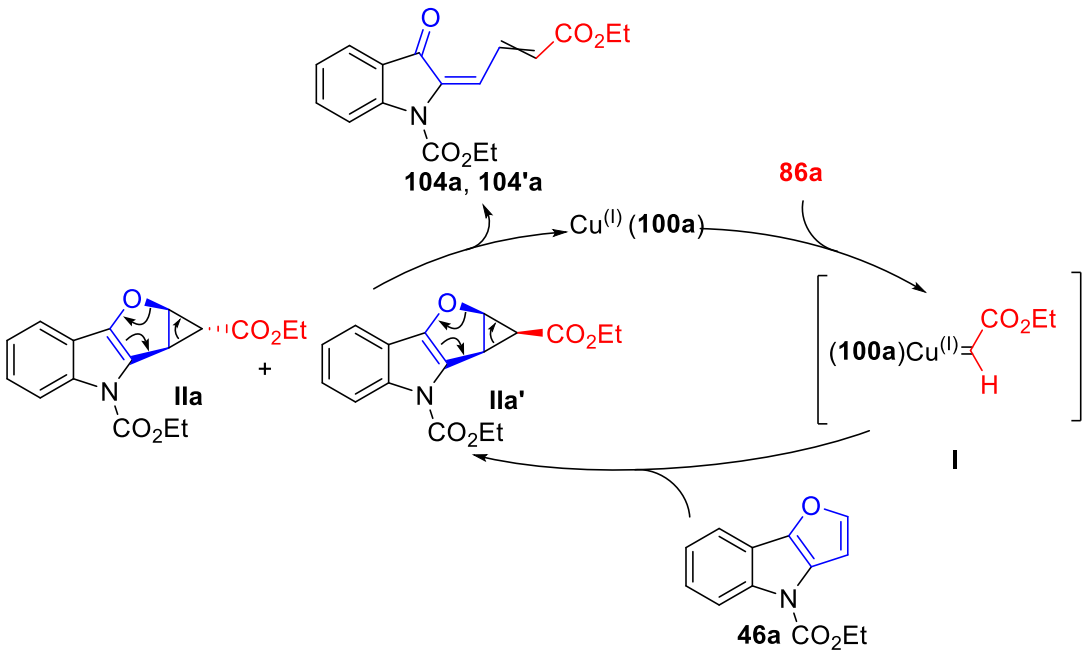
[a]All reactions were carried out using **46** (0.2 mmol) and **86** (0.3 mmol) in DCE (0.07 M) in the presence of 4 Å MS. *E/Z* > 98:2. [b]Isolated yield. [c]*E/Z* = 95:5. [d]*E/Z* 88:12. [e]*E/Z* = 85:15. [f]*E/Z* = 94:6

At the beginning, the reaction between **46a** and **86a** was conducted under the best reaction conditions reported in table 1, entry 10. The crude reaction mixture was treated with iodine to induce isomerization of **104'a** to **104a**, allowing for the isolation of the single isomer **104a** in almost quantitative yield (entry 1). The next step was the study of the influence of the nitrogen protecting group on the outcome of the reaction. Thus, a more hindered electron-withdrawing group like Boc was employed and the corresponding product **104b** was isolated in lower 68% yield (entry 2). Successively, the use of electron-donating methyl group on nitrogen showed a small increase in the isolated yield of **104c** (entry 3). Next, the investigation shifted on the study of the influence of electron-donating and electron-withdrawing substituents on the indole core. A weak ED methyl group on C6 position did not result in significant differences, and compound **104e** was isolated in 94% yield (entry 5), while a stronger ED methoxy substituent in the same position had a negative influence, reducing the yield of **104d** to 73% (entry 4). Shifting the methoxy group from C6 to C7, the same decrease in the yield was observed and compound **104f** was isolated in good 66% yield (entry 6).

Successively, furoindoles bearing the EW fluorine atom on C6 and C7 were tested with **86a**, reporting a similar decrease in the isolation of the corresponding products **104g** and **104h** (respectively 73 and 61% yields, entries 7 and 8). It is important to notice that without any distinction on the nature of the substituents, the C7 substitution is less tolerated than C6. Finally, in order to test other diazo compounds, the donor/acceptor carbenoid precursor methyl 2-diazo-2-phenylacetate **86b** was synthetized. The peculiarity of this compound is the superior stability of the corresponding carbene intermediate, resulting in a significant reduction of the dimerization.[158] Firstly, **86b** was tested with the non-substituted furoindole **46a**, giving rise to the desired compound **104i** in good 69% yield (entry 9). The employment of C6 and C7 substituted furoindole, led in all cases to excellent results. In this case, any significant difference was noticed performing the reaction with C6 or C7 methoxy substituted furoindoles with **86b**, and the corresponding **104i** and **104j** were isolated in 93 and 95% yields respectively (entries 10 and 11). Shifting from methoxy to fluorine atom, a trend similar to that described for **86a** was observed, and the fluorine derivative **104l** and **104m** were formed in 97 and 80% yields, respectively (entries 12 and 13). However, thanks to the enhanced selectivity and stability of methyl 2-diazo-2-phenylacetate **86b**, the corresponding indole derivatives bearing methoxy and fluorine groups were isolated in higher yields than the corresponding compounds obtained from **86a**.

3.2.3.3 Proposed mechanism

The proposed mechanism for this transformation is easily outlined taking into consideration the reactivity of copper carbene complexes[142] and the rearrangement of furan ring under electrophilic addition.[88,89] In fact, the first step is the activation of the diazo compound **86** by the copper(I) catalyst leading to the formation of copper-carbene intermediate **I** (scheme 3.22). Successively, the nucleophilic furan moiety attacks the carbene leading to the cyclopropanated intermediate **IIa-IIa'** which after ring opening gives rise to the two final isomers **104a** and **104'a**. The different geometry around the second double bond is connected to the diasteroselection of the cyclopropanation step which occurs mainly at the less hindered side of furoindole (intermediate **IIa**) giving rise to the major product **104a**. Reaction at the opposite side of the starting furoindole gives rise to a cyclopropane ring with the CO_2Et group and the furoindole moiety in cis position (intermediate **IIa'**) and finally leads to the minor isomer **104'a**.



Scheme 3.22

3.2.3.4 Second-order nonlinear optical properties

Nonlinear optic (NLO) is a field of physic that studies the interaction of matter with the electromagnetic radiation.[159–163] In particular, instead of the study of the response of a material to the variation of the frequency of irradiation, NLO studies the response to the variation of the radiation intensity. Thus, NLO describes all the optical phenomena caused by the interaction of a strong oscillating electric field and matter with the consequence of the emission of a new electric field different from the first one for incidental phase, frequency, and propagation characteristics. For organic compounds, the *push-pull* molecules, in which an electron donor group is separated from an electron acceptor group by π-conjugated spacer, can induce a huge response of second-order NLO. The measure of the response is done by using the quadratic hyperpolarizability β expressed in electrostatic unit of charge (esu). It is important to underline that the planarity and the length of the spacer can influence the response value. In particular, a lack in the planarity of the spacer reduces the values while an increase in the number of double bonds can rise β. The prototypical example of a *push-pull* organic molecule with high second-order NLO response is *p*-nitroaniline.

In order to measure the quadratic hyperpolarizability β in dipolar neutral molecules the Electric Field Induced Second Harmonic (EFISH) technique can be used.[164,165] This method allows to determine the product μβ, where β is quadratic hyperpolarizability, while μ is the dipole moment determined independently from EFISH technique. The molecule is dissolved in a diluted solution and it is placed into an electric field that tends to orient the molecules *via* their permanent electric dipole moments.

Successively, a laser with ω frequency irradiate the solution and a second radiation, with frequency 2ω generated from the interaction between the radiation and the sample, is registered as output. *Push-pull* molecules with second-order NLO properties are important building blocks in the field of molecular photonics, in particular for optical communications, optical data processing and electro-optical devices.[159,163]

2-(penta-2,4-dien-1-ylidene)3-oxoindolines **104** present a planar quite long π-conjugated system with electron donor and electron acceptor groups interesting for the investigation of NLO properties. Thus, compounds **104a**, **104c**, **104d**, **104e**, **104g**, **104h**, **104l** and **104m** were dissolved in chloroform and UV-visible absorption spectra and μβ measurements were conducted. The figure 3.6 reports the absorption spectra in chloroform solution of compound compounds a) **104a**, **104c**, **104g**, **104h** and b) **104l**, **104m**, **104d**, **104e**. From the figure a) 3.6 it is possible to observe a red shift in the band at lower energy for compounds **104a** and **104c**, reporting the different influence of the nitrogen protecting groups (ethyl ester vs methyl). Comparing the spectra of **104a** with the fluorine substituted **104g** and **104h**, it is evident the increase in the epsilon values for both compounds. Figure b) 3.6 shows the influence of methoxy or methyl groups in C6 position (compounds **104d** and **104e**, respectively), revealing an increase of epsilon value with the methyl substituent. Moreover, derivatives bearing the phenyl substituent on the lateral chain presents a red shift of the band at lower energy (cfr **104g** with **104l** and **104h** with **104m**).

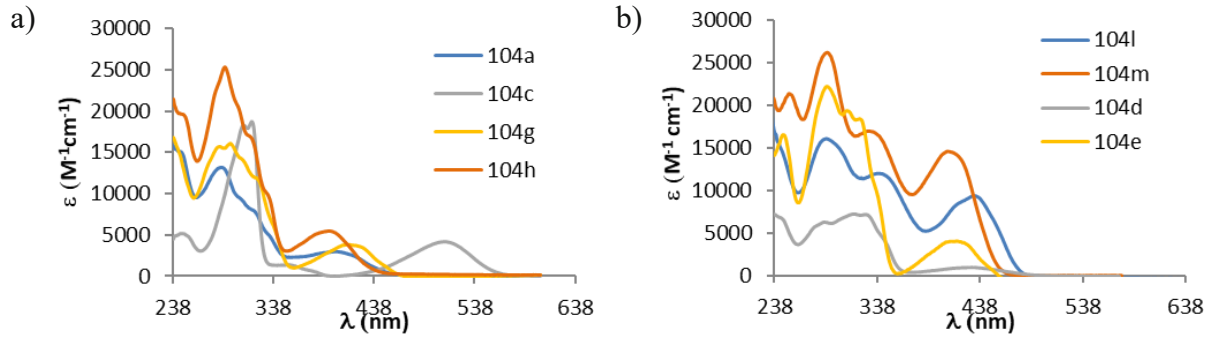


Figure 3.6

Table 3.3 reports the main absorption maxima and the μβ results. The μβ values recorded show a fair to good second-order NLO response. Compounds with μβ values superior to 500x10^{-48} esu, the value reached by standard Disperse Red One [trans-4,4'-$O_2NC_6H_4N$ = $NC_6H_4NEt(CH_2CH_2OH)$],[166] can be considered of particular interest for optical applications. From the results, there is a clear dependence of the determined μβ values from the substituents of the investigated molecules. Comparing the electron donor methyl and methoxy substituted derivatives **104e** and **104d**, with the unsubstituted compound **104a**, it is evident a better NLO response (230, 400, 410 x10^{-48} esu, respectively) for the former compounds. As reported in literature,[167] the substitution of a methyl

group with a fluorine atom leads to an increase in the NLO response. In fact, **104g** presents higher μβ values 480 x10^{-48} esu than **104e**. In addition, the change in the position of the fluorine atom results in a modification of the NLO response. In particular, fluorine in C7 position in compounds **104h** results in higher μβ (540 x10^{-48} esu) than **104g**. Finally, in agreement with literature results,[162,163,168] an expansion of π-delocalization obtained from the addition of a phenyl moiety at the terminal double bond leads to a good increase of the second-order NLO response: μβ is 640x10^{-48} and 680x10^{-48} esu for **104l** and **104m**, respectively. The best second-order NLO response is obtained with the two compounds **104l** and **104m** characterized by the most intense bands at low energy in the UV-visible region, in agreement with the two-level model.[169,170] In addition, μβ values of these two compounds are of particular interest because of their superiority to the value reached by standard Disperse Red One compound.

Table 3.3 Main absorption bands in the UV-visible spectra and second-order NLO response

Compound	Absorption[a] λmax/nm (ε/M^{-1} cm^{-1})	μβ (x10^{-48} esu)[b]
104a	246(14898), 283(13033), 317(8362), 396(2993)	230
104c	247(5379), 308(19024), 316(1849), 509(3929)	190
104d	287(18279), 317(7274), 330(6598), 426(2793)	410
104e	246(18388), 310(10333), 322(18326), 417(5029)	400
104g	284(14646), 295(15141), 320 sh(11436), 413(3559)	480
104h	250(19419), 289(25362), 315 sh(16742), 330 sh(10016), 393(5291)	540
104l	289(15846), 343(11980), 416 sh(8861), 432(9516)	640
104m	252(2218), 289(26299), 332(19758), 409(17182)	680

[a]In $CHCl_3$; UV-vis spectra recorded in toluene are almost identical to the ones recorded in chloroform solution. [b]In $CHCl_3$ 10^{-3} M working at 1.907 μm; estimated uncertainty in EFISH measurements is ± 20%.

3.2.4 Experimental data

3.2.4.1 Preface

3.2.4.1.1 General methods

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

3.2.4.1.2 Reagents

This study was carried out using 4*H*-furo[3,2-*b*]indoles **46a,f,g,l-p** which syntheses have already been described in section 2.2.4.1 and 2.3.3.1.
Methyl 2-diazo-2-phenylacetate **86b** is known compound and was prepared according to literature procedures.[155]
PcL ligand **100a** and [$Cu^{(I)}$(**100a**)] are known compounds and were prepared according to literature procedure.[153]
$Rh_2(Oct)_4$ JohnPhosAuSbF$_6$, IPrAuCl, $Cu(OTf)_2$, $(CuOTf)_2{*}C_6H_6$, and $NaBAr_4^F$ were purchased from commercial suppliers and used as received; $(ArO)_3PAuNTf_2$ catalyst was prepared following literature procedure.[43]

3.2.4.1.3 Solvents

Solvents, used for reactions sensitive to oxygen and hydrolysis, were purchased from commercial suppliers.

3.2.4.1.4 Immersion cooler

The immersion cooler *Julabo FT 402* was used for reactions carried out at -20 °C or -35 °C.

3.2.4.1.5 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade* 9385 60Å (230-400 mesh).
For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm).

3.2.4.1.6 NMR spectroscopy

^{1}H-NMR analyses were performed with a *Varian-Gemini 230* or with *Brucker 300, 500, 600 Avance* spectrometers at room temperature, respectively at 300, 500 or 600 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shift (δ) in ppm. The multiplicities of the proton spectra were described by following abbre*via*tions: s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double dublet).
^{13}C-NMR analyses were performed with the same instruments at 75.45, 125.75 MHz; APT sequences were used to distinguish the methane and methyl carbon signals from those arising from methylene and quaternary carbon atoms.
Two-dimensional NMR techniques (COSY, HSQC, HMBC, NOESY) were performed, where appropriate, to aid the correct assignment of structures.

3.2.4.1.7 Mass Spectroscopy

Low resolution MS spectra were recorded with *a FISONS MD 800* spectrometer with electron impact source and a *Thermo-Finnigan LCQ-advantage AP* electron spray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown
in brackets.

3.2.4.1.8 Melting points

The melting points of the solid products were measured in capillary tube with the device *StuarScientific* SMP3.

3.2.4.1.9 Syringe pump

Slow additions were performed using NE-1000 Programmable Single Syringe Pump of the New Era Pump Systems Inc.

3.2.4.1.10 EFISH measurements

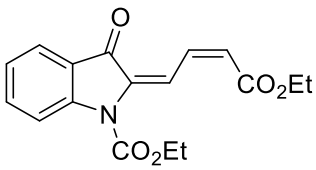
EFISH measurements were carried out by using a non-resonant incident wavelength of 1.907 μm, achieved by Raman-shifting the fundamental 1.064 μm wavelength given by a Q-switched, mode-locked Nd^{3+}:YAG laser (from Atalaser).

3.2.4.2 Experimental data

3.2.4.2.1 General procedure for the synthesis of compounds 104a-m

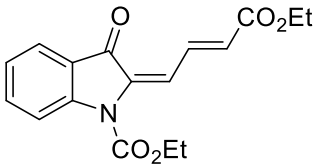
To a N_2-flushed solution of 4*H*-furo[3,2-*b*]indole **46** (0.2 mmol, 1 equiv), [$Cu^{(I)}$(**100a**)] (8 mol%) and 4 Å molecular sieves (200 mg) in anhydrous DCE (1 mL), a solution of diazo compound **86** (1.5 equiv.) in anhydrous DCE (2 mL) was added dropwise in 2 h with a syringe pump at room temperature. Then the reaction mixture was warmed to room temperature and further stirred for 2 h in the presence of one crystal of I_2. Then, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to yield the desired product **104**.

Ethyl (*E*)-2-((*Z*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104'a)



To a N_2-flushed solution of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (45.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol),and 4 Å molecular sieves (200 mg) in anhydrous DCE (1 mL), a solution of ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (2 mL) was added dropwise in 2 h with a syringe pump at room temperature. The crude residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yield **104'a** (62.5 mg, 25%) as a yellow solid with an inseparable impurity probably deriving from the dimerization of diazo compound. (Reaction of the screening, entry 8). **^{1}H NMR** (300 MHz, $CDCl_3$): 9.02 (dd, *J* = 12.1, 1.2 Hz, 1H), 8.45 (t, *J* = 11.7 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 6.8 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.23 (m, 1H), 6.05 (dd, *J* = 11.4, 1.2 Hz, 1H), 4.51 (m, 2H), 4.24 (qd, *J* = 7.1, 3.7 Hz, 2H, overlapped with the impurity), 1.52 (t, *J* = 7.1 Hz, 3H), 1.39 – 1.16 (m, 3H, overlapped with impurity). **^{13}C NMR** (75 MHz, $CDCl_3$): 185.16 (C), 165.75 (C), 151.60 (C), 147.90 (C), 137.27 (CH), 136.31 (CH), 135.08 (C), 129.74 (CH), 124.73 (CH), 124.13 (CH), 123.73 (C), 121.64 (CH), 117.28 (CH),63.52 (CH_2), 60.22 (CH_2), 14.25 (CH_3), 14.21 (CH_3). **ESI(+)-MS**: m/z(%) = 316 (100) $[M+H]^+$; $C_{17}H_{17}NO_5$ [315.33]: calcd. for: C 64.75; H 5.43; N 4.44, found: C 64.56, H 5.43, N 4.45.

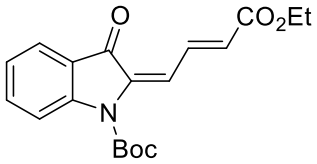
Ethyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104a)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (45.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **104a** (62.5 mg, 99%) as a yellow solid (m.p. 99-102 °C). **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.92 (dd, *J* = 15.4, 12.0 Hz, 1H), 8.04 (m, 1H), 7.79 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 1H), 7.73

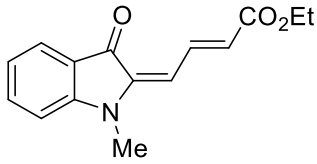
(dd, *J* = 12.0, 1.0 Hz, 1H), 7.65 (m, 1H), 7.26 (td, *J* = 7.6, 0.8 Hz, 1H), 6.25 (dd, *J* = 15.4, 1.0 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 184.51 (C), 166.11 (C), 151.56 (C), 147.62 (C), 137.83 (CH), 136.31 (CH), 135.19 (C), 129.33 (CH), 124.23 (CH), 124.00 (CH), 123.60 (C), 123.27 (CH), 117.28 (CH), 63.51 (CH_2), 60.55 (CH_2), 14.08 (CH_3), 14.03 (CH_3). **EI(+)-HRMS**: m/z(%) = calcd for $C_{17}H_{17}NO_5$: 315.110673, found: 315.110760 (40) $[M]^+$

***tert*-butyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104b)**



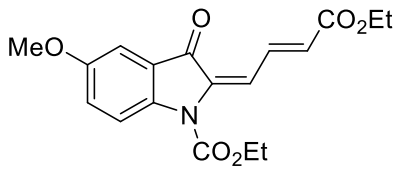
General procedure was followed using *tert*-butyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46l** (51.5 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **104b** (47.0 mg, 68%) as a yellow solid (m.p. 128-131 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.99 (m, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 12.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.24 (m, 1H overlapped with $CDCl_3$), 6.22 (d, *J* = 15.4 Hz, 1H), 4.28 (q, *J* = 6.8 Hz, 2H), 1.71 (s, 9H), 1.36 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.71 (C), 166.33 (C), 150.23 (C), 147.93 (C), 138.32 (CH), 136.23 (CH), 135.33 (C), 129.37 (CH), 124.24 (CH), 124.08 (CH), 123.67 (CH), 123.60 (C), 117.25 (CH), 84.83 (C), 60.61 (CH_2), 28.28 (3xCH_3), 14.28 (CH_3). **ESI(+)-HRMS**: m/z(%) = calcd for $C_{19}H_{21}NO_5$: 343.141973, found: 343.141340 (60) $[M]^+$.

Ethyl (*E*)-4-((*E*)-1-methyl-3-oxoindolin-2-ylidene)but-2-enoate (104c)



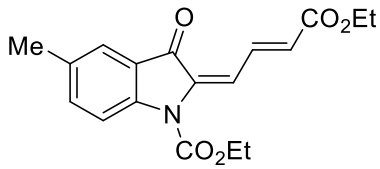
General procedure was followed using 4-methyl-4*H*-furo[3,2-*b*]indole **46m** (34.2 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **104c** (39.5 mg, 77%) as a purple solid (m.p. 150-152 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.84 (dd, *J* = 15.3, 12.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.00 – 6.78 (m, 2H), 6.10 – 5.95 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.27 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 185.99 (C), 166.87 (C), 152.73 (C), 139.36 (C), 138.48 (CH), 136.36 (CH), 124.91 (CH), 124.30 (CH), 121.15 (C), 120.17 (CH), 110.45 (CH), 108.73 (CH), 60.36 (CH_2), 28.63 (CH_3), 14.35 (CH_3). **ESI(+)-HRMS**: m/z(%) = calcd for $C_{15}H_{15}NO_3$: 257.105194, found: 257.105930 (45) $[M]^+$.

Ethyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-5-methoxy-3-oxoindoline-1-carboxylate (104d)



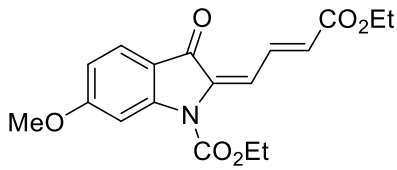
General procedure was followed using ethyl 7-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46n** (51.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **104d** (50.0 mg, 73%) as a yellow solid (m.p. 155-157 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.96 (m, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 11.9 Hz, 1H), 7.32 – 7.13 (m, *J* = 15.0 Hz, 2H), 6.24 (d, *J* = 15.4 Hz, 1H), 4.49 (m, 2H), 4.28 (m, 2H), 3.86 (s, 3H), 1.50 (t, *J* = 6.8 Hz, 3H), 1.36 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.32 (C), 166.29 (C), 156.74 (C), 151.50 (C), 141.97 (C), 138.14 (CH), 135.53 (C), 129.62 (CH), 124.82 (CH), 124.45 (C), 123.97 (CH), 118.51 (CH), 105.63 (CH), 63.30 (CH_2), 60.63 (CH_2), 55.80 (CH_3), 14.37 (CH_3), 14.27 (CH_3). **ESI(+)-HRMS**: m/z(%) = calcd for $C_{18}H_{19}NO_6$: 345.121238, found: 345.121340 (60) $[M]^+$.

Ethyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-5-methyl-3-oxoindoline-1-carboxylate (104e)



General procedure was followed using ethyl 7-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46f** (48.6 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **104d** (62.0 mg, 94%) as a yellow solid (m.p. 106-108 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.98 (dd, *J* = 15.4, 12.0 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 11.9 Hz, 1H), 7.60 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.23 (d, *J* = 15.4 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 4.28 (q, 7.1 Hz, 2H), 2.41 (s, 3H), 1.51 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.55 (C), 166.32 (C), 151.64 (C), 145.63 (C), 138.18 (CH), 137.37 (CH), 135.37 (C), 134.31 (C), 129.49 (CH), 124.13 (CH), 123.78 (C), 123.62 (CH), 117.08 (CH), 63.34 (CH_2), 60.63 (CH_2), 20.64 (CH_3), 14.38 (CH_3), 14.29 (CH_3). **ESI(+)-HRMS**: m/z(%) = calcd for $C_{18}H_{19}NO_5$: 329.126323, found: 329.126700 (50) $[M]^+$.

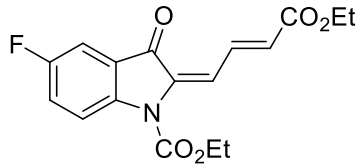
Ethyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-6-methoxy-3-oxoindoline-1-carboxylate (104f)



General procedure was followed using ethyl 6-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46o** (51.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **104f** (45.5 mg, 66%) as a yellow solid (m.p.

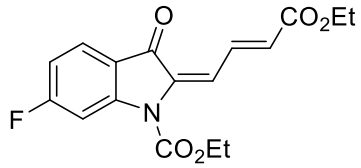
157-159 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.96 (dd, *J* = 15.5, 11.9 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.57 (dd, *J* = 11.9, 0.8 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.15 (dd, *J* = 15.5, 0.8 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 182.58 (C), 166.59 (C), 166.26 (C), 151.47 (C), 149.69 (C), 138.17 (CH), 135.83 (C), 129.01 (CH), 125.81 (CH), 122.85 (CH), 117.26 (C), 111.69 (CH), 102.15 (CH), 63.40 (CH_2), 60.52 (CH_2), 55.81 (CH_3), 14.25 (CH_3), 14.24 (CH_3). **ESI(+)-MS**: m/z(%) = 368 (100) $[M+Na]^+$; $C_{18}H_{19}NO_6$ [345.35]: calcd. for: C 62.60, H 5.55, N 4.06; found: C 62.44, H 5.56, N 4.08.

Ethyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-5-fluoro-3-oxoindoline-1-carboxylate (104g)



General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46g** (49.4 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, toluene) yielded **104g** (48.5 mg, 73%) as a yellow solid (m.p. 106-109 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.94 (dd, *J* = 14.8, 12.6 Hz, 1H), 8.03 (m, 1H), 7.74 (d, *J* = 12.1 Hz, 1H), 7.57 – 7.19 (m, 2H), 6.27 (d, *J* = 15.2 Hz, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 183.57 (C), 166.16 (C), 159.50 (d, *J* = 246.8 Hz, C), 151.42 (C), 143.69 (d, *J* = 1.7 Hz, C), 137.77 (CH), 135.16 (C), 130.31 (CH), 124.73 (CH), 123.45 (d, *J* = 24.3 Hz, CH), 118.94 (d, *J* = 7.3 Hz, CH), 110.04 (d, *J* = 23.5 Hz, CH), 63.61 (CH_2), 60.73 (CH_2), 14.36 (CH_3), 14.26 (CH_3). One quaternary carbon is missing, probably overlapped. **ESI(+)-HRMS**: m/z(%) = calcd for $C_{17}H_{16}FNO_5$: 333.101251, found: 333.101330 (10) $[M]^+$.

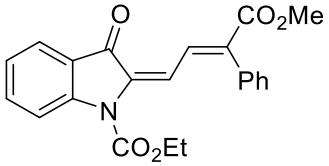
Ethyl (*E*)-2-((*E*)-4-ethoxy-4-oxobut-2-en-1-ylidene)-5-fluoro-3-oxoindoline-1-carboxylate 1042h)



General procedure was followed using ethyl 6-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46p** (49.4 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), ethyl 2-diazoacetate **86a** (34.2 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **104h** (40.5 mg, 61%) as a yellow solid (m.p. 111.5-113.8 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.92 (dd, *J* = 15.5, 12.0 Hz, 1H), 7.79 (dd, *J* = 8.5, 5.8 Hz, 1H), 7.74 – 7.65 (m, 2H), 6.93 (td, *J* = 8.5, 2.2 Hz, 1H), 6.22 (dd, *J* = 15.5, 0.9 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75

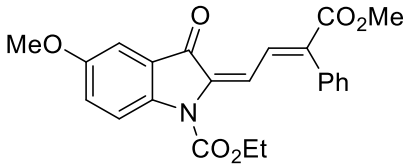
MHz, $CDCl_3$): 182.71 (C), 167.78 (d, *J* = 255.3 Hz, C), 166.12 (C), 151.24 (C), 149.03 (d, *J* = 13.9 Hz, C), 137.66 (CH), 135.13 (C), 130.08 (CH), 126.36 (d, *J* = 11.6 Hz, CH), 124.03 (CH), 120.14 (C), 112.37 (d, *J* = 24.1 Hz, CH), 105.38 (d, *J* = 30.0 Hz, CH), 63.78 (CH_2), 60.66 (CH_2), 14.29 (CH_3), 14.23 (CH_3). **ESI(+)-MS**: m/z(%) = 334 (100) $[M+H]^+$; $C_{17}H_{16}FNO_5$ [333.32]: calcd. for: C 61.26, H 4.84, N 4.20; found: C 61.39, H 4.84, N 4.21.

Ethyl (*E*)-2-((*E*)-4-methoxy-4-oxo-3-phenylbut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104i)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (45.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), methyl 2-diazo-2-phenylacetate **86b** (52.8 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, toluene) yielded **104i** (52.0 mg, 69%) as a yellow solid with traces of minor isomer (*E/Z* = 95:5) (m.p. 102-104 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): 9.19 (d, *J* = 12.2 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.84 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 12.2 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.35 – 7.30 (m, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.88 (d, *J* = 0.5 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 184.73 (C), 167.49 (C), 151.47 (C), 147.79 (C), 140.11 (C), 136.32 (CH), 134.70 (C), 134.49 (C), 133.63 (CH), 130.47 (2xCH), 128.38 (CH), 128.07 (2xCH), 124.32 (CH), 124.17 (CH), 123.78 (C), 122.55 (CH), 117.26 (CH), 63.32 (CH_2), 52.44 (CH_3), 13.90 (CH_3). **ESI(+)-MS**: m/z(%) = 378 (100) $[M+H]^+$; $C_{22}H_{19}NO_5$ [377.40]: calcd. for: C 70.02, H 5.07, N 3.71; found: C 69.83, H 5.09, N 3.70.

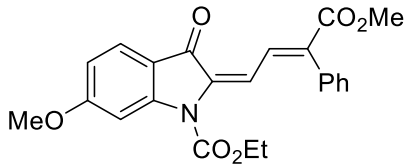
Ethyl (*E*)-5-methoxy-2-((*E*)-4-methoxy-4-oxo-3-phenylbut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104j)



General procedure was followed using ethyl 7-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46n** (51.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), methyl 2-diazo-2-phenylacetate **86b** (52.8 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 98:2) yielded **104j** (75.5 mg, 93%) as an orange solid (m.p. 136-138 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 9.17 (d, *J* = 12.2 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 12.2 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.32 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.27 (d, *J* = 5.2 Hz, 1H), 7.20 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H) 3.87 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 184.55 (C), 167.50 (C), 156.72 (C), 151.39 (C), 142.31 (C), 140.07 (C), 135.18 (C), 134.50 (C), 133.68 (CH), 130.45 (2xCH), 128.36 (CH), 128.05 (2xCH), 124.75 (CH), 124.53 (C), 122.66 (CH), 118.44 (CH), 105.54 (CH), 63.15

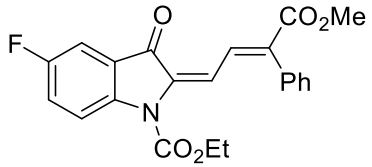
(CH_2), 55.81 ,(CH_3) 52.41 (CH_3), 13.92 (CH_3). **ESI(+)-MS**: m/z(%) = 430 (100) $[M+Na]^+$; $C_{23}H_{21}NO_6$ [407.42]: calcd. for: C 67.81, H 5.20, N 3.44; found: C 67.65, H 5.19, N 3.44.

Ethyl (*E*)-6-methoxy-2-((*E*)-4-methoxy-4-oxo-3-phenylbut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104k)



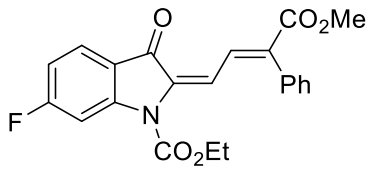
General procedure was followed using ethyl 6-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46o** (51.8 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), methyl 2-diazo-2-phenylacetate **86b** (52.8 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **104k** (77.0 mg, 95%) as a yellow solid with traces of the minor isomer (*E/Z* = 88:12) (m.p. 140-142 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 9.19 (d, *J* = 12.1 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.36 (m, 4H), 7.29 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.75 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 182.83 (C), 167.46 (C), 166.63 (C), 151.45 (C), 150.13 (C), 139.50 (C), 135.50 (C), 134.63 (C), 133.70 (CH), 130.43 (2xCH), 128.19 (CH), 127.98 (2xCH), 125.67 (CH), 121.54 (CH), 117.38 (C), 112.11 (CH), 101.67 (CH), 63.24 (CH_2), 55.83 (CH_3), 52.29 (CH_3), 13.79 (CH_3). **ESI(+)-MS**: m/z(%) = 430 (100) $[M+Na]^+$; $C_{23}H_{21}NO_6$ [407.42]: calcd. for: C 67.81, H 5.20, N 3.44; found: C 67.93, H 5.18, N 3.45.

Ethyl (*E*)-5-fluoro-2-((*E*)-4-methoxy-4-oxo-3-phenylbut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104l)



General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46g** (49.4 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), methyl 2-diazo-2-phenylacetate **86b** (52.8 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, toluene/ethyl acetate 98:2) yielded **104l** (73.0 mg, 92%) as a yellow solid with traces of the minor isomer, (*E/Z* = 85:15) (m.p. 146-148 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 9.12 (d, *J* = 12.2 Hz, 1H), 8.13 (dd, *J* = 9.1, 4.0 Hz, 1H), 7.57 (d, *J* = 12.2 Hz, 1H), 7.48 – 7.38 (m, 4H), 7.35 – 7.28 (m, *J* = 3.2, 2.1 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 183.75 (C), 167.36 (C), 159.47 (d, *J* = 246.5 Hz, C), 151.31 (C), 143.93 (C), 140.73 (C), 134.75 (C), 134.39 (C), 133.32 (CH), 130.44 (2xCH), 128.46 (CH), 128.08 (2xCH), 124.91 (d, *J* = 7.6 Hz, C), 123.39 (d, *J* = 24.0 Hz, CH), 123.39 (CH),118.91 (t, *J* = 6.2 Hz, CH), 109.74 (d, *J* = 23.5, 11.8 Hz, CH), 63.45 (CH_2), 52.48 (CH_3), 13.86 (CH_3). **ESI(+)-MS**: m/z(%) = 396 (100) $[M+H]^+$; $C_{22}H_{18}FNO_5$ [395.39]: calcd. for: C 66.83, H 4.59, N 3.54; found: C 67.02, H 4.58, N 3.53.

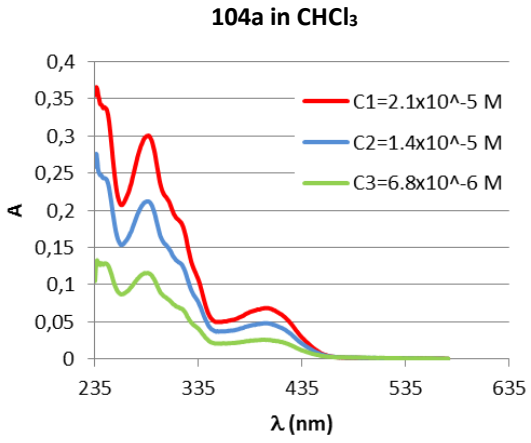
Ethyl (*E*)-6-fluoro-2-((*E*)-4-methoxy-4-oxo-3-phenylbut-2-en-1-ylidene)-3-oxoindoline-1-carboxylate (104m)

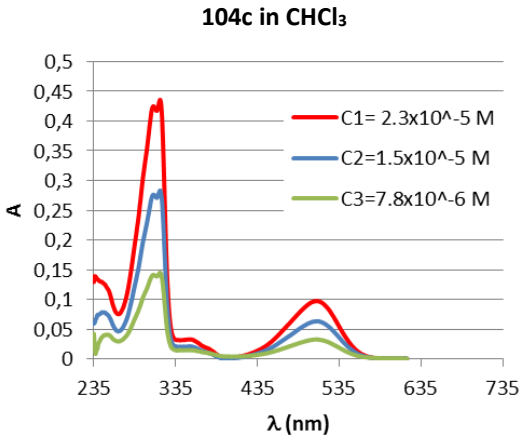


General procedure was followed using ethyl 6-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46p** (49.4 mg, 0.2 mmol), [$Cu^{(I)}$(**100a**)] (13.8 mg, 0.016 mmol), methyl 2-diazo-2-phenylacetate **86b** (52.8 mg, 0.3 mmol) in anhydrous DCE (1+2 mL). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 95:1) yielded **104m** (63.0 mg, 80%) as a yellow solid with traces of minor isomer (*E*/*Z* = 94:6) (m.p. 136.7-139.2 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 9.14 (d, *J* = 12.2 Hz, 1H), 7.92 – 7.78 (m, 2H), 7.55 (d, *J* = 12.2 Hz, 1H), 7.49 – 7.36 (m, 3H), 7.36 – 7.23 (m, 2H), 6.95 (td, *J* = 8.5, 2.2 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 182.97 (C), 167.78 (d, *J* = 255.4 Hz, C), 167.38 (C), 151.19 (C), 149.33 (d, *J* = 14.0 Hz, C), 140.52 (C), 134.80 (C), 134.41 (C), 133.24 (CH), 130.44 (2xCH), 128.43 (CH), 128.08 (2xCH), 126.15 (t, *J* = 11.1 Hz, CH), 122.70 (CH), 120.24 (C), 112.28 (dd, *J* = 24.1, 10.8 Hz, CH), 105.29 (d, *J* = 30.0 Hz, CH), 63.64 (CH_2), 52.45 (CH_3), 13.84 (CH_3). **ESI(+)-MS**: m/z(%) = 396 (100) $[M+H]^+$; $C_{22}H_{18}FNO_5$ [395.39]: calcd. for: C 66.83, H 4.59, N 3.54; found: C 66.74, H 4.59, N 3.55.

3.2.4.2.2 UV spectra for compounds 104a, 104c, 104d, 104e, 104g, 104h, 104l and 104m

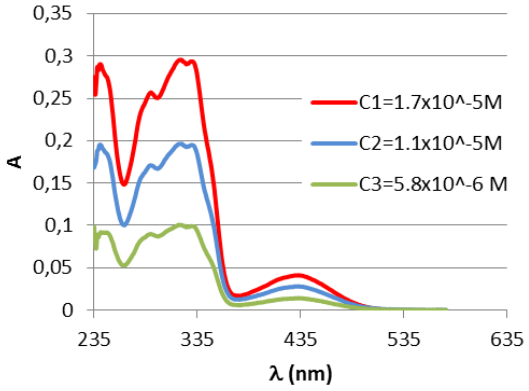
EFISH measurements were carried out by using a non-resonant incident wavelength of 1.907 µm, achieved by Raman-shifting the fundamental 1.064 µm wavelength given by a Q-switched, mode-locked Nd^{3+}:YAG laser (from Atalaser). All compounds were dissolved in chloroform at a concentration of 10^{-3} M. The reported $\mu\beta_{1.907}$ values are the mean values of 16 measurements performed on the same sample

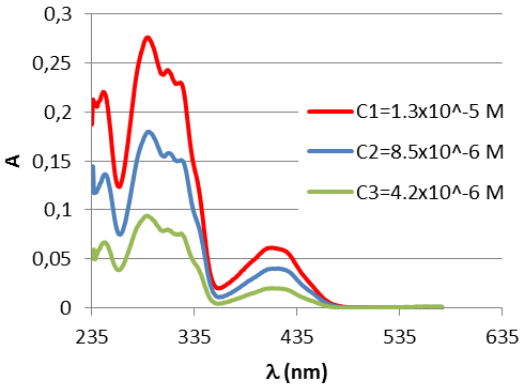




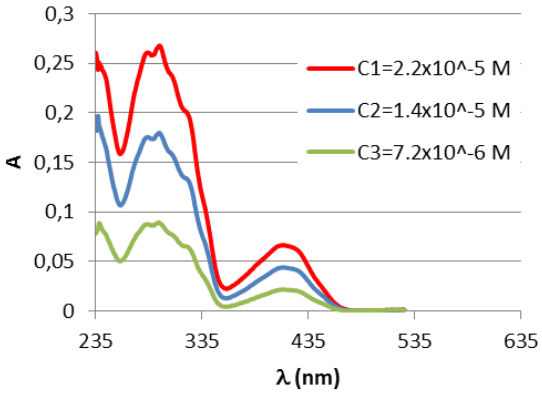
104d in CHCl3

104e in CHCl3

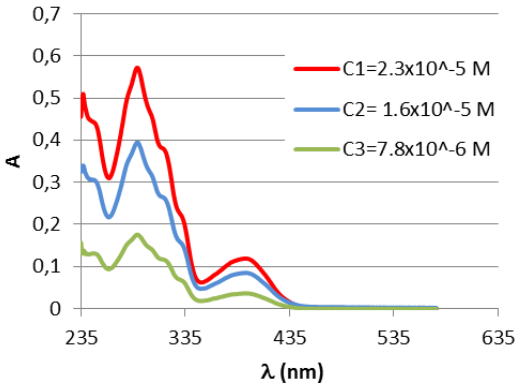




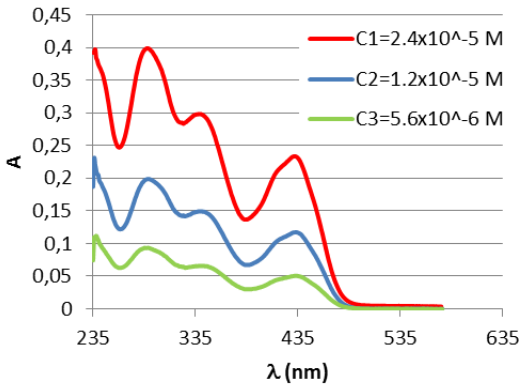
104g in $CHCl_3$



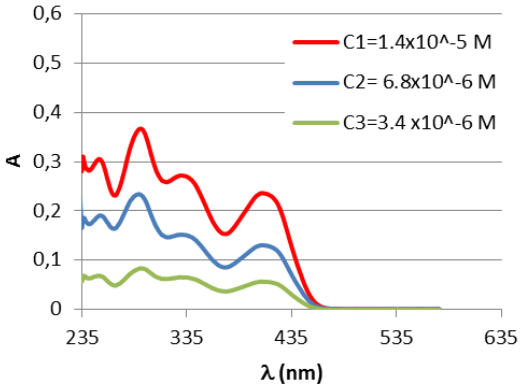
104h in $CHCl_3$



104l in $CHCl_3$



104m in $CHCl_3$



Chapter 4. Metal free cycloaddition reactions

The work described in this chapter has been published in *J. Org. Chem.* **2020**, *85*, 3265-3276 as "Synthesis of Cyclohepta[*b*]indoles by (4+3) Cycloaddition of 2-Vinylindoles or 4*H*-Furo[3,2-*b*]indoles with Oxyallyl Cations".

4.1 (4+3) cycloaddition reactions

Simple and condensed seven-member rings are present in numerous natural products and among these the class of tropane alkaloids is probably the most famous and studied.[171–175] Tropane alkaloids present a *N*-methyl-8-azabicyclo[3.2.1]octane core and are mainly isolated from the family plants of Solanaceae. Tropane alkaloids are characterized by a powerful anticholinergic activity and the most prominent alkaloids of this class are scopolamine, atropine and cocaine. In addition, other natural compounds containing this nucleus are pervilleine, himandrine and stemofoline (figure 4.1).

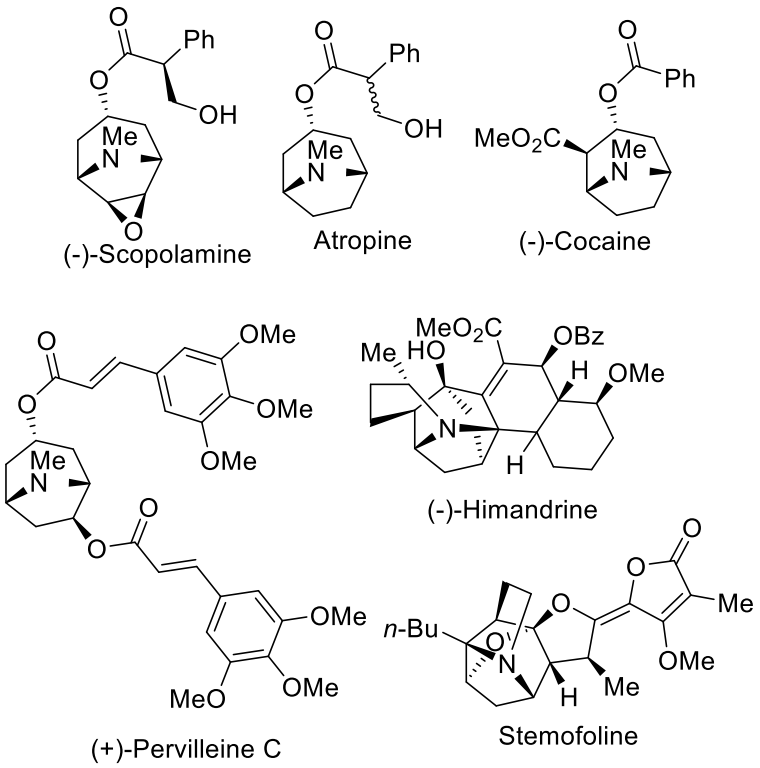
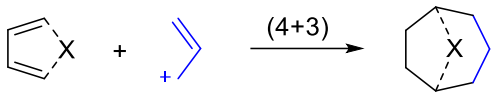


Figure 4.1

Due to their importance, the study of new synthetic methodologies for their preparation and more in general for the preparation of their analogues for the drug discovery processes led to the development of a plethora of new reactions and various synthetic strategies. Among these, the synthesis of the seven-member ring exploiting (4+3) cyclization reactions has been recognized as one of the most powerful methodology giving rise to complex structures with a high degree of chemo, stereo and enantioselectivity.[176–183] The (4+3) annulation/cyclization process takes advantage of the employment of two building blocks, a four atoms synthon as 4π system and an electrophilic three atoms partner as 2π system (Scheme 4.1).



Scheme 4.1

It is important to underline that the (4+3) notation is referred to the number of atoms that takes part in the formation of the seven-member ring. Thus, taking into account the electron count, this transformation is formally a [4+2] cycloaddition, the C3 synthon participating in the reaction with only two π electrons. In fact, the (4+3) cyclization can be considered homologous of the Diels-Alder reaction.[177]

The most employed 4π systems are cyclic electron rich dienes with rigid *s-cis* conformation, such as cyclopentadienes and furans, but also pyrroles and cyclohexadienes. Moreover, hexahydro-s-triazines and simple open chain 1,4-dienes or α,β-unsaturated carbonyl compounds have been used (figure 4.2).

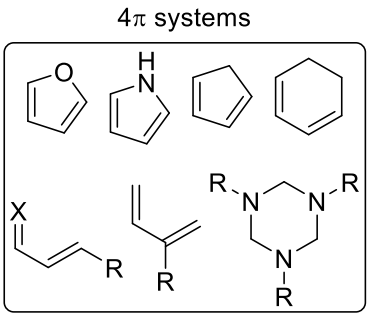


Figure 4.2

For the three atom systems, the most common synthons are oxyallyl cations obtained from halo or pseudo-halo ketones or preformed halo or pseudo-halo enolates (figure a) 4.3). Moreover, several non-traditional routes can be followed for the generation of the appropriate dienophile from allenes, vinyl diazo compounds and cyclopropanes (figure b) 4.3).[182]

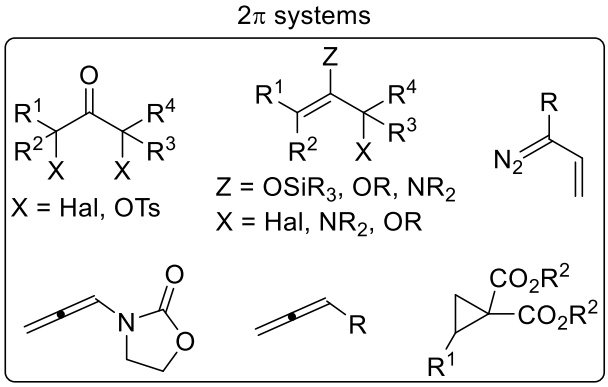
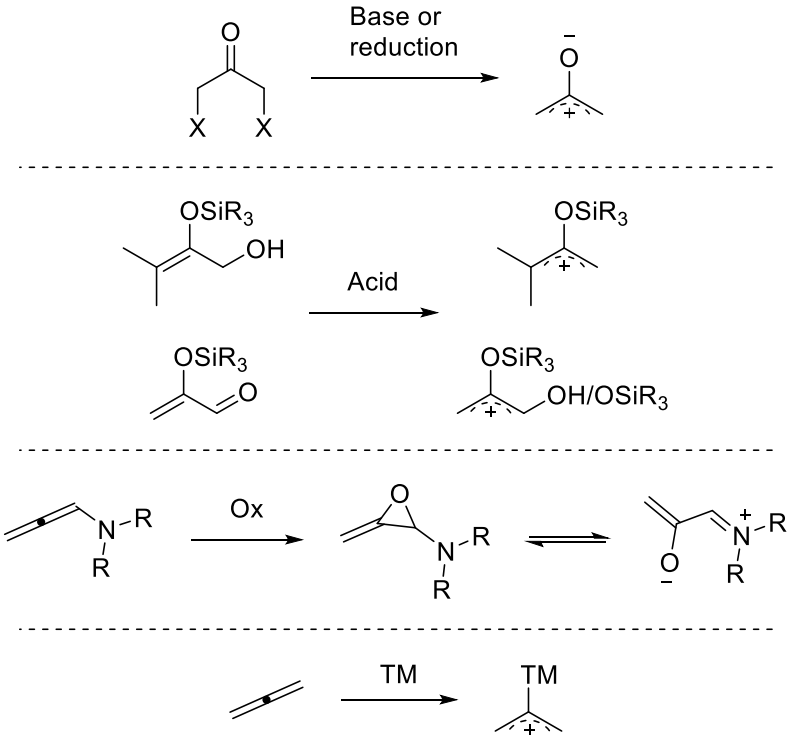


Figure 4.3

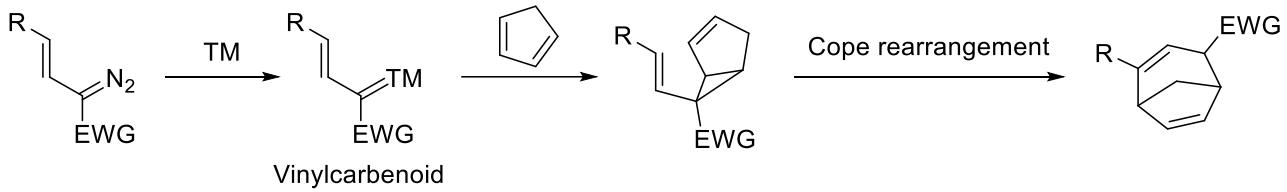
According to the reactants employed, the generation of the dienophile can require the use of promoters such as bases, Lewis acids or metal catalysts. More specifically, the (4+3) cycloadditions can be divided in two main classes, the classical (4+3) cycloadditions following a mechanism similar to a typical [4+2] cycloaddition and the formal (4+3) cycloadditions, these latter occurring *via* domino cyclopropanation/Cope rearrangement. Classical (4+3) cycloadditions involve dienes of the general structure reported in figure 4.2 and allyl cations mostly generated *in situ* from the precursor shown in figure 4.3a (scheme 4.2).



Scheme 4.2

In particular, the oxyallyl cations can be obtained *in situ* from mono or poly haloketones, under basic or ionizing conditions in the first case and under reductive conditions in the second case.[184,185] Moreover, silyloxiallylic alcohol derivatives and siloxyacroleins can be involved in (4+3) cycloadditions *via* an acid activated process.[186,187] Finally, allenamides can take part in the formation of seven-membered ring by epoxidation followed by generation of an iminium-stabilized oxyallyl cation *via* epoxide ring opening.[188–190] In all these cases, the activation of the dienophile requires a stoichiometry amount of an external activating agent. However, more recently, catalytic transformations involving the use of transition metal catalysts have been developed allowing the involvement of simple allenes, in the form of allylic cations, in the cyclization process. [178,191,192]

Instead, the formal (4+3) cycloaddition pathway involves the formation of a vinyl carbene as key intermediate in an overall domino transformation. In most cases, diazo compounds under transition metal catalysis are the source for vinyl carbenes. The transformation is a domino reaction because the first step is the cyclopropanation on the diene, forming a *cis*-divinylcyclopropane intermediate that after Cope rearrangement leads to the formation of the cycloheptadiene derivative (scheme 4.3).[183,193]

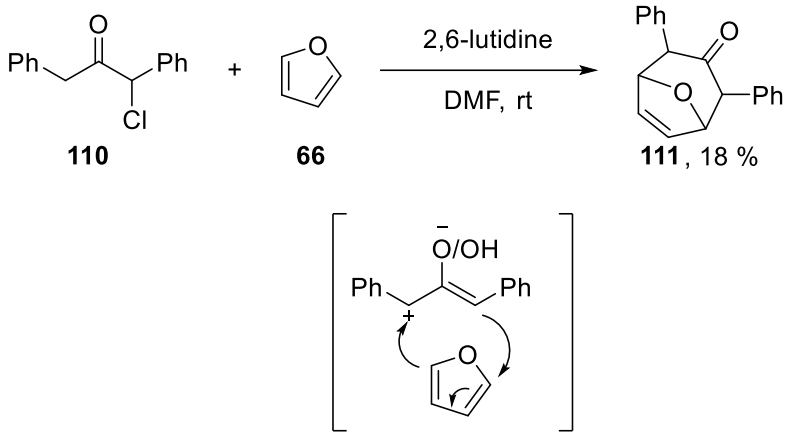


Scheme 4.3

The advantage of this transformation lies in the possibility to develop a stereoselective process employing chiral ligands or chiral auxiliaries.[176,179,180,183] In addition, classical (4+3) cycloadditions can give rise to enantioenriched cycloadducts using chiral dienes or chiral precursor for the oxyallyl cations, even if the assessment of these reactions seems to be more challenging.

4.1.1 Classical (4+3) cycloadditions involving allyl cations

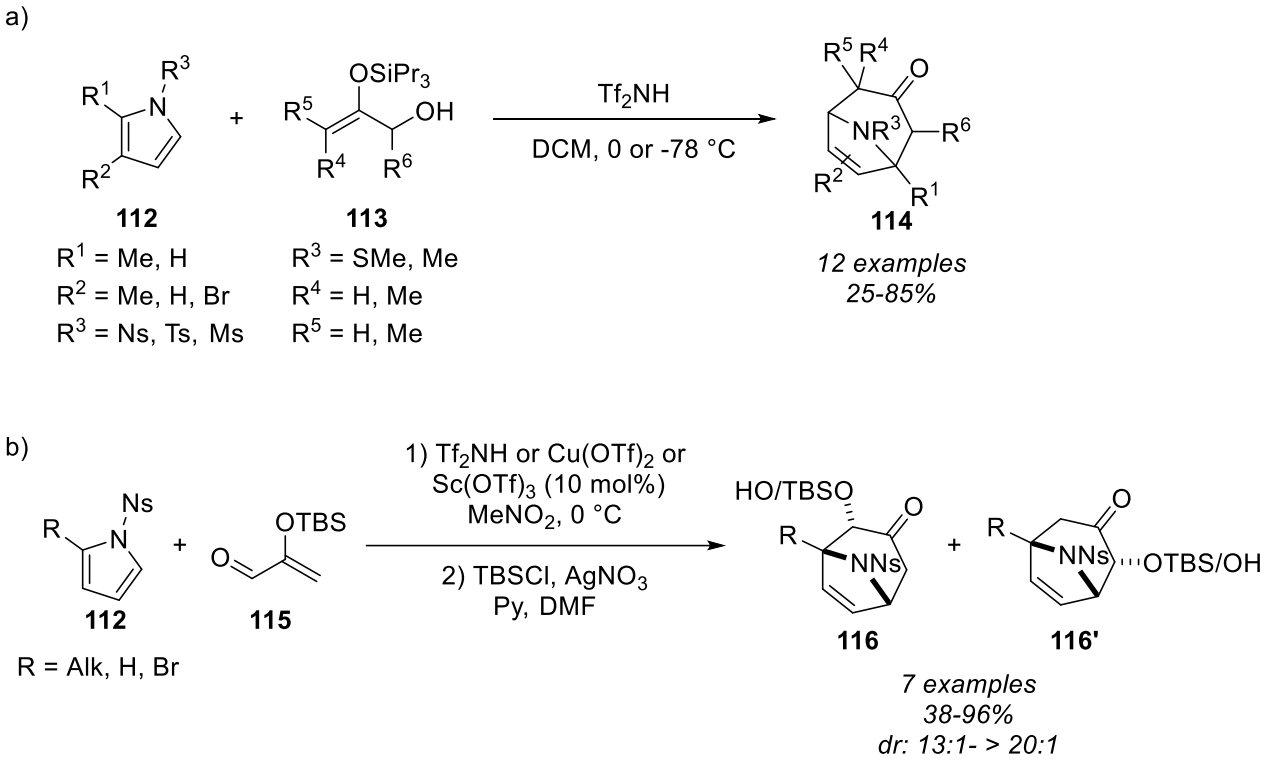
One of the first example of seven-member ring synthesis using oxyallyl cations was reported by Fort in 1962. In particular, he reported the preparation of cycloadduct **111** starting from α-chloroketone **110** and furan **66** in the presence of 2,6-lutidine in DMF (scheme 4.4).[184] Probably, the synthesis of the product was promoted by the formation of an enol or enolate able to undergo heterolysis of the carbon-halogen bond and to generate the oxyallyl cation, i.e. the active species in the cycloaddition reaction with furan for the production of the seven member ring.



Scheme 4.4

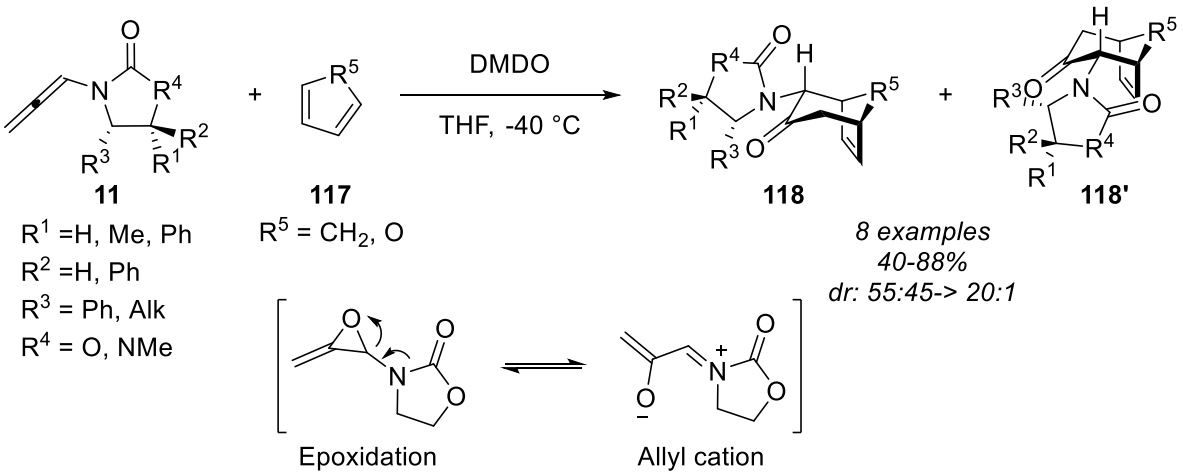
Furthermore, Föhlisch[194] and Handy separately developed the synthesis of seven-member rings changing the leaving group from halogen to mesyl or tosyl substituents in the starting ketones. The main problem encountered for these transformations are the low yields and the need of a large excess of the diene, forbidding the employment of more complex/expensive dienes.

Successively, Tanino and co-workers demonstrated the possibility to use sulfur- and oxygen-substituted derivatives **113** and **115** in order to form heteroatom-stabilized silyloxyallyl cations under acidic conditions. The use of these more stable substrates allowed for the reduction of the equivalents of the employed diene (scheme 4.5).[186,187]



Scheme 4.5

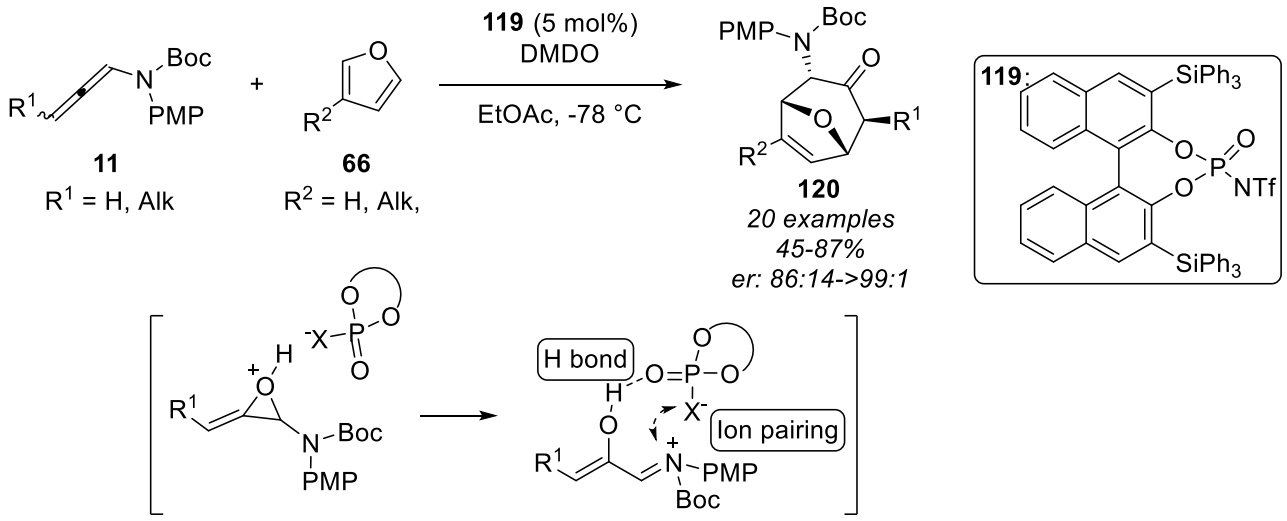
More recently, Hsung and co-workers proposed a straightforward strategy for the synthesis of an iminium-stabilized oxyallyl cation. They developed a diastereoselective (4+3) cycloaddition with chiral nitrogen-substituted oxyallyl cations obtained *in situ* from chiral allenamides **11** *via* oxidation/epoxide ring opening sequence (scheme 4.6).[188]



Scheme 4.6

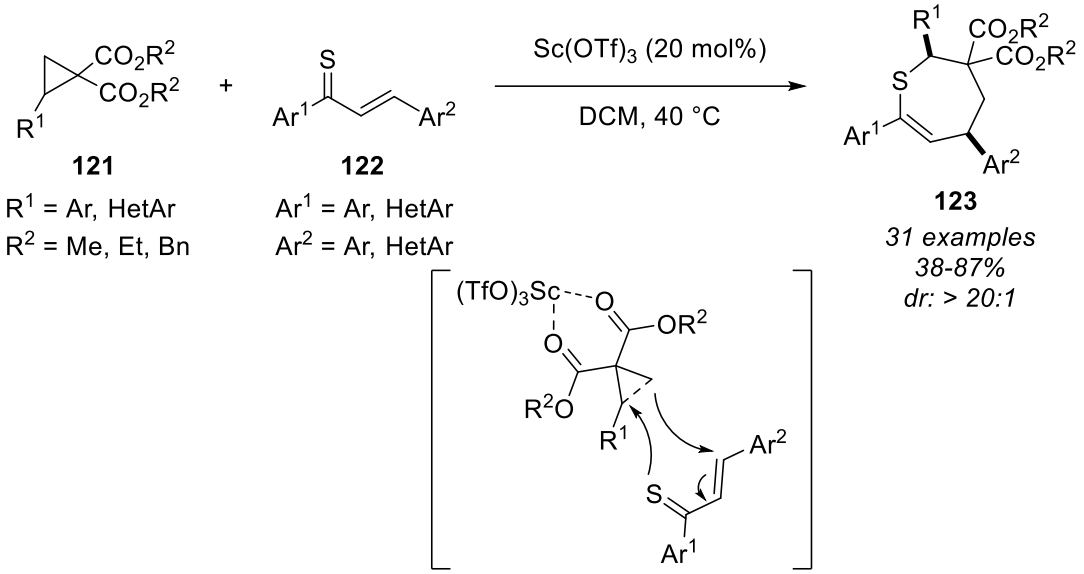
In 2005, the same group proposed the enantioselective version of their (4+3) cycloadditions using Lewis acid and chiral ligands.[189] More recently, Vicario and co-workers reported another

enantioselective (4+3) cycloaddition between allenamides **11** and furans **66**, in this case promoted by BINOL-based *N*-trifluoromethanesulfonyl phosphoramides **119**.[190] They obtained the desired cycloheptenes with a high degree of regio-, diastereo- and enantiocontrol by exploiting the bifunctional activation mode of the phosphoroamide catalyst. Thus, these catalysts combine the possibility of formation of both hydrogen bonds and electrostatic interactions with the iminium-stabilized oxyallyl cation intermediate (scheme 4.7).



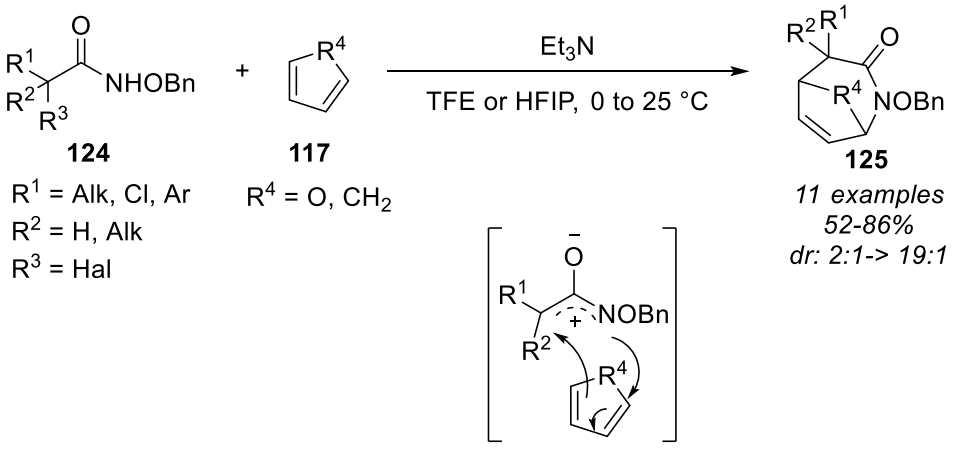
Scheme 4.7

More recently, the use of donor-acceptor cyclopropanes **121** as allyl cation precursors was investigated by Werz and co-worker.[195] They reported the synthesis of tetrahydrothiepines **123** from thiochalcones **122** as sulfur containing dienes and donor-acceptor cyclopropanes **121** as allyl cation precursors. Thus, donor-acceptor cyclopropanes are activated by scandium triflate and undergo cleavage of the C−C single bond between the donor and the acceptor substituted carbon atoms generating a 1,3-zwitterion able to react with the sulfur nucleophile. The reaction allowed for the construction of a series of seven-member rings in a stereospecific fashion (scheme 4.8).



Scheme 4.8

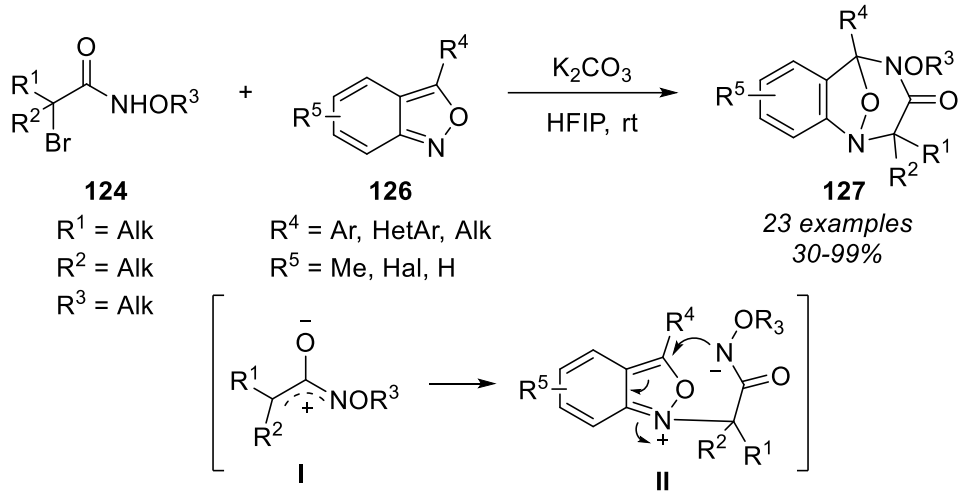
Furthermore, aza-oxyallyl cations have been taken into consideration for (4+3) cycloadditions. In particular, aza-oxyallyl cations could be generated from α-haloamides **124** by dehydrohalogenation as reported by Jeffrey and co-workers in 2011.[196] They reported the synthesis of a series of bicyclic lactam rings **125** from cyclic dienes **117** and different α-haloamides **124** with good diastereoselection under basic conditions (scheme 4.9). In addition, through computational studies, they revealed the importance of the presence of an alkoxy group bound to the nitrogen of the α-haloamides **124** able to stabilize the cationic intermediate.



Scheme 4.9

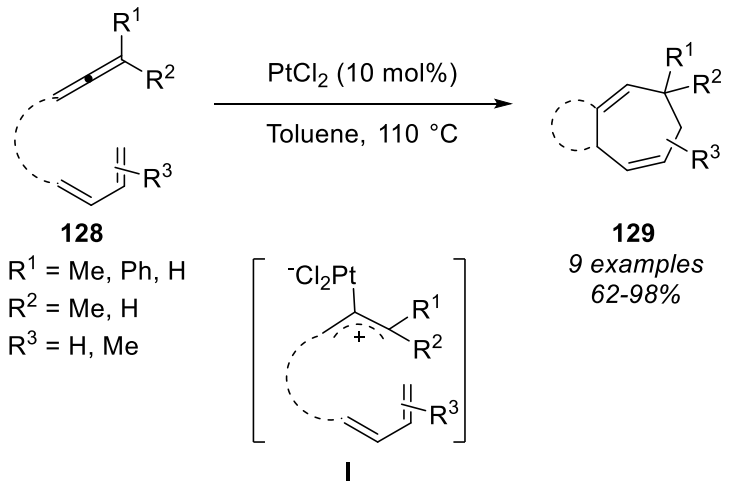
Moreover, α-haloamides **124** were employed by Zhao and co-workers in 2019 for the synthesis of benzodiazepine derivatives **127** using anthranils (benzo[*c*]isoxazole) **126** as four atom sources.[197]

The generation of the 1,3-dipole was promoted by base in a fluorinated solvent, giving rise to high yields of the desired compounds (scheme 4.10).



Scheme 4.10

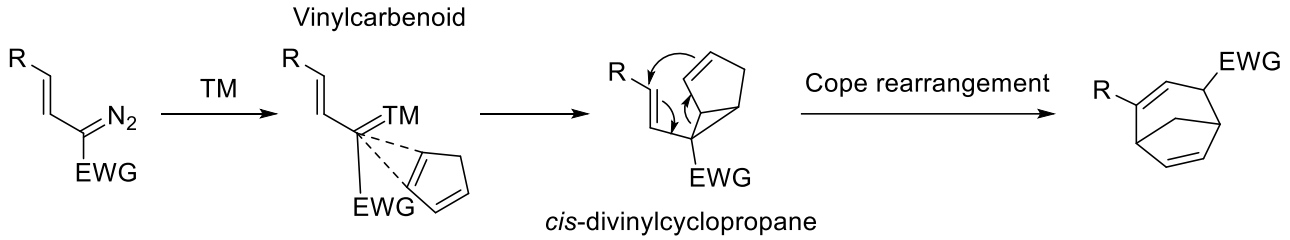
It is important to underline that in the last years, a series of publications reported the use of transition metals to activate allenes towards (4+3) cycloadditions.[178] One of the first examples was reported by Mascareñas and co-workers using $PtCl_2$ as catalyst for the diasteroselective transformation of allene-tethered 1,3-dienes **128** into bicycle [5.3.0] decane skeletons **129** (scheme 4.11).[191] The research group proposed also experimental and computational studies suggesting the involvement of a metal-allyl cation intermediate **I** generated *via* π-activation of the allene moiety by the metal, which underwent a concerted (4+3) cycloaddition reaction. The formation of the final product was due to a subsequent 1,2-proton shift.



Scheme 4.11

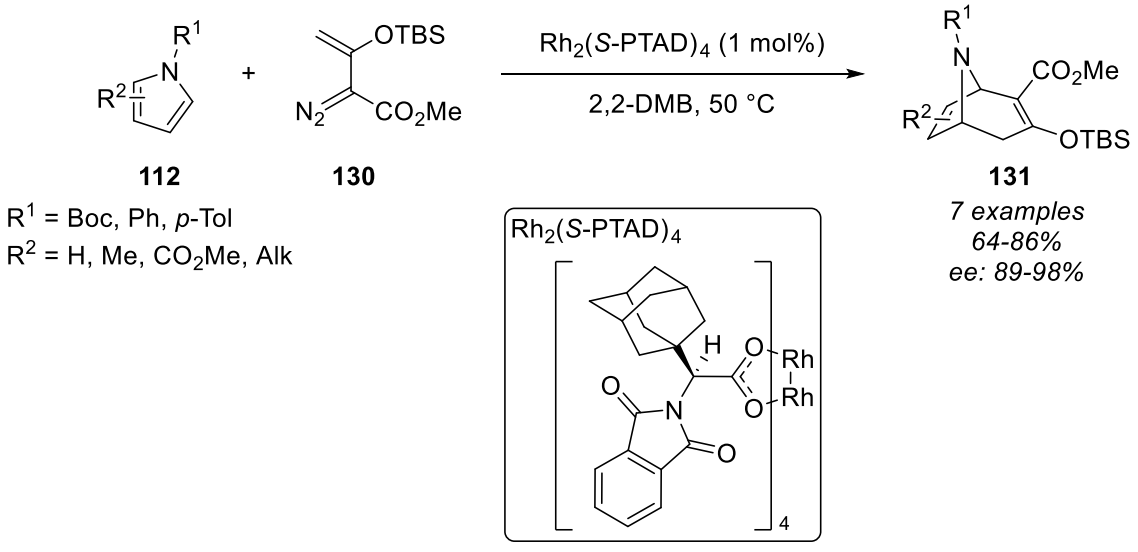
4.1.2 Formal (4+3) cycloaddition *via* domino cyclopropanation/Cope rearrangement

Formal (4+3) cycloaddition reactions are a useful method for the synthesis of seven-member rings and involves the use of a diene and a vinyldiazo compound under transition metal catalysis. The vinyldiazo compound in presence of a metal decomposes giving rise to a highly reactive vinyl carbene. When a diene is present in the reaction media, the carbene reacts with one of the two double bond of the diene forming a cyclopropanated derivative that undergoes Cope rearrangement to the corresponding seven-member ring (scheme 4.12).[193] The Cope rearrangement is the isomerization of a 1,5-diene forming a new regioisomeric 1,5-diene.[198] The cyclopropanation occurs with generation of a *cis*-divinylcyclopropane that after isomerization affords the seven-member ring (scheme 4.12).



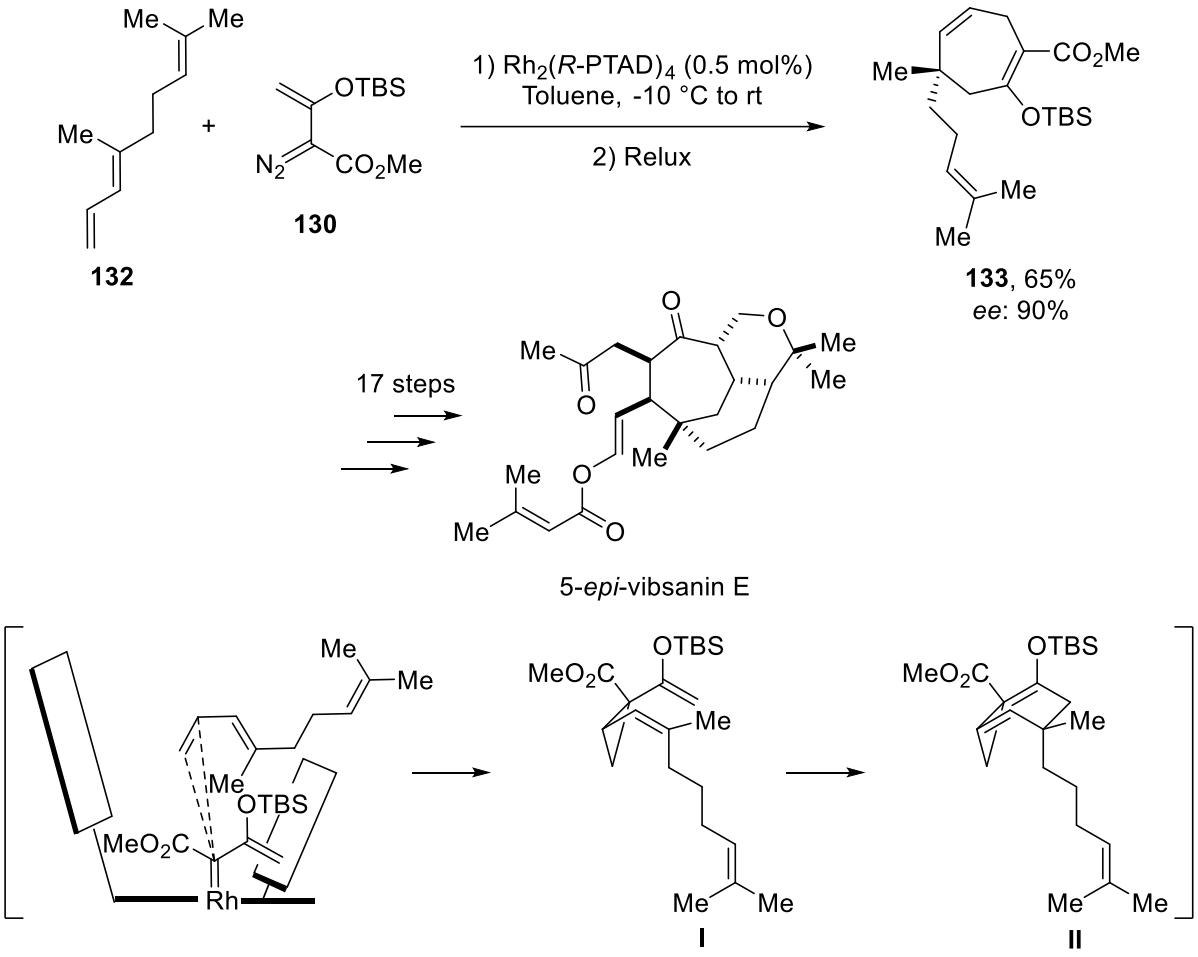
Scheme 4.12

Inter alias, this methodology was developed by Davies and co-worker in 2007 for the synthesis of tropanes **131**.[199] In particular, they proposed the asymmetric rhodium-catalyzed (4+3) cycloaddition between 2-(siloxy)vinyldiazoacetates **130** and pyrroles **112** (scheme 4.13). Thanks to the chiral rhodium ligand, the reaction proceeded with high enantioselectivity *via* a domino cyclopropanation/Cope rearrangement mechanism.



Scheme 4.13

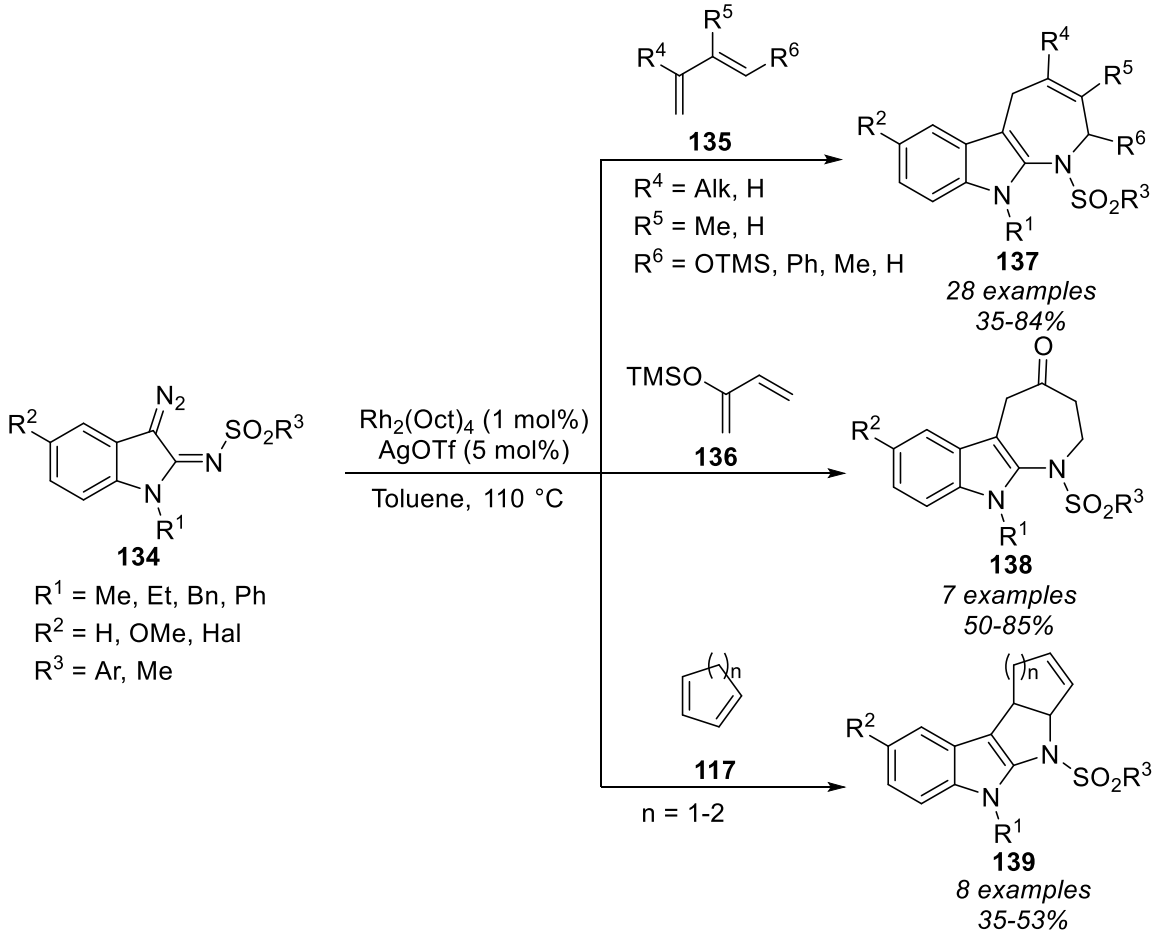
Successively, Davis, Williams and co-workers exploited the same transformation developing the synthesis of the natural product (-)-5-*epi*-vibsanin E employing 2-(siloxy)vinyldiazoacetate **130** and linear diene **132** for the construction of the seven-member ring **133** (scheme 4.14).[200] The use of dirhodium Rh_2(*R*-PTAD)$_4$ in the (4+3) cycloaddition allowed for the obtainment of good level of enantioselection thanks to the steric hindrance exerted by the catalyst that prevented the cyclization on one face of the carbene.



Scheme 4.14

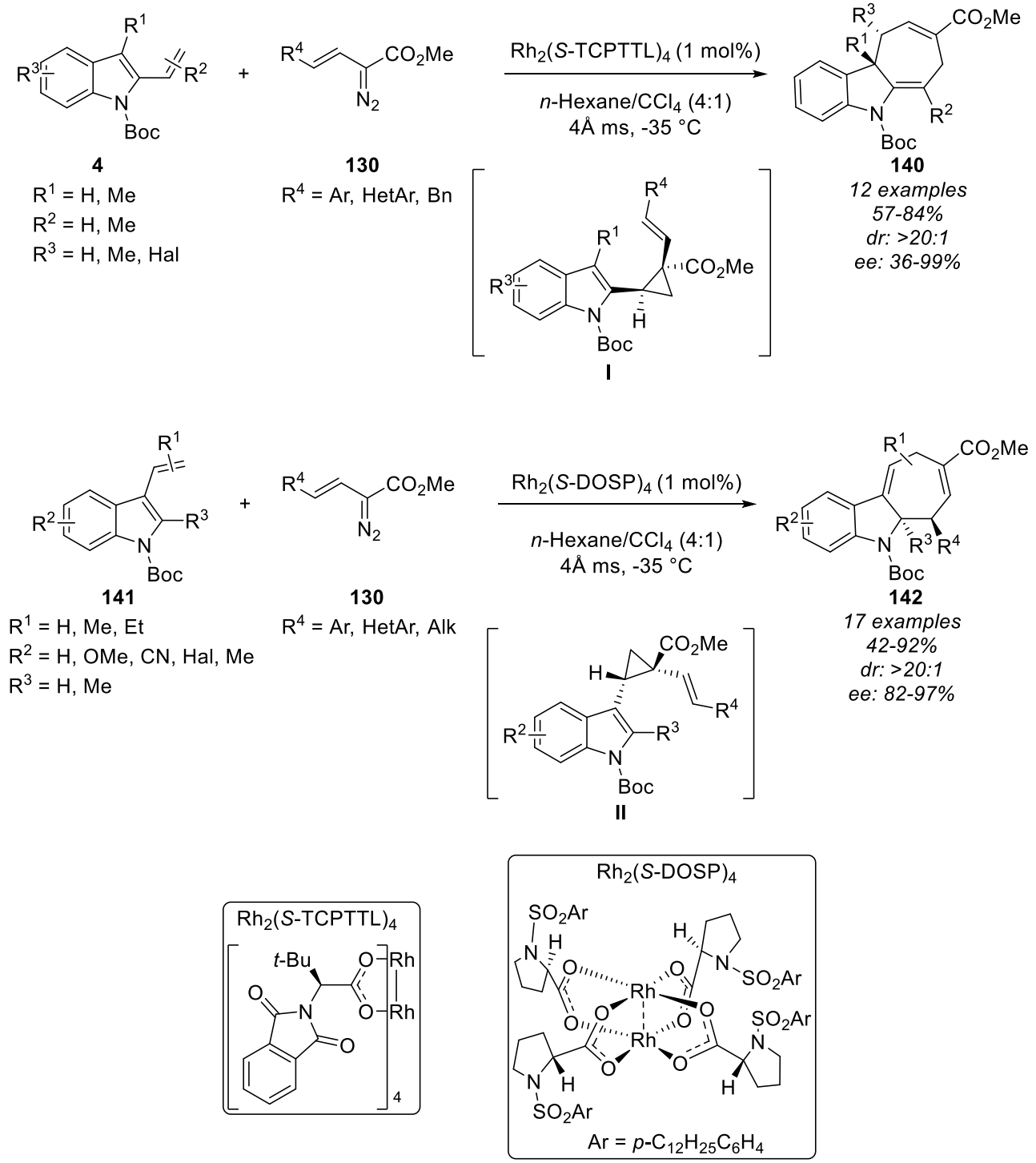
Recently, several indole derivatives have been involved in formal (4+3) cycloaddition in a cyclopropanation/Cope rearrangement sequence catalyzed by rhodium. In particular, in 2017 Wang and co-workers proposed the synthesis of azepino[2,3-*b*]indoles employing 3-diazoindolin-2-imines and dienes in the presence of Rh_2(Oct)$_4$.[201] In this case, the cycloaddition is an aza (4+3) cycloaddition in which the indole derivative **134** acted as an azavinyl rhodium carbene generated *in situ* by rhodium mediated decomposition of the diazo group in the starting material. Wang reported

that using linear 1,3-dienes **135**, azepino[2,3-*b*]indoles **137** were regioselectively synthetized, while using 2-[(trimethylsilyl)oxy]-1,3-butadienes **136** the corresponding azepino[2,3-*b*]indol-4(1*H*)-ones **138** were the expected reaction products. In addition, under the same reaction conditions, cyclic dienes **117** gave rise to the corresponding [3+2] cycloaddition products (scheme 4.15). The behavior of cyclic dienes was related to the unfavorable geometry of the cyclic diene that hindered the aza-Cope rearrangement.



Scheme 4.15

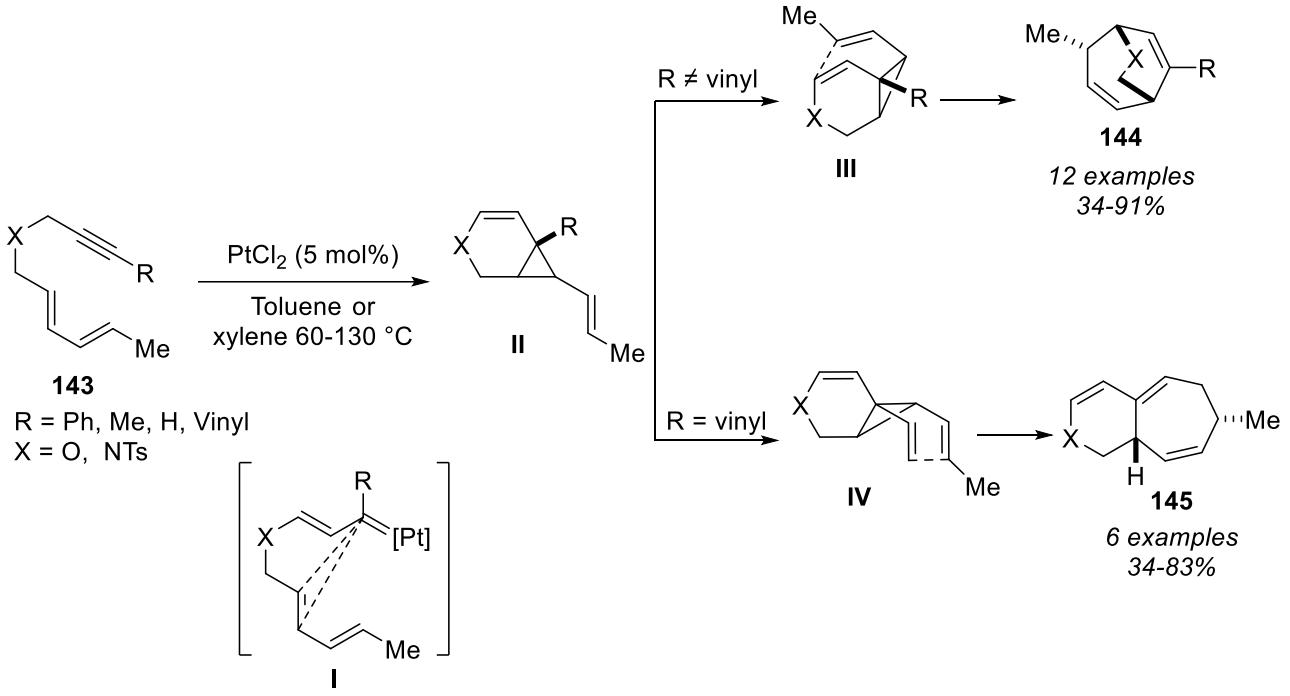
In 2018, Sun and co-workers proposed the formal (4+3) cyclization of 2- and 3-vinylindoles **4** and **141** as C4 partners with vinyldiazoacetates **130** as C3 synthons under chiral rhodium catalysis.[202] The transformation led to the synthesis of dearomatized indole derivatives **140** and **142** fused with a seven-member ring in good to excellent enantiomeric ratios (scheme 4.16). The enantioselection was induced by asymmetric cyclopropanation on the external double bond of the vinylindoles and the subsequent Cope rearrangement led to the obtainment of the desired seven-member rings.



Scheme 4.16

The formal (4+3) cycloadditions involving cyclopropanation and Cope rearrangement can be performed also in the presence of metal carbenes arising from the metal catalyzed rearrangement of compounds bearing triple bonds.[203] In particular in 2010, Chung and co-workers developed the synthesis of bicyclo[3.2.2]nonadienes **144** and 1,6,7,9a-tetrahydro-cyclohepta[*c*]pyrans and -pyridines **145** starting from dienyne derivatives **143** under platinum catalysis (scheme 4.17).[204] As

reported in scheme 4.17, the different outcome of the reaction was due to the different bonds interested in the Cope rearrangement.



Scheme 4.17

4.2 Synthesis of cyclohepta[*b*]indoles by (4+3) cycloaddition of 2-vinylindoles or 4*H*-furo[3,2-*b*]indoles with oxyallyl cations

4.2.1 Cyclohepta[*b*]indoles

The cyclohepta[*b*]indole nucleus is embedded in numerous natural and non-natural compounds showing a great variety of biological properties, from inhibition of adipocyte fatty-acid-binding protein (A-FABP), deacetylation of histones, inhibition of leukotriene p53 production, antituberculosis activities, and anti-HIV activities. The seven-member core is often inserted in more complex polycyclic structures both in natural and synthetic derivatives. In particular, Gaich and Stempel described a series of different alkaloids family that present this nucleus, the simplest examples are exotines or ervatamine, while the more complex are actinophillyc acid and ambiguines (figure 4.4).[205]

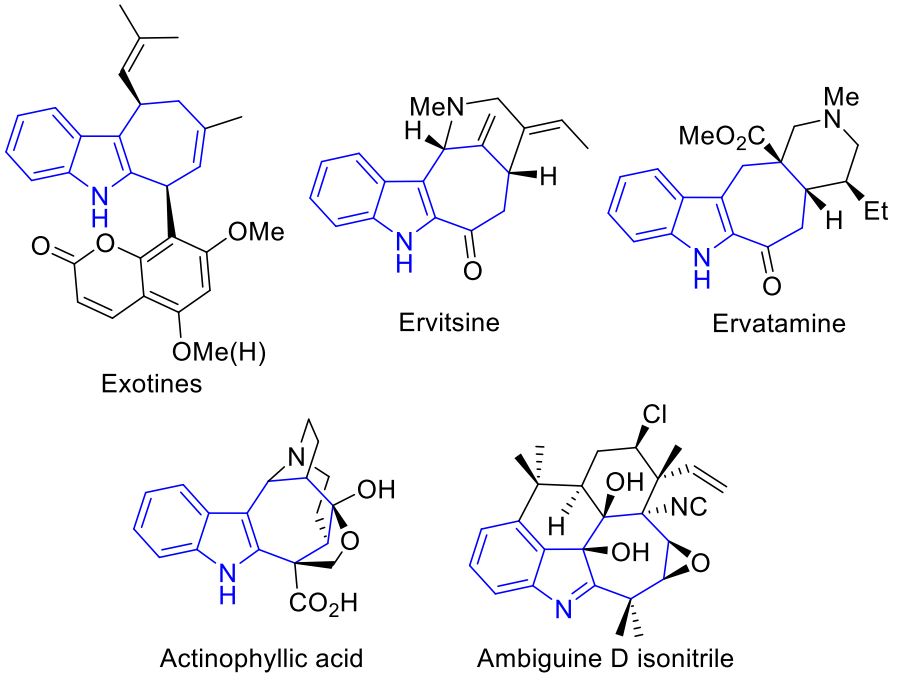


Figure 4.4

Starting from the biological activities of the natural compounds, different synthetic compounds and efficient synthesis have been developed in order to obtain new therapeutic agents. In this context, the most promising compounds are LTB4 inhibitors, anti-tubercular compounds, SIRT1 inhibitors and opioid receptor ligands (figure 4.5).

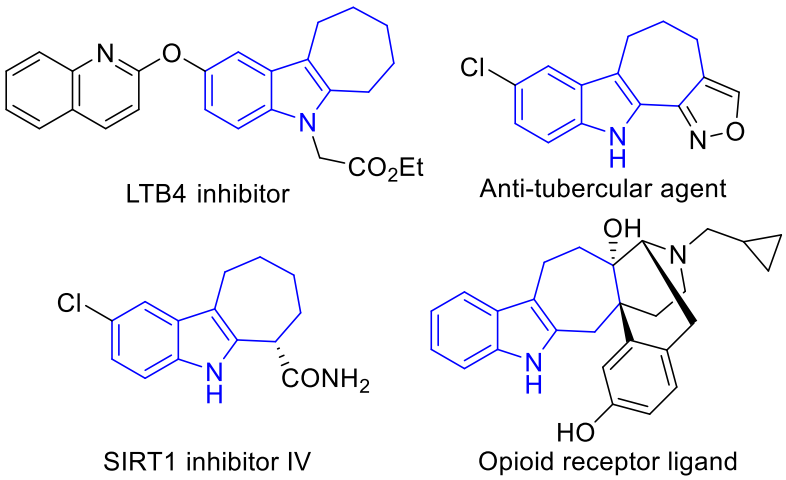
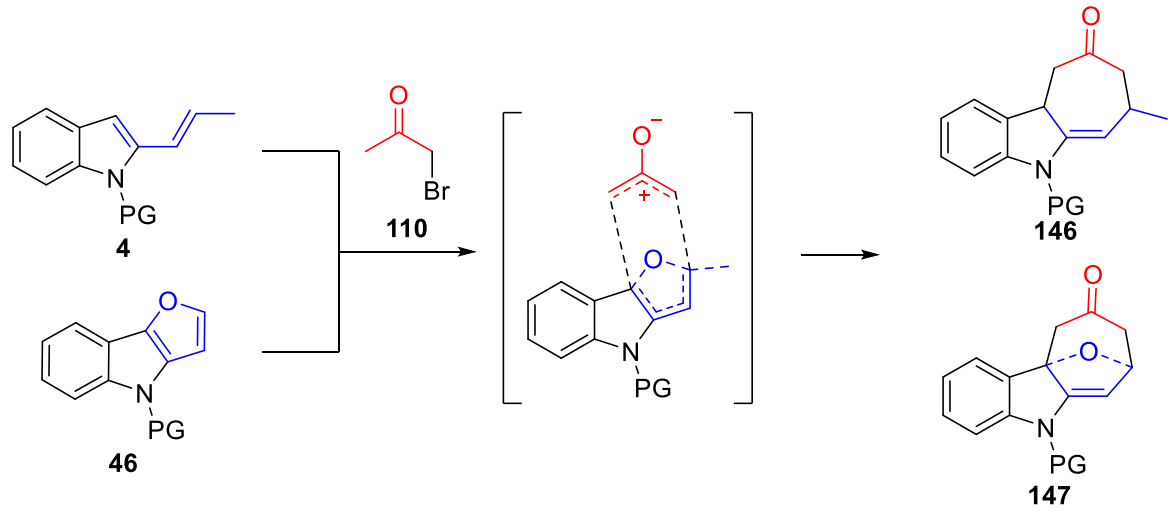


Figure 4.5

On this topic, Gaich and Stempel published an exhaustive review reporting the main methodologies for the construction of this important nucleus. In particular, beside the (4+3) cycloaddition reactions reported before, they summarized other applicable methodologies such as (5+2) cycloadditions, sigmatropic rearrangements and palladium-catalyzed cyclizations.[205]

4.2.2 Objectives

Knowing the ability of indole derivatives to participate in (4+3) cycloaddition reactions[20,202,206] and our expertise in the synthesis of complex indole derivatives using cycloaddition reactions,[6,14,27] we decided to test the reactivity of 2-vinylindoles with oxyallyl cations. Among the different methods for the generation of these cations, we chose the base-mediated dehydrohalogenation of α-bromoketones in order to employ easy-accessible starting materials to generate molecular complexity. The reaction between 2-vinylindoles and oxyallyl cations generated from α-bromoketones could result in the synthesis of cyclohepta[*b*]indole derivatives (scheme 4.18). In addition, taking into consideration the previously reported transformation of 4*H*-furo[3,2-*b*]indoles (see chapters 2 and 3), we decided to investigate the reactions of these compounds with oxyallyl cations to understand if the rigid diene of the furan moiety could present different reactivity with respect to the non-embedded diene of 2-vinylindoles (scheme 4.18).



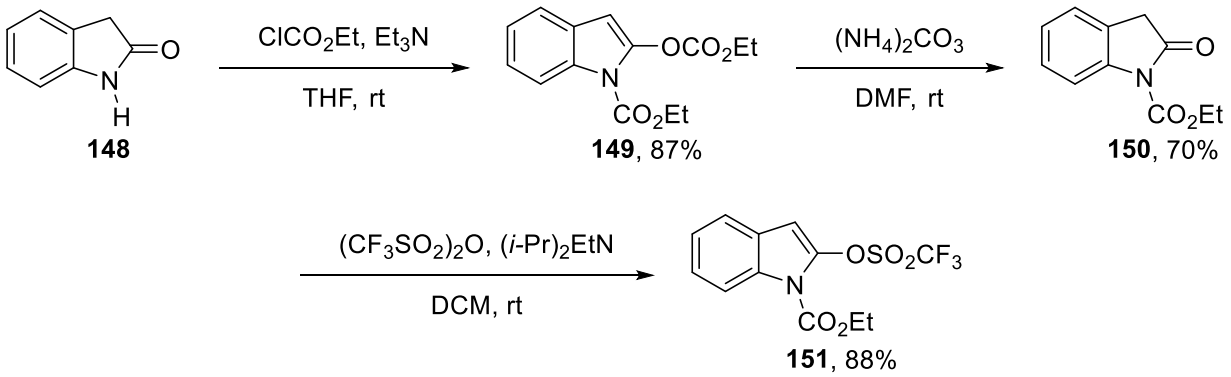
Scheme 4.18

4.2.3 Synthesis of starting materials

In this work 2-vinylindoles **4a−j**, ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a,b,f,g,n**, ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **141**, α-haloketones **110a−e**, and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124** have been synthetized and used.

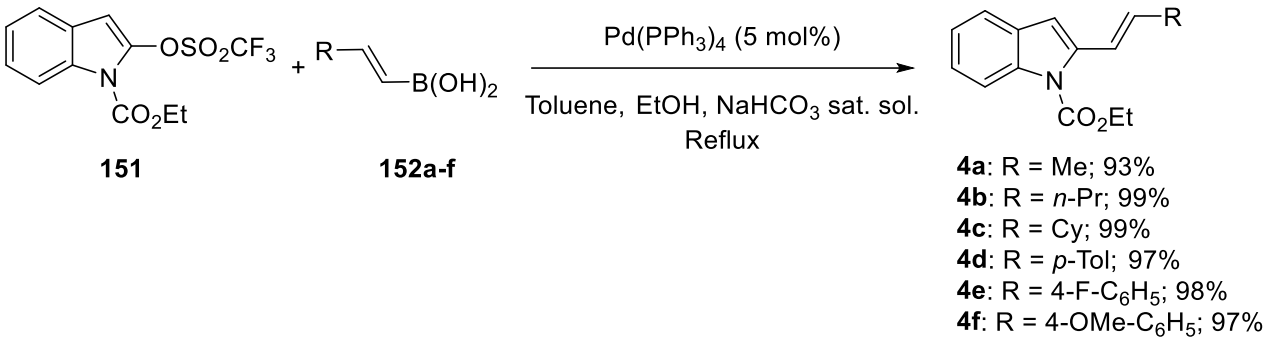
*4.2.3.1 Synthesis of 2-vinylindoles **4a-j***

In 2006, the research group of Professor Rossi reported a new synthetic pathway for the preparation of 2-vinylindoles.[127] The key step was a palladium-catalyzed cross-coupling reaction of 2-trifluoromethansulfonyloxyindole-1-carboxylic acid ethyl ester **151** and vinylboronic acids **152** to form the new C-C bond between the indole and the vinyl moiety.



Scheme 4.19

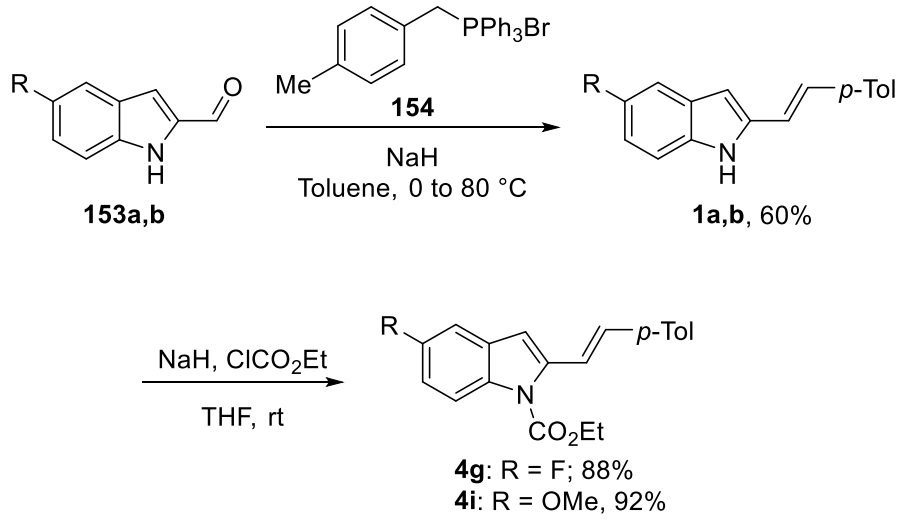
The synthesis of compound **151** started from the treatment of 2-indolinone **148** with ethylchloroformate in the presence of triethylamine at room temperature leading to the formation of **149** in 87% yield. Successively, compound **149** was partially hydrolyzed with ammonium carbonate in DMF yielding 70% of ethyl 2-oxoindoline-1-carboxylate **150**. Treatment of **150** with trifluoromethansulfonic anhydride in anhydrous dichloromethane and in presence of diisopropylethylamine afforded **151** in 88% yield. Then **151** was employed in Suzuki cross-coupling reactions catalyzed by $Pd(PPh_3)_4$ with boronic acids **152a-f** in a mixture of solvents consisting of toluene, ethanol and aqueous saturated solution of $NaHCO_3$ (Scheme 4.20).



Scheme 4.20

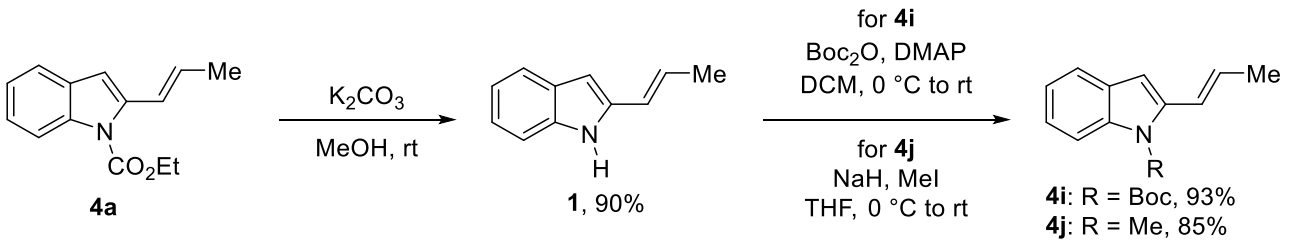
This synthetic approach allowed for the construction of a small library of 2-vinylindoles **4a-f** in good to quantitative yields, starting from a single precursor. More importantly, the geometry of the vinylboronic acid **152** was unaltered, enabling the access to the single (*E*)-isomer (scheme 4.20).

Instead, 2-vinylindoles **4g,h** were prepared by Wittig reaction between commercially available 2-formylindoles **153a,b** and (4-methylbenzyl)triphenylphosphonium bromide **154** followed by protection of the nitrogen atom of the indole nucleus with ethylchloroformate and NaH in THF (scheme 4.21)[109]



Scheme 4.21

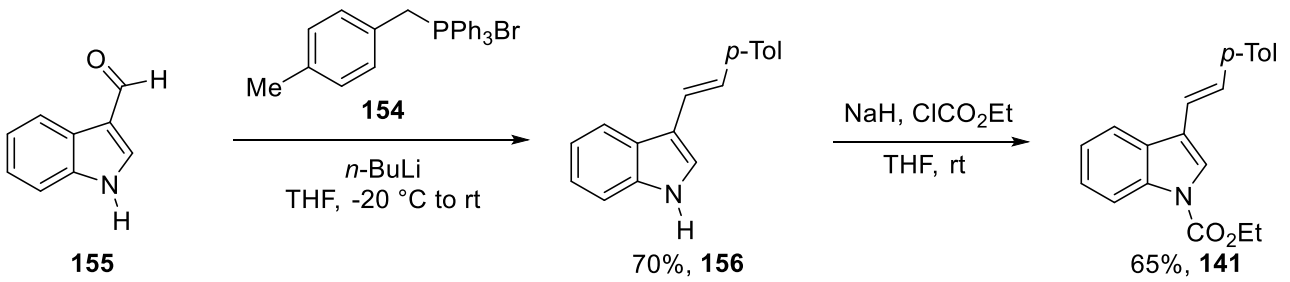
The last two 2-vinylindoles **4i,j** were prepared from 2-vinylindole **4a** in two step. The first common step was the deprotection on the nitrogen using K_2CO_3 in methanol. Successively, for compound **4i** the unprotected indole was treated with Boc_2O, DMAP and triethylamine in DCM,[207] whereas for compound **4j** the unprotected indole was treated with NaH and MeI (scheme 4.22).[62]



Scheme 4.22

*4.2.3.2 Synthesis of 3-vinylindoles **141***

3-vinylindoles **141** is a known compound and was preparaed according to literature procedure.[208] 3-vinylindoles **141** was prepared by Wittig reaction between commercially available 3-formylindoles **155** and (4-methylbenzyl)triphenylphosphonium bromide **154** followed by protection of the nitrogen atom of the indole nucleus with ethylchloroformate and NaH in THF (scheme 4.23)



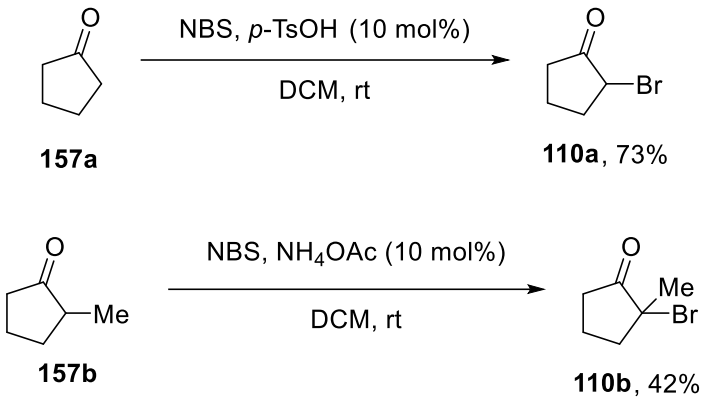
Scheme 4.23

*4.2.3.3 Synthesis of 4H-furo[3,2-b]indole **46a,b,f,g,n***

Ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates **46a,b,f,g,n** were prepared according to the procedure described in section 2.2.4.1 and 2.3.3.1.

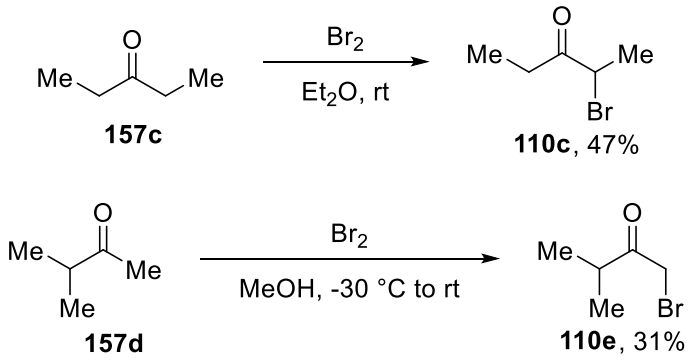
*4.2.3.4 Synthesis of α-haloketones **110a-e***

α-Haloketones **110a-e** are known compounds and were prepared according to literature procedure. α-Haloketones **157a,b** were brominated using NBS and, respectively, *para*-toluenesulfonic acid[209] or ammonium acetate[210] as catalysts. In this way, the desired haloketones **110a,b** were obtained in good yields (scheme 4.24)



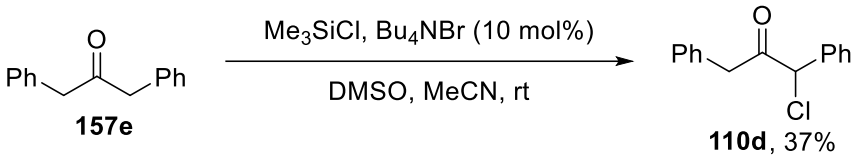
Scheme 4.24

Instead, the bromination of linear ketones **157c,d** took place using bromine and afforded compounds **110c,e** in moderate yields (scheme 4.25)[211,212]



Scheme 4.25

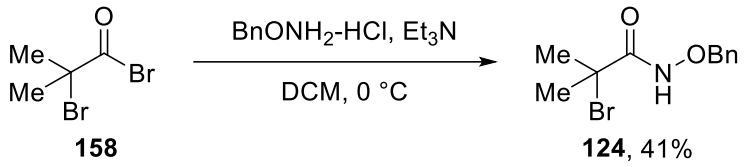
In addition, chloro-ketone **110d** was prepared using 1,3-diphenylpropan-2-one **157e** and trimethylsilyl chloride.[213] The reaction was promoted by a catalytic amount of Bu_4NBr and **110d** was obtained in modest 37% yield (scheme 4.26).



Scheme 4.26

*4.2.3.5 Synthesis of N-(benzyloxy)-2-bromo-2-methylpropanamide **124***

N-(benzyloxy)-2-bromo-2-methylpropanamide **124** is a known compound and it was prepared starting from *O*-benzylhydroxylamine HCl and 2-bromo-2-methylpropanoyl bromide **158** giving rise to **124** in moderate yield (scheme 4.27).[214]



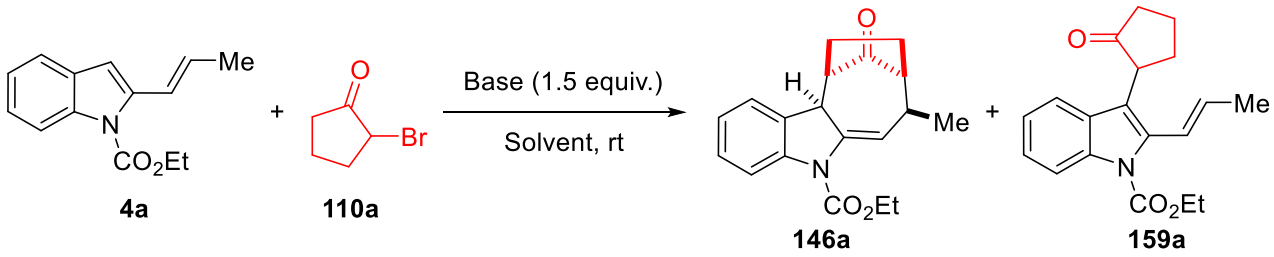
Scheme 4.27

4.2.4 (4+3) cyclization reactions between 2-vinylindoles or 4*H*-furo[3,2-*b*]indoles and oxyallyl cations

*4.2.4.1 Screening of the reaction condition for the synthesis of compound **146a***

In order to determine the best reaction conditions, 2-vinylindole **4a** and α-bromoketone **110a** were reacted using different bases and solvents at room temperature. It is important to underline that all reactions were conducted in presence of a fluorinated solvent because of the reported ability of this particular solvent of activating the carbonyl groups and of stabilizing cationic intermediates in related (4+3) cycloadditions.[215,216] The results are summarized in Table 4.1

*Table 4.1 Optimization of reaction conditions for the synthesis of **146a***



Entry	Base	Solvent	Time, h	146a,[b] %	159a,[b] %
1	Na_2CO_3	TFE (1 M)	3	67	17
2	Et_3N	TFE (1 M)	1	56	26
3	DIPEA	TFE (1 M)	1	75	17
4	DBU	TFE (1 M)	3	50	15
5[c]	DIPEA	TFE (1 M)	2	53	32
6	DIPEA	HFIP (1 M)	1	53	47
7	DIPEA	TFE (1 equiv.) Toluene (0.5 M)	22	32	<5
8	DIPEA	TFE (3 equiv.) Toluene (0.5 M)	6	53	<5
9	DIPEA	TFE (6 equiv.) Toluene (0.5 M)	1	88	<5
10	DIPEA	TFE (6 equiv.) DCM (0.5 M)	1	74	13
11	DIPEA	$LiClO_4$ (1 equiv.) Et_2O (0.5 M)	22	27	<5

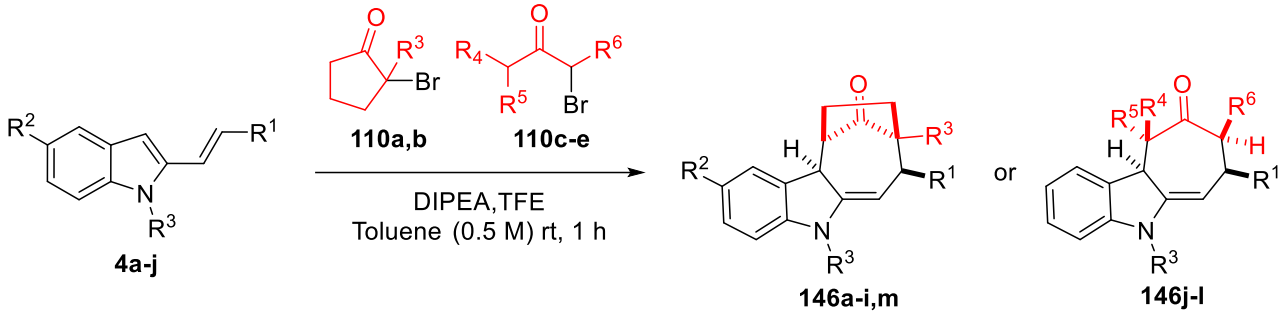
[a]All reactions were carried out using **4a** (0.2 mmol), **110a** (0.28 mmol), base (0.3 mmol) in the stated solvent or in TFE/solvent mixture at rt for 1-22 h. [b]Isolated Yield. [c]Reaction performed at -20 °C.

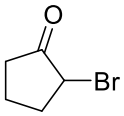
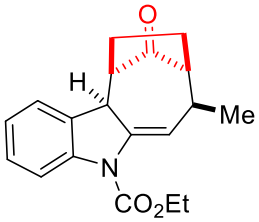
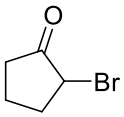
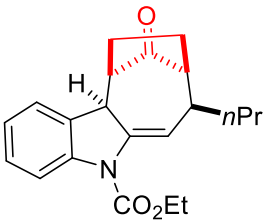
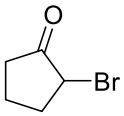
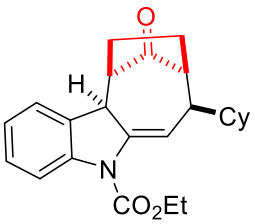
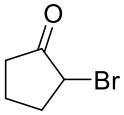
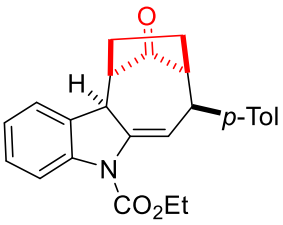
At the beginning, different bases, organic and inorganic, were investigated in TFE as solvent. Entries 1-4 show the outcome of the reaction using $NaCO_3$, Et_3N, DIPEA and DBU furnishing the desired dearomatized polycyclic indole derivative **146a** in good yields beside a small amount of the product **159a** arising from the nucleophilic attack of the C3 carbon of the indole on the oxyallyl cation generated *in situ* from the α-bromoketone **110a**. The base chosen for the screening of other parameters was the DIPEA because of the better ratio obtained between **146a** and **159a** (entry 3). Successively, to reduce the competitive nucleophilic addition, the transformation was conducted at -20 °C. However, any improvement in term of selectivity was reached (entry 5). Changing the fluorinated solvent in favor of HFIP caused the reduction of the formation of **146a** in favor of **159a**, obtaining nearly a 1:1 ratio (entry 6). In order to test the influence of the fluorinated solvent in this transformation, different equivalents of TFE in a solution of toluene 0.5 M were employed. Entries 7-9 show the inhibition of undesired reaction (less than 5% of **159a**) in favor to the formation of **146a**, beside an increase of the reaction time. In particular, using only one equivalent of TFE, the reaction required a prolonged reaction time resulting in an unsatisfying 32% yield (entry 7). Tripling the equivalents, the yield and the reaction time underwent to a small improvement (entry 8), even if, the best results were obtained using 6 equivalents of TFE, 88% of yield in only one hour (entry 9). Successively, toluene was replaced by dichloromethane, however it induced a decrease in term of **146a**/**159a** ratio and yield (entry 10). At the end, a classical Lewis acid employed in this kind of transformation[203] was tested. $LiClO_4$ in diethyl ether was used inducing a significant decrease in the yield, despite of a prolonged reaction time (entry 11). In all tested conditions, the reaction induced the synthesis of only a single diastereoisomer, which structure was fully assigned by 1D and 2D NMR investigations.

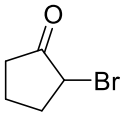
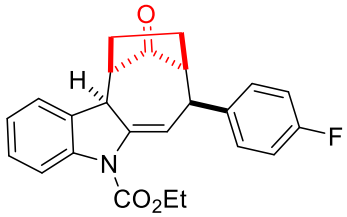
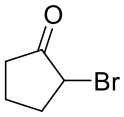
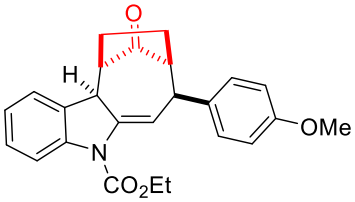
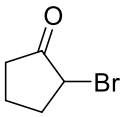
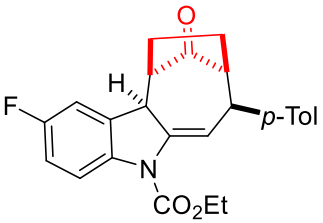
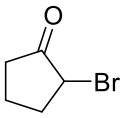
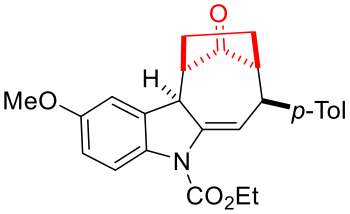
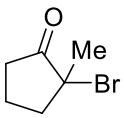
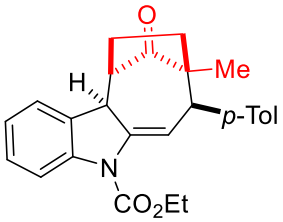
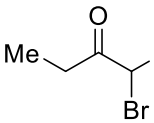
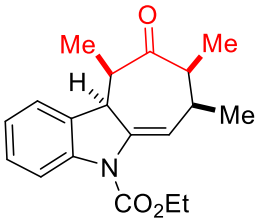
*4.2.4.2 Scope with 2-vinylindoles **4a-j***

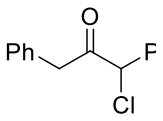
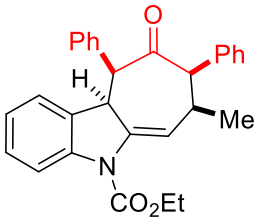
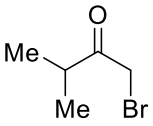
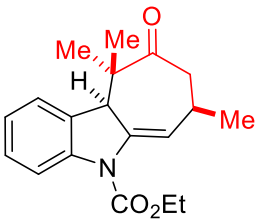
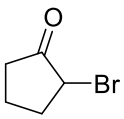
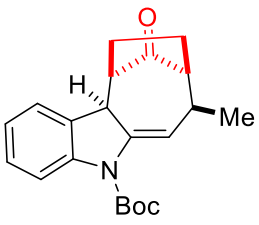
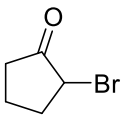
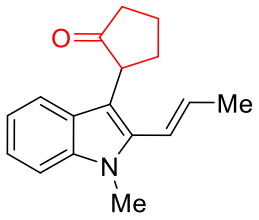
With the best reaction conditions in hands, the scope of the transformation was then explored using 2-vinylindoles **4a-j** and α-bromoketones **110a-e**. The results are summarized in Table 4.2.

*Table 4.2 Scope for the synthesis of compound **146a-m***



Entry	4	R^1	R^2	R^3	110	Product	Yield,[b] %
1	**4a**	Me	H	CO_2Et	 **110a**	 **146a**	88
2	**4b**	*n*-Pr	H	CO_2Et	 **110a**	 **146b**	58
3	**4c**	Cy	H	CO_2Et	 **110a**	 **146c**	69
4	**4d**	4-Me-C_6H_4	H	CO_2Et	 **110a**	 **146d**	80

5	**4e**	4-F-C_6H_4	H	CO_2Et	 **110a**	 **146e**	70
6	**4f**	4-OMe-C_6H_4	H	CO_2Et	 **110a**	 **146f**	79
7	**4g**	4-Me-C_6H_4	F	CO_2Et	 **110a**	 **146g**	68
8	**4h**	4-Me-C_6H_4	OMe	CO_2Et	 **110a**	 **146h**	70
9	**4d**	4-Me-C_6H_4	H	CO_2Et	 **110b**	 **146i**	72[c]
10	**4a**	Me	H	CO_2Et	 **110c**	 **146j**	78[c]

11	**4a**	Me	H	CO_2Et	 **110d**	 **146k**	55[c]
12	**4a**	Me	H	CO_2Et	 **110e**	 **146l**	37[d]
13	**4i**	Me	H	Boc	 **110a**	 **146m**	72
14	**4j**	Me	H	Me	 **110a**	 **159b**	55

[a]All reactions were carried out using **4** (0.2 mmol), **110** (0.28 mmol), DIPEA (0.3 mmol), TFE (1.2 mmol) in toluene (0.4 ml) for 1 h at rt. [b]Isolated yield. [c]TFE (1 M) was used as solvent for 24 h at rt. [d]Na_2CO_3 was used as base in TFE (1 M) for 48 h at 40 °C.

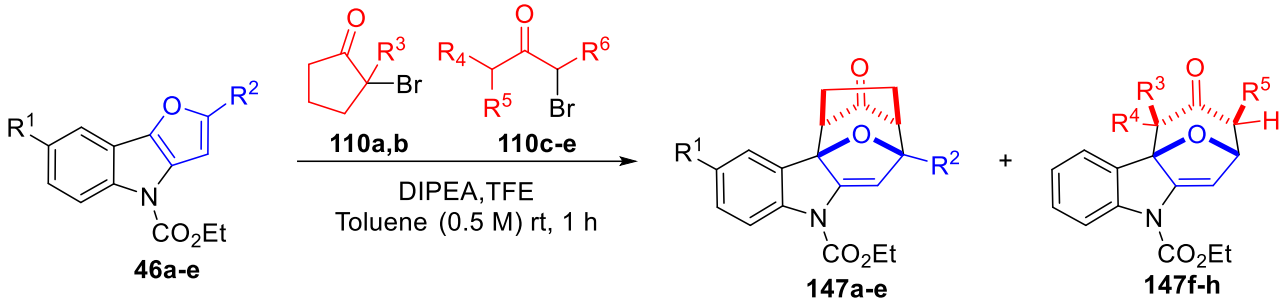
At the beginning the influence of different β-alkyl and β-aryl substituted 2-vinylindoles **4** was investigated. Firstly, β-*n*-propyl and β-cyclohexyl derivatives **4a** and **4b** were used yielding **146b** and **146c** in 58% and 69% yield, respectively, beside small amount of starting material and less than 10% of nucleophilic substitution adducts (entries 2 and 3). Shifting to β-aryl moieties, the results were satisfying. 4-methylstyrylvinylindole **4d** was well tolerated, allowing to obtain the corresponding seven-member ring **146d** in 80% yield (entry 4). Moving to electron-withdrawing group in *para* position the yield remained good (entry 5) and similar results were achieved with electron-donor 4-methoxystyrylvinylindole **4f** (entry 6). Successively, different 5-substituted 2-vinylindoles were

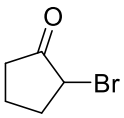
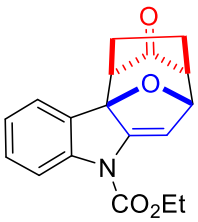
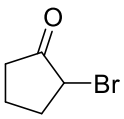
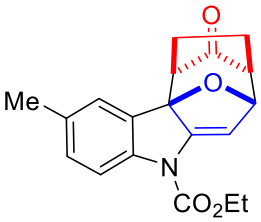
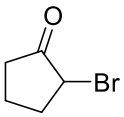
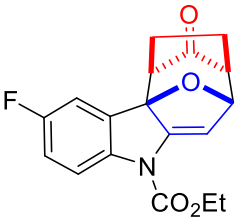
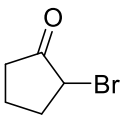
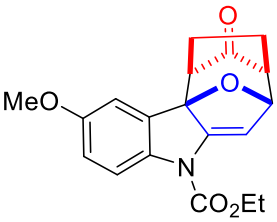
tested in order to evaluate the influence of electron-rich or electron-poor groups on the nucleophilicity of the C3 carbon of the indole. Fortunately, both 5-fluoro and 5-methoxy substituents were well tolerated giving rise to **146g** and **146h** respectively in 68 and 70% yields (entries 7 and 8). Finally, different α-bromoketones were employed. Using the more substituted 2-bromo-2-methylcyclopenta-1-one **110b** with indole **4d**, the conversion underwent to a significant decrease and even after a prolonged reaction time, the reaction resulted in the isolation of the desired compound in very low yield. In order to improve the result, the reaction was conducted in pure TFE giving rise to an unexpected and satisfying 72% yield for **146i** without any product arising from the nucleophilic substitution reaction (entry 9). Successively, linear symmetric ketones **110c** and **110d** were employed, leading to the isolation of product **146j** and **146k** in respectively 78% and 55% yield always using pure TFE as solvent (entries 10 and 11). Finally, linear non-symmetrically disubstituted ketone **110e** were employed in TFE at 40 °C. With this challenging substrate, a brief screening was required and changing the organic base in favor to inorganic Na_2CO_3 and performing the reaction at 40 °C for a prolonged reaction time, the isolation of **146l** as a single isomer was possible in modest 37% yield (entry 12). At the end, the influence of the nitrogen protecting group was investigated, using a more hindered electron-withdrawing Boc group and an electron-donating methyl group. The outcome of the two reactions were completely different. In the first case, a good 72% yield of the desired seven-member ring **146m** was obtained (entry 13). While with *N*-methyl substituted indole **4j** the only isolated product (beside unreacted starting material) was the nucleophilic addition adduct **159b** in 55% yield, underling the importance of the presence of electron-withdrawing protecting group at the indole nitrogen.

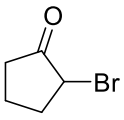
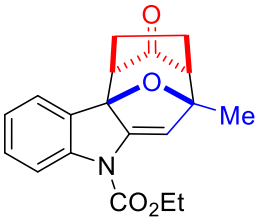
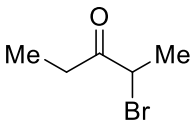
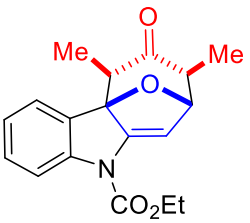
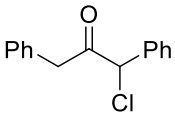
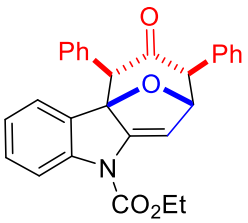
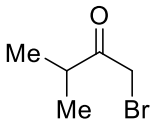
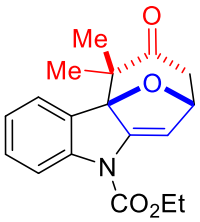
*4.2.4.3 Scope with 4*H*-furo[3,2-*b*]indoles* **46a,b,f,g,n**

As reported before, 4*H*-furo[3,2-*b*]indoles present the same diene system of 2-vinylindoles, but embedded in a rigid furan ring with a forced *s*-cis conformation. Thus, we decided to test a series of 4*H*-furo[3,2-*b*]indoles **46a,b,f,g,n** in the (4+3) cycloadditions with oxyallyl cations under the previously optimized reaction conditions. The results are summarized in Table 4.3

Table 4.3 Scope for the synthesis of compound ***157a-h***



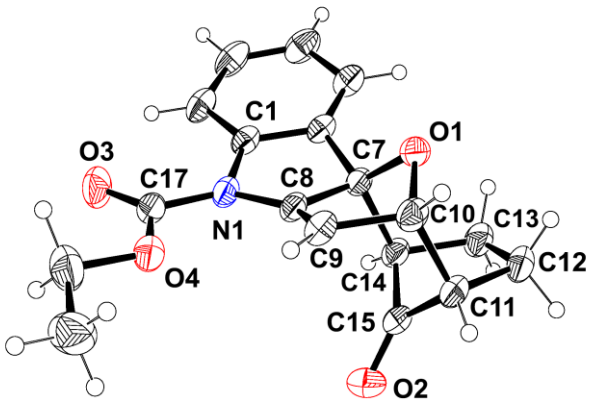
Entry	46	R^1	R^2	110	Product	Yield,[b] %
1	**46a**	H	H	 **110a**	 **147a**	77
2	**46f**	Me	H	 **110a**	 **147b**	80
3	**46g**	F	H	 **110a**	 **147c**	70
4	**46n**	OMe	H	 **110a**	 **147d**	73

5	**46b**	H	Me	 **110a**	 **147e**	77
6	**46a**	H	H	 **110c**	 **147f**	78[c]
7	**46a**	H	H	 **110d**	 **147g**	95[c]
8	**46a**	H	H	 **110e**	 **147h**	57[d]

[a]All reactions were carried out using **46** (0.2 mmol), **110** (0.28 mmol), DIPEA (0.3 mmol), TFE (1.2 mmol) in toluene (0.4 ml) for 2-3 h at rt. [b]Isolated yield. [c]TFE (1 M) was used as solvent for 24 h at rt. [d]Na_2CO_3 was used as base in TFE (1 M) for 48 h at 40 °C.

At the beginning 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** was tested with 2-bromocyclopentan-1-one **110a** in toluene with TFE and DIPEA. After 2 hours the isolation of 7,8-dihydro-5*H*-7,10a-epoxycyclohepta[*b*]indole derivative **147a** was possible in good 72% yield (entry 1). It was important to note that the product was obtained as a single isomer without any traces of the nucleophilic addition product. In order to confirm the structure of **147a**, a series of 1D, 2D NMR and X-ray diffraction analysis (figure 4.6) were conducted. Also in this case, the influence of the functional group in 5 position of the furoindole on the outcome of the reaction was investigated. In particular, electron-withdrawing fluorine group and electron-donating methyl and methoxy groups were tested

(furoindoles **46f**, **46g** and **46n**) and the corresponding products **147b-d** were obtained in all cases in good yield (respectively 70, 80 and 73%) (entries 2-4). 4*H*-furo[3,2-*b*]indole **46b** with a methyl group in 2 position of the furan ring was employed leading to the formation of the corresponding product **147e** in good 77% yield in 3 hours (entry 5). As for 2-vinylindoles, finally, linear symmetric and non-symmetric bromoketones **110c-e** were used. As reported before, also in these experiments, with symmetric ketones **110c,d** the reaction with **46a** required pure TFE as solvent and 24 hours of reaction time affording the corresponding compounds **147f-g** in good 78% and 95% yield (entries 6 and 7). In addition, the non-symmetric 1-bromo-3-methylbutan-1-one **110e** needed Na_2CO_3 as base at 40 °C in TFE to obtain from **46a** the corresponding product **147h** in good 57% yield after 48 hours (entry 8).

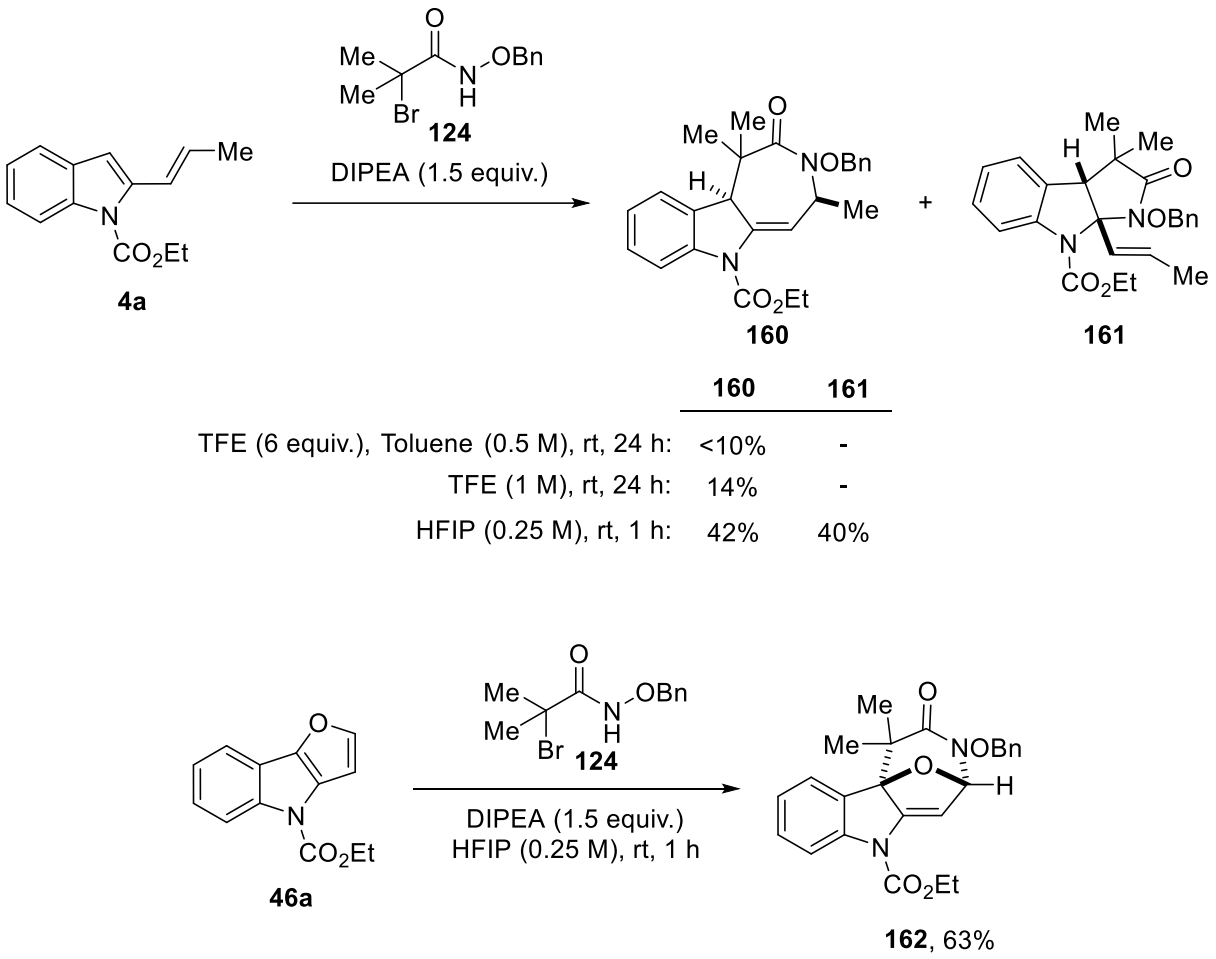


147a

Figure 4.6

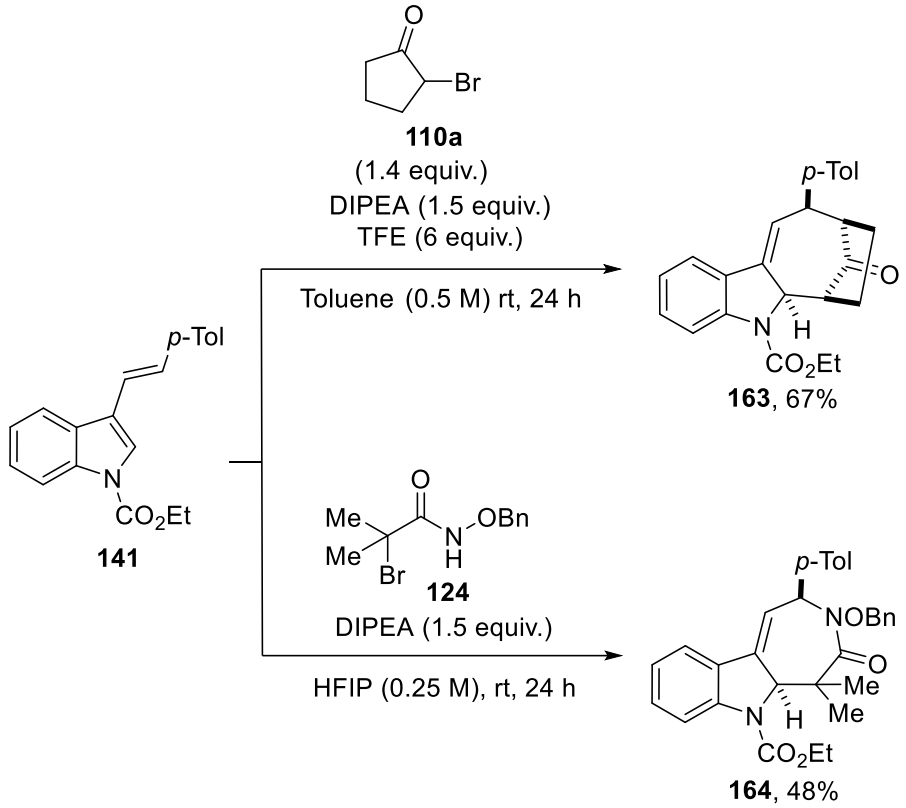
4.2.4.4 Additional (4+3) cycloaddition products

As reported before, another class of suitable reaction partners for (4+3) cycloaddition reactions are the aza-oxyallyl cations.[196,197] Thus, *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124** was tested under the best reaction conditions with 2-vinylindole **4a**. Unfortunately, the reaction was extremely slow and after 24 hours only traces of the cycloaddition product **160** were detected. Thus, a brief screening of the reaction conditions was performed: using TFE as sole solvent, the isolation of the product underwent to a small increase, obtaining **160** in unsatisfying 14% yield. Successively, TFE was substituted by HFIP that induced an improvement of the reaction time and a total conversion of the starting material. Unfortunately, the outcome of the reaction led to the isolation of two products in a 1:1 ratio and arising from a (4+3) and [3+2] cycloaddition pathway (scheme 4.28). Successively, also 4*H*-furo[3,2-*b*]indole **46a** was employed in HFIP and DIPEA, affording the cycloadduct **162** as a single product in good 63% yield (scheme 4.28)



Scheme 4.28

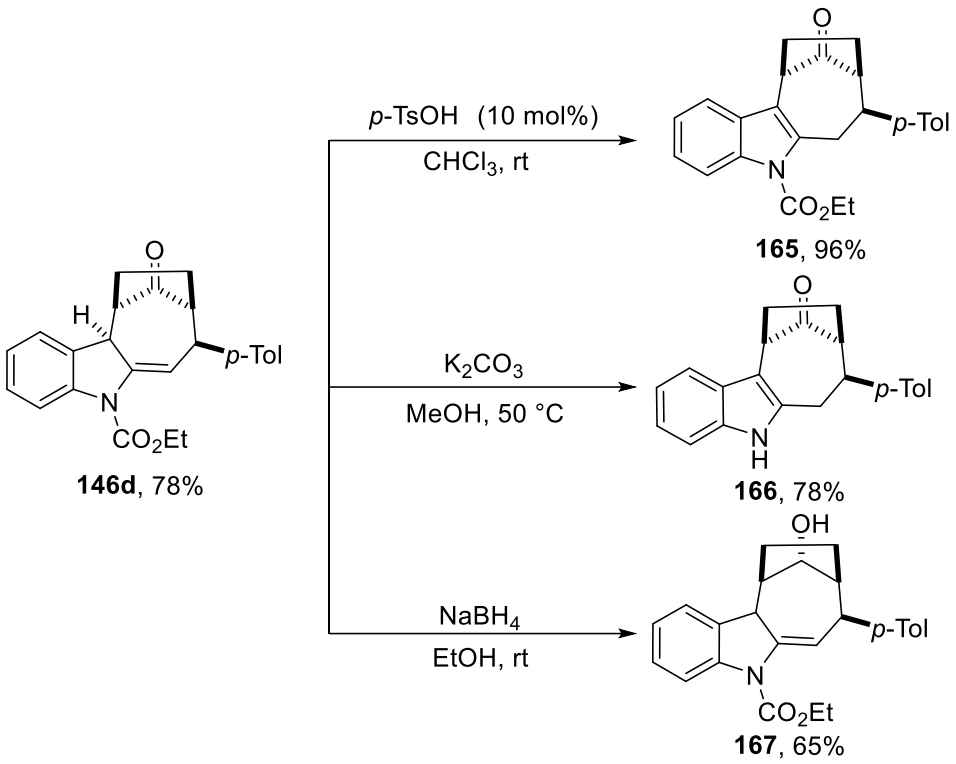
The last scope development was conducted with 3-vinylindole **141**. In this case, 3-vinylindole **141** was reacted with both α-bromoketone **110a** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124** under the best reaction conditions reported in table 4.1, entry 9. The substrate **141** resulted less reactive than 2-vinyilindole in both transformations requiring prolonged reaction times to isolate the corresponding products. In the first case, cycloadduct **163** was obtained in good 67% yield, while in the second case, product **164** was isolated in only 48% yield as a single product beside unreacted starting materials (scheme 4.29).



Scheme 4.29

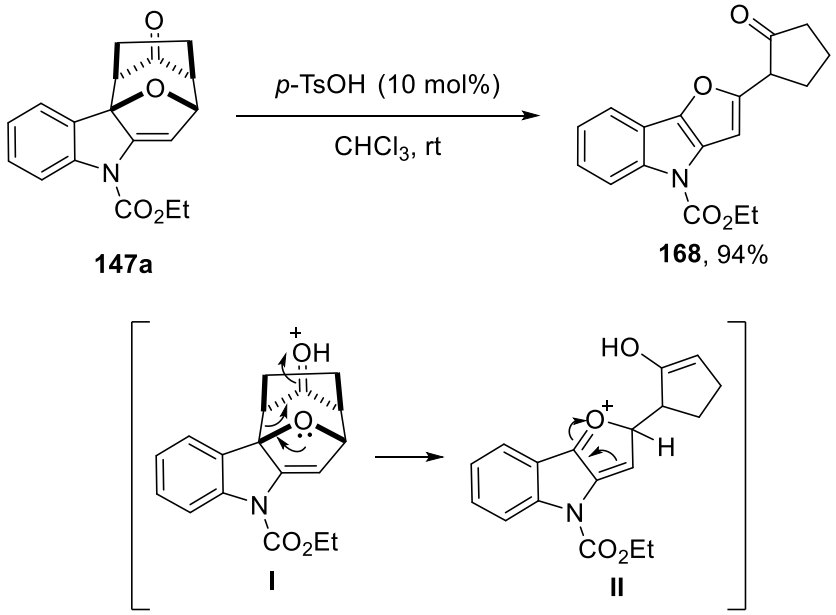
*4.2.4.5 Synthetic elaboration of cyclohepta[b]indoles **146d** and **147a***

Finally, having in hands a series of cyclohepta[*b*]indoles some simple transformations were carried out in order to test the stability and reactivity of this system. To this aim, cyclohepta[*b*]indole **146d** was synthetized in 1 gram scale and successively employed in different test reactions. Firstly, it was tested under catalytic acidic conditions. In particular, *p*-TsOH was used at 10 mol% concentration in chloroform and the corresponding aromatized derivative **165** was the sole isolated compounds (scheme 4.30). Successively, **146d** was treated in basic hydrolytic conditions in order to cleave the nitrogen protecting group. In this case, K_2CO_3 in methanol was employed and the corresponding NH-free aromatic indole derivative **166** was isolated in good 78% yield (scheme 4.30). The last investigated transformation was under chemical reductive conditions ($NaBH_4$) and gave rise to the non-aromatized alcohol derivative **167** in good 65% yield (scheme 4.30).



Scheme 4.30

In order to understand if the cyclic product arising from furoindole could also undergo a re-aromatization of the indole core after a ring opening event of the furan moiety, cycloadduct **147a** was treated with catalytic amount of *p*-TsOH. However, after 1.5 hours the 2-(2-oxocyclopentyl)-4*H*-furo[3,2-*b*]indole derivative **168** was isolated in high 94% yield (scheme 4.31).

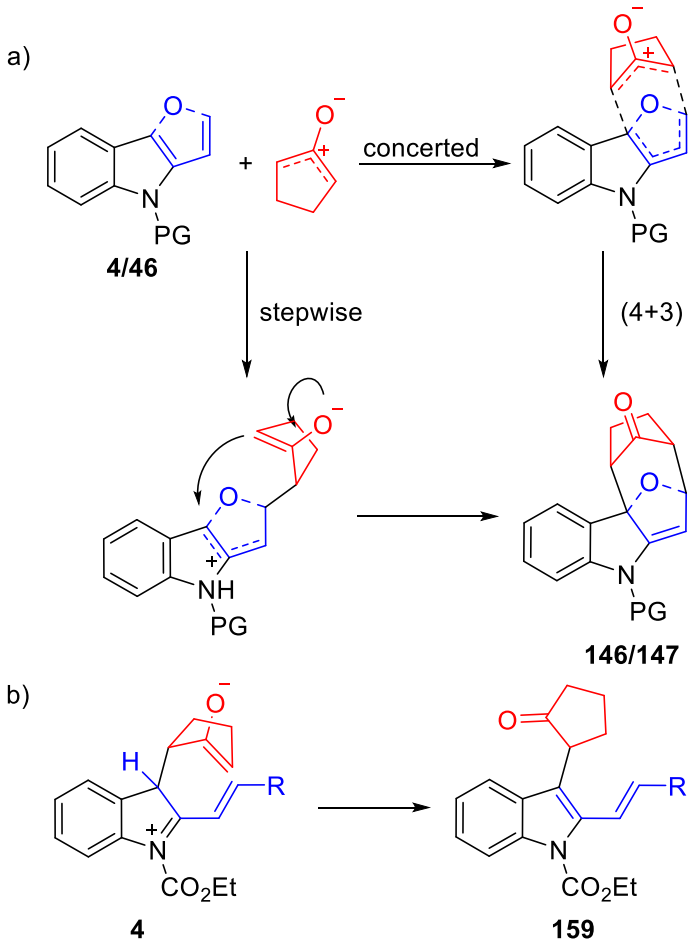


Scheme 4.31

A similar transformation was reported by Harmata treating the cycloadduct obtained from 2-chorocyclopentanones and furans in acidic condition.[217] A plausible mechanism that justify the product could be described with the Grob fragmentation[218] in which the protonation of the carbonyl group of **147a** induces the re-aromatization of the furan moiety. Successively the keto-enol tautomerism regenerate the cyclopentanone ring (scheme 4.31).

4.2.4.6 Proposed mechanism

As reported before the (4+3) cycloadditions, from an electronic point of view, stand as homologous of the [4+2] Diels-Alder reactions. Thus, this kind of transformations can occur in a classical pure concerted pathway or in a stepwise fashion (scheme 4.32).[177,203,219]



Scheme 4.32

However, the exact prediction of the mechanism it not easy and only some hypothesis could be suggested based on the chemical and stereochemical results. The chemical and the stereochemical

outcome of the reactions can be affected by the substitution pattern of the reactants and by the reaction conditions settled for the transformation. Thus, our cycloadditions occur with complete regio- and diastereselectivity probably through an *endo* approach between the diene and the dienophile (figure 4.67.

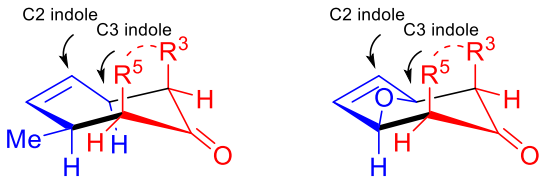


Figure 4.7

The two different diene systems employed in this study led to similar results in term of stereoselectivity with both linear and cyclic oxyallyl cations. Thus, based on these results, the transformation could be seen as a concerted cycloaddition. Nevertheless, a fast-stepwise or pseudo-concerted mechanism cannot be excluded because of the electronic features of the dienes (polarized and electron-rich) and dienophiles (electrophilic and TFE-stabilized). A computational study on the mechanism of similar reaction was conducted by Cramer and co-workers and confirms our hypotheses.[220,221] In particular, they showed that a stepwise mechanism is more favored for electron-rich dienes and electrophilic oxyallyl cations. In our case, the isolation of product **159a** arising *via* a stepwise process from the first intermediate by proton elimination and re-aromatization reaction supports the conclusion made by Cramer and co-workers (scheme b) 4.30). Finally, it is important to remark the role of the fluorinated solvent in the acceleration of the deprotonation of the α-haloketone and in the subsequent ionization *via* stabilization of the oxyallyl cation by hydrogen bond. The different amount of TFE required for cyclic or linear α-haloketones probably depend on the different reactivity of the two classes of compounds. Cyclic ketones are sufficiently reactive and an increase of TFE causes a loss in selectivity favoring the undesired nucleophilic addition product. Instead, open chain and hindered ketones need harder reaction condition, with pure TFE and a stronger base other than DIPEA.

4.2.5 Experimental data

4.2.5.1 Preface

4.2.5.1.1 General methods

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

4.2.5.1.2 Reagents

This study was carried out using 2-vinylindoles **4a-j**,[30,62,109,127] ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **141**,[208] which are known compounds and were prepared following the procedure described in section 4.2.3.1 according to literature procedure.
4*H*-furo[3,2-*b*]indoles **46a,b,f,g,n** were synthetized as described in section 2.2.4.1.
α-haloketones **110a-e**[209,211,213,222] and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124**[214] are known compounds and were prepared following the procedure 4.2.3 according to literature procedure.

4.2.5.1.3 Solvents

Solvents, used for reactions sensitive to oxygen and hydrolysis, were purchased from commercial suppliers.

4.2.5.1.4 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade* 9385 60Å (230-400 mesh).
For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm).

4.2.5.1.5 NMR spectroscopy

^{1}H-NMR analyses were performed with a *Varian-Gemini 300* or with *Brucker 300, 500, 600 Avance* spectrometers at room temperature, respectively at 300, 500 or 600 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shift (δ) in ppm. The multiplicities of the proton spectra were described by following abbre*via*tions: s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet),

m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double dublet).

^{13}C-NMR analyses were performed with the same instruments at 75.45, 125.75 MHz; APT sequences were used to distinguish the methane and methyl carbon signals from those arising from methylene and quaternary carbon atoms.

Two-dimensional NMR techniques (COSY, HSQC, HMBC, NOESY) were performed, where appropriate, to aid the correct assignment of structures.

4.2.5.1.6 Mass Spectroscopy

Low resolution MS spectra were recorded with *a FISONS MD 800* spectrometer with electron impact source and a *Thermo-Finnigan LCQ-advantage AP* electron spray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets.

4.2.5.1.7 X-ray diffraction

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of ethyl acetate solution of **147a** at ambient temperature. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 1964975). Copy may be obtained, free of charge, on application to CCDC e-mail:deposit@ccdc.cam.ac.uk.

4.2.5.1.8 Melting points

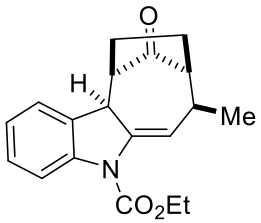
The melting points of the solid products were measured in capillary tube with the device *StuarScientific* SMP3.

4.2.5.2 Experimental data

4.2.5.2.1 General procedure for the reaction between 2-vinylindoles 4-i and α-haloketones 110a-e

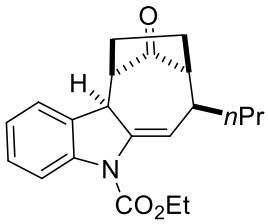
To a stirring solution of 2-vinylindole **4a-i** (0.2 mmol, 1.0 equiv.), α-haloketone **110a-e** (0.28 mmol, 1.4 equiv.) TFE (86.4 µl, 1.2 mmol, 6.0 equiv.) in toluene (0.4 ml, 0.5 M), DIPEA (52.3 µl, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 1 h at room temperature. Solvent was then removed and the crude was purified by column chromatography to yield the corresponding cyclohepta[*b*]indole **146a-m.**

Ethyl 7-methyl-12-oxo-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146a)



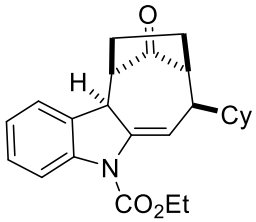
General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4a** (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146a** (55 mg, 88%) as a yellow thick wax. **^{1}H NMR** (300 MHz, C_6D_6): 7.91 (d, *J* = 8.2 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.70 (t, *J* = 3.1 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.69 (m, 1H), 2.69 (m, 1H), 2.49 (m, 1H), 2.14 (m, 1H), 1.41 – 1.28 (m, 3H), 1.10 (m, 1H), 1.02 – 0.90 (m, 6H). **^{13}C NMR** (126 MHz, C_6D_6): 219.3 (C), 152.5 (C), 142.7 (C), 141.1 (C), 130.1 (C), 127.9 (CH), 123.5 (CH), 123.2 (CH), 116.7 (CH), 116.2 (CH), 61.7 (CH_2), 54.3 (CH), 49.4 (CH), 47.6 (CH), 36.6 (CH), 22.7 (CH_3), 21.1 (CH_2), 20.4 (CH_2), 13.9 (CH_3). **ESI(+)-MS**: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found C, 73.44; H, 6.77; N, 4.51.

Ethyl 12-oxo-7-propyl-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146b)



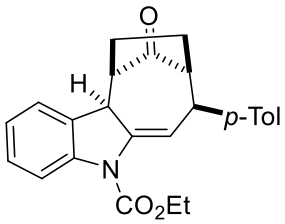
General procedure was followed using ethyl (*E*)-2-(pent-1-en-1-yl)-1*H*-indole-1-carboxylate **4b** (51.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146b** (39 mg, 58%) as a yellow thick wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.76 (d, *J* = 8.2 Hz, 1H), 7.26 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.60 (t, *J* = 3.1 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 1H), 2.86 (m, 1H), 2.44 (d, *J* = 7.0 Hz, 1H), 2.31 (s, 1H), 1.85 – 1.76 (m, 2H), 1.66 – 1.48 (m, 2H), 1.44 (m, 6H), 1.29 (m, 1H), 0.96 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6): 219.5 (C), 152.5 (C), 142.7 (C), 141.5 (C), 130.2 (C), 128.0 (CH), 123.5 (CH), 123.3 (CH), 116.2 (CH), 115.5 (CH), 61.7 (CH_2), 52.6 (CH), 50.1 (CH), 47.5 (CH), 41.9 (CH), 38.9 (CH_2), 21.2 (CH_2), 20.9 (CH_2), 20.7 (CH_2), 13.9 (CH_3), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 393 (100) $[M+CH_3ONa]^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found C, 74.23; H, 7.45; N, 4.12.

Ethyl 7-cyclohexyl-12-oxo-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146c)



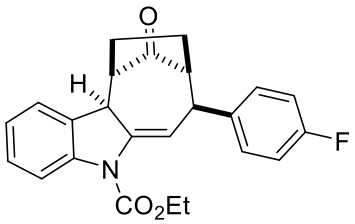
General procedure was followed using ethyl (*E*)-2-(2-cyclohexylvinyl)-1*H*-indole-1-carboxylate **4c** (59.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146c** (52 mg, 69%) as a white thick wax. **^{1}H NMR** (500 MHz, C_6D_6): 7.97 (d, J = 8.2 Hz, 1H), 7.09 (m, 1H), 6.97 (t, J = 3.6 Hz, 1H), 6.85 (td, J = 7.4, 1.0 Hz, 1H), 6.81 (m, 1H), 4.06 (m, 2H), 3.66 (m, 1H), 2.69 (dq, J = 7.9, 1.8 Hz, 1H), 2.45 (m, 1H), 2.17 (m, 1H), 1.74 – 1.59 (m, 4H), 1.56 (m, 1H), 1.48-1.39 (m, 3H), 1.33 (m, 1H), 1.18 – 1.05 (m, 6H), 0.99 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6): 219.4 (C), 152.6 (C), 142.7 (C), 141.9 (C), 130.3 (C), 128.0 (CH), 123.5 (CH), 123.5 (CH), 116.2 (CH), 113.9 (CH), 61.7 (CH_2), 51.6 (CH), 50.4 (CH), 48.1 (CH), 47.4 (CH), 44.3 (CH), 30.7 (CH_2), 30.2 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 22.3 (CH_2), 21.3 (CH_2), 13.9 (CH_3). **ESI(+)-MS**: m/z(%) = 380 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found C, 75.84; H, 7.73; N, 3.70.

Ethyl 12-oxo-7-(*p*-tolyl)-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146d)



General procedure was followed using ethyl 2-(4-methylstyryl)-1*H*-indole-1-carboxylate **4d** (61.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **146d** (60 mg 80%) as a yellow solid (m.p. 94-99° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.13 (d, J = 8.2 Hz, 1H), 7.41 (m, 1H), 7.31 – 7.18 (m, 3H overlapped with C_6D_6), 7.07 (d, J = 7.9 Hz, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 4.12 (m, 2H), 3.87 (s, 2H), 2.87 (m, 1H), 2.71 (m, 1H), 2.21 (s, 3H), 1.78 (m, 1H), 1.44 (m, 2H), 1.34 (m, 1H), 1.03 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 218.2 (C), 152.6 (C), 143.0 (C), 142.9 (C), 142.0 (C), 135.8 (C), 130.1 (C), 129.5 (2xCH), 128.2 (CH), 127.6 (2xCH), 123.6 (CH), 123.3 (CH), 116.3 (CH), 115.1 (CH), 61.9 (CH_2), 56.0 (CH), 49.8 (CH), 48.1 (CH), 47.6 (CH), 21.2 (CH_2), 21.0 (CH_2), 20.7 (CH_3), 14.0 (CH_3). **ESI(+)-MS**: m/z(%) = 388 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found C, 77.63; H, 6.52; N, 3.60.

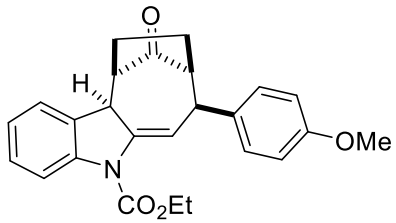
Ethyl 7-(4-fluorophenyl)-12-oxo-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146e)



General procedure was followed using ethyl (*E*)-2-(4-fluorostyryl)-1*H*-indole-1-carboxylate **4e** (62.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **146e** (55 mg,

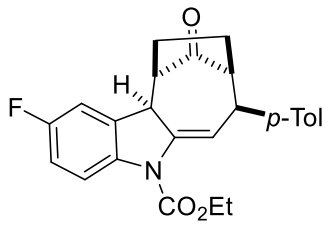
70%) as a white solid (m.p. 108-112° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.08 (d, *J* = 8.2 Hz, 1H), 7.27 (m, 1H, overlapped with C_6D_6), 7.23 (m, 1H), 7.04 (m, 2H), 6.98 (m, 1H), 6.93 – 6.82 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.84 (m, 1H), 3.73 (m 1H), 2.86 (m, 1H), 2.55 (d, *J* = 6.8 Hz, 1H), 1.71 – 1.56 (m, 1H), 1.50 – 1.19 (m, 3H), 1.03 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 218.0 (C), 161.6 (d, *J* = 240.2 Hz, C), 152.6 (C), 142.8 (C), 142.2 (C), 141.6 (d, *J* = 3,1 Hz, C), 129.9 (C), 129.1 (d, *J* = 8,1 Hz, 2xCH), 128.3 (CH), 123.7 (CH), 123.3 (CH), 116.3 (CH), 115.5 (d, *J* = 20.6 Hz, 2xCH), 114.6 (CH), 62.0 (CH_2), 55.7 (CH), 49.7 (CH), 48.1 (CH), 47.1 (CH), 21.2 (CH_2), 20.8 (CH_2), 14.0 (CH_3). **ESI(+)-MS**: m/z(%) = 392 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{22}FNO_3$: C, 73.64; H, 5.67; N, 3.58. Found C, 73.71 H, 5.69; N, 3.59.

Ethyl 7-(4-methoxyphenyl)-12-oxo-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146f)



General procedure was followed using ethyl 2-(4-methoxystyryl)-1*H*-indole-1-carboxylate **4f** (64.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **146f** (64 mg, 79%) as a yellow solid (m.p. 135-138° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.12 (d, *J* = 8.2 Hz, 1H), 7.41 (s, 1H), 7.26 (m, 1H, overlapped with C_6D_6), 7.22 (m, 2H), 6.98 (td, *J* = 7.4, 0.9 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6,84 (m, 2H), 4.17 – 4.10 (m, 2H), 3.86 (m, 2H), 3.42 (s, 3H), 2.88 (m, 1H), 2.71 (d, *J* = 7.5 Hz, 1H), 1.80 (m, 1H), 1.51 – 1.28 (m, 3H), 1.04 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 218.3 (C), 158.7 (C), 152.7 (C), 142.9 (C), 141.9 (C), 138.0 (C), 130.1 (C), 128.6 (2xCH), 127.2 (CH), 123.6 (CH), 123.3 (CH), 116.3 (CH), 115.3 (CH), 114.3 (2xCH), 61.9 (CH_2), 56.2 (CH_3),54.6 (CH), 49.8 (CH), 48.1 (CH), 47.3 (CH), 21.3 (CH_2), 21.0 (CH_2), 14.0 (CH_3). **ESI(+)-MS**: m/z(%) = 404 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found C, 74.35; H, 6.27; N, 3.48.

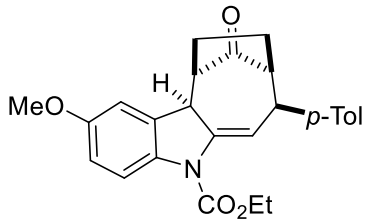
Ethyl 2-fluoro-12-oxo-7-(*p*-tolyl)-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146g)



General procedure was followed using ethyl 5-fluoro-2-(4-methylstyryl)-1*H*-indole-1-carboxylate **4g** (64.6 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **146g** (59 mg, 68%) as a yellow solid (m.p. 151-153° C). **^{1}H NMR** (300 MHz, C_6D_6): 7.77 (dd, *J* = 9.0, 4.6 Hz, 1H), 7.18 (t, *J* = 3.2 Hz, 1H), 7.11 (m, 2H, overlapped with C_6D_6), 6.91 (m, 2H), 6.71 (m, 1H), 6.44 (m, 1H), 3.94 (m, 2H), 3.69 (m, 1H), 3.58 (m, 1H), 2.53 (m,

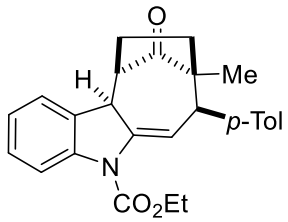
2H), 2.06 (s, 3H), 1.61 (m, 1H), 1.27 (m, 2H), 1.08 (m, 1H), 0.86 (t, J = 7.1, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 217.6 (C), 158.5 (d, J = 242,2 Hz, C), 152.3 (C), 142.7 (C), 141.6 (C), 138.7 (C), 135.8 (C), 131.9 (d, J = 8,4 Hz, C), 129.4 (2xCH), 127.4 (2xCH), 117.1 (d, J = 7,8 Hz, CH), 115.3 (CH), 114.4 (d, J = 22,8 Hz, CH), 110.4 (d, J = 24,3 Hz, CH), 61.8 (CH_2), 55.7 (CH), 49.2 (CH), 47.8 (CH), 47.4 (CH), 21.0 (CH_2), 20.8 (CH_2), 20.5 (CH_3), 13.8 (CH_3). **ESI(+)-MS**: m/z(%) = 428 (100) $[M+Na]^+$. Anal. Calcd for $C_{25}H_{24}FNO_3$: C, 74.06; H, 5.97; N, 3.45. Found C, 73.88; H, 5.99; N, 3.44.

Ethyl 2-methoxy-12-oxo-7-(*p*-tolyl)-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (146h)



General procedure was followed using ethyl 5-methoxy-2-(4-methylstyryl)-1*H*-indole-1-carboxylate **4h** (67.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146h** (57 mg, 70%) as a white solid (m.p. 83-85° C). **^{1}H NMR** (300 MHz, C_6D_6): 7.91 (d, J = 8.9 Hz, 1H), 7.28 (m, 1H), 7.12 (m, 2H overlapped with C_6D_6), 6.92 (d, J = 7.8 Hz, 2H), 6.69 (m, 1H), 6.59 (m, 1H), 4.00 (m, 2H), 3.73 (m, 2H), 3.26 (s, 3H), 2.72 (m, 1H), 2.56 (m, 1H), 2.06 (s, 3H), 1.66 (dt, J = 10.6, 4.7 Hz, 1H), 1.38 – 1.17 (m, 3H), 0.91 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 218.0 (C), 156.7 (C), 152.4 (C), 142.9 (C), 142.1 (C), 136.3 (C), 135.7 (C), 131.3 (C), 129.3 (2xCH), 127.4 (2xCH), 116.9 (CH), 114.9 (CH), 113.3 (CH), 109.0 (CH), 61.6 (CH_2), 55.8 (CH), 54.8 (CH), 49.7 (CH), 48.2 (CH), 47.5 (CH_3), 21.1 (CH_2), 20.9 (CH_2), 20.5 (CH_3), 13.9 (CH_3). **ESI(+)-MS**: m/z(%) = 418 (100) $[M+H]^+$. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found C, 74.92; H, 6.51; N, 3.34.

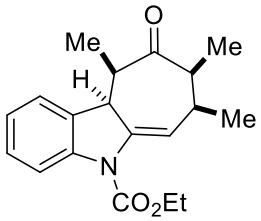
Ethyl 7,8,10-trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[*b*]indole-5(7*H*)-carboxylate (146i)



General procedure was followed using ethyl 2-(4-methylstyryl)-1*H*-indole-1-carboxylate **4d** (61.0 mg, 0.2 mmol) and 2-bromo-5-methylcyclopentan-1-one **110b** (49.5 mg, 0.28 mmol) for 24 at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **146i** (58 mg 72%) as thick white wax. **^{1}H NMR** (500 MHz, C_6D_6): 8.02 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 3.2 Hz, 1H), 7.12(m, 1H), 7.03 (bs, 2H), 6.93 (d, J = 7.9 Hz, 2H), 6.89 – 6.86 (m, 2H), 3.98 (m, 2H), 3.86 (d, J = 2.6 Hz, 1H), 3.23 (t, J = 3.1 Hz, 1H), 2.91 (m, 1H), 2.15 (m, 1H), 2.11 (s, 3H), 1.35 (m, 1H), 1.22 (m, 1H), 1.10 (m, 1H), 0.92 – 0.86 (m, J = 12.4, 5.2 Hz, 6H). **^{13}C NMR** (126 MHz, C_6D_6): 220.4 (C), 152.5 (C), 142.9 (C), 141.6 (C), 140.8 (C), 135.9 (C), 130.1 (C), 128.9 (2xCH), 128.1 (2xCH), 128.0

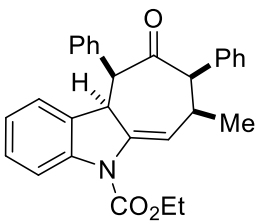
(CH), 123.5 (CH), 123.1 (CH), 117.4 (CH), 116.2 (CH), 61.7 (CH_2), 53.8 (C), 52.2 (CH), 50.6 (CH), 48.1 (CH), 30.0 (CH_2), 21.7 (CH_3), 20.6 (CH_3), 19.6 (CH_2), 13.8 (CH_3). **ESI(+)-MS**: m/z(%) = 402 (100) $[M+H]^+$. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found C, 77.62; H, 6.76; N, 3.50.

Ethyl 7,8,10-trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[*b*]indole-5(7*H*)-carboxylate (146j)



General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4a** (51.5 mg, 0.2 mmol) and 2-bromopentan-3-one **110c** (46.0 mg, 0.28 mmol) for 24 h at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **146j** (49 mg 78%) as thick white wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.12 (d, *J* = 8.3 Hz, 1H), 7.24 (m, 1H overlapped with C_6D_6), 7.09 (d, *J* = 7.4 Hz, 1H), 6.96 (td, *J* = 7.4, 0.8 Hz, 1H), 6.74 (dd, *J* = 5.8, 2.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.51 (m, 1H), 2.48 – 2.28 (m, 2H), 2.06 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.19 – 1.05 (m, 6H). **^{13}C NMR** (75 MHz, C_6D_6): 212.2 (C), 152.3 (C), 143.8 (C), 142.7 (C), 130.0 (C), 128.2 (CH), 125.8 (CH), 122.8 (CH), 117.1 (CH), 116.3 (CH), 61.9 (CH_2), 55.5 (CH), 53.2 (CH), 46.2 (CH), 35.9 (CH), 19.5 (CH_3), 15.6 (CH_3), 14.8 (CH_3), 14.0 (CH_3). **ESI(+)-MS**: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found C, 72.69; H, 7.38; N, 4.46.

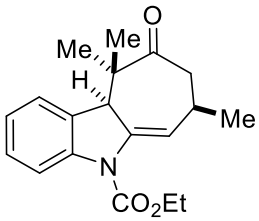
Ethyl 7-methyl-9-oxo-8,10-diphenyl-8,9,10,10a-tetrahydrocyclohepta[*b*]indole-5(7*H*)-carboxylate (146k)



General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4a** (46.0 mg, 0.2 mmol) and 1-chloro-1,3-diphenylpropan-2-one **110d** (63.0 mg, 0.28 mmol) for 24 h at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146k** (48 mg 55%) as a thick yellow wax. **^{1}H NMR** (300 MHz, C_6D_6): 7.99 (d, *J* = 8.3 Hz, 1H), 7.09 – 6.97 (m, 6H), 6.93 – 6.82 (m, 5H), 6.68 (dd, *J* = 5.8, 2.4 Hz, 1H), 6.55 (td, *J* = 7.5, 1.0 Hz, 1H), 6.46 (dd, *J* = 6.9, 0.7 Hz, 1H), 4.74 (dd, *J* = 11.0, 2.1 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 11.0 Hz, 1H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.16 (m, 1H), 1.06 – 0.91 (m, 6H). **^{13}C NMR** (75 MHz, C_6D_6): 205.8 (C), 152.3 (C), 142.5 (C), 142.3 (C), 136.8 (C), 136.2 (C), 130.9 (C), 129.1 (2xCH), 128.6 (4xCH), 128.1 (CH), 128.0 (2xCH), 126.9 (CH), 126.5 (CH), 124.1 (CH), 123.0 (CH), 116.0 (CH), 115.0 (CH), 66.8 (CH), 65.2 (CH), 61.9 (CH_2), 43.1 (CH), 32.5 (CH), 20.1 (CH_3), 13.9 (CH_3). **ESI(+)-MS**:

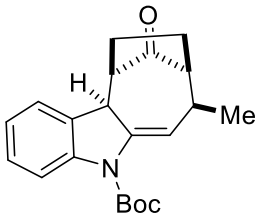
m/z(%) = 438 (100) $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.61; H, 6.22; N, 3.20. Found C, 79.75; H, 6.23; N, 3.21.

Ethyl 7,10,10-trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[b]indole-5(7H)-carboxylate (146l)



General procedure was followed using ethyl (*E*)-2-(pent-1-en-1-yl)-1*H*-indole-1-carboxylate **4a** (46.0 mg, 0.2 mmol) and 1-bromo-3-methylbutan-2-one **110e** (46.0 mg, 0.28 mmol) for 24 h at 40 °C. TFE (0.2 ml, 1 M) was used as solvent instead than toluene, while Na_2CO_3 (32.0 mg, 0.3 mmol) was used as base. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146l** (23 mg, 37%) as a thick yellow wax. **^{1}H NMR** (300 MHz, C_6D_6): 8.11 (d, *J* = 8.3 Hz, 1H), 7.25 (m, 1H, overlapped with C_6D_6), 7.09 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 1H), 2.98 (dd, *J* = 11.7, 5.7 Hz, 1H), 2.62 (bs, 1H), 2.22 (dd, *J* = 11.8, 5.3 Hz, 1H), 1.30 – 1.14 (m, 6H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 211.0 (C), 152.4 (C), 143.5 (C), 141.0 (C), 128.6 (C), 128.2 (CH), 125.7 (CH), 122.7 (CH), 116.4 (CH), 115.7 (CH), 61.8 (CH_2), 54.5 (C), 49.0 (CH), 45.1 (CH_2), 31.2 (CH), 23.6 (CH_3), 23.6 (CH_3), 17.4 (CH_3), 13.9 (CH_3). **ESI(+)-MS**: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found C, 72.63; H, 7.38; N, 4.48.

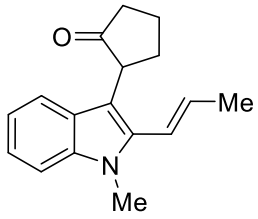
Tert-butyl 7-methyl-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (146m)



General procedure was followed using tert-butyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4i** (51.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol). Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **146m** (49 mg, 72%) as a white solid (m.p. 149-154° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.08 (d, *J* = 8.2 Hz, 1H), 7.22 (m, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 3.1 Hz, 1H), 3.79 (s, 1H), 2.80 (m, 1H), 2.62 (m, 1H), 2.24 (s, 1H), 1.53 (s, 9H), 1.43 (m, 4H), 1.09 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 219.3 (C), 151.5 (C), 143.1 (C), 141.5 (C), 130.3 (C), 128.0 (CH), 123.4 (CH), 123.3 (CH), 116.7 (CH), 116.3 (CH), 81.9, (C) 54.4 (CH), 49.5 (CH), 47.7 (CH), 36.8 (CH), 27.9 (3xCH_3), 22.9 (CH_3), 21.2 (CH_2), 20.5 (CH_2). **ESI(+)-MS**: m/z(%) = 361 (65) $[M+Na]^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found C, 74.57; H, 7.44; N, 4.15.

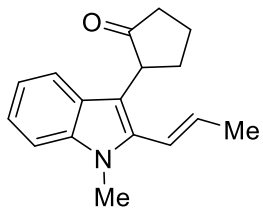
4.2.5.2.2 Preparation and characterization data for compounds 159a-b

Ethyl (*E*)-3-(2-oxocyclopentyl)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate (159a)



147a was isolated during the screening of reaction conditions (see Table 1) as secondary product by reacting ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4a** (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) in a fluorinated alcohol (TFE or HFIP, 0.2 ml, 1 M) and in the presence of a base (1.5 equiv.) at the temperature and for the time stated in Table 1. Removal of the solvent and purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded progressively **159a** (see previous section for characterization) and **147a**. **^{1}H NMR** (300 MHz, CD_2Cl_2): 8.18 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.30 (m, 1H), 7.23 – 7.18 (m, 2H), 6.66 (dq, *J* = 15.8, 1.8 Hz, 1H), 5.86 (dq, *J* = 15.8, 6.6 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.70 (m, 1H), 2.62 – 2.22 (m, 5H), 2.04 (m, 1H), 1.97 (dd, *J* = 6.6, 1.8 Hz, 3H), 1.49 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 218.2 (C), 151.7 (C), 137.5 (C), 135.6 (C), 130.8 (CH), 128.0 (C), 124.1 (CH), 122.8 (CH), 122.4 (CH), 119.2 (CH), 116.4 (C), 115.9 (CH), 63.1 (CH_2), 47.8 (CH), 38.5 (CH_2), 30.9 (CH_2), 21.3 (CH_2), 18.3 (CH_3), 14.1 (CH_3). **ESI(+)-MS**: m/z(%) = 334 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found C, 73.17; H, 6.78; N, 4.52.

(*E*)-2-(1-methyl-2-(prop-1-en-1-yl)-1*H*-indol-3-yl)cyclopentan-1-one (159b)



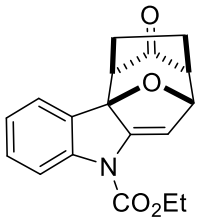
General procedure employed for the synthesis of **146a-m** was followed using (*E*)-1-methyl-2-(prop-1-en-1-yl)-1*H*-indole **4j** (34 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46 mg, 0.28 mmol). Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **159b** (28 mg, 55%) as a thick wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.28 – 7.22 (dd, *J* = 7.5, 4.1 Hz, 2H), 7.17 (m, 1H), 7.02 (m, 1H), 6.39 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.00 (dq, *J* = 15.8, 6.6 Hz, 1H), 3.75 – 3.54 (m, 4H), 2.63 – 2.47 (m, 2H), 2.42 – 2.31 (m, 2H), 2.25 (m, 1H), 2.06 – 1.88 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): 219.6 (C), 137.2 (C), 137.0 (C), 132.9 (CH), 125.8 (C), 121.5 (CH), 120.2 (CH), 119.1 (CH), 119.0 (CH), 109.4 (CH), 109.0 (C), 48.1 (CH), 38.6 (CH_2), 31.6 (CH_2), 30.4 (CH_3), 21.4 (CH_2), 19.1 (CH_3). **ESI(+)-MS**: m/z(%) = 252 (65) $[M-H]^-$. Anal. Calcd. for $C_{17}H_{19}NO$: calcd. for C, 80.60; H, 7.56; N, 5.53. Found C, 80.83; H, 7.58; N, 5.54.

4.2.5.2.3 General procedure for the reaction between 4*H*-furo[3,2-*b*]indole **46a,b,f,g,n** and α-haloketones **110a,c-e**

To a stirring solution of 4*H*-furo[3,2-*b*]indole **46a,b,f,g,n** (0.2 mmol, 1.0 equiv.), α-haloketone **110a,c-e** (0.28 mmol, 1.4 equiv.) TFE (86.4 µl, 1.2 mmol, 6.0 equiv.) in toluene (0.4 ml, 0.5 M), DIPEA (52.3 µl, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 2-3 h at room

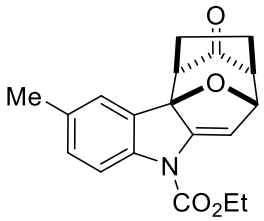
temperature. Solvent was then removed and the crude was purified by column chromatography to yield the corresponding cyclohepta[*b*]indoline **147a-h.**

Ethyl 13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[*b*]indole-5(7*H*)-carboxylate (147a)



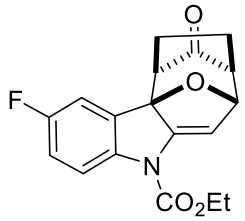
General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) for 3 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **147a** (48 mg, 77%) as a yellow solid (m.p. 116-118° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.98 (d, *J* = 6.4 Hz, 1H), 7.48 (m, 1H), 7.41 (td, *J* = 8.2, 1.2 Hz, 1H), 7.14 (td, *J* = 7.5, 0.6 Hz, 1H), 5.81 (s, 1H), 4.99 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.40 (m, 2H), 2.67 (m, 1H), 2.42 – 2.27 (m, 2H), 2.15 (m, 1H), 1.98 – 1.87 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 208.2 (C), 151.3 (C), 150.6 (C), 145.3 (C), 130.6 (CH), 128.4 (C), 124.2 (CH), 123.3 (CH), 116.3 (CH), 107.3 (CH), 91.9 (C), 87.4 (CH), 62.9 (CH_2), 56.7 (CH), 51.0 (CH), 22.4 (CH_2), 21.1 (CH_2), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found C, 69.34; H, 5.48; N, 4.52.

Ethyl 2-methyl-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[*b*]indole-5(7*H*)-carboxylate (147b)



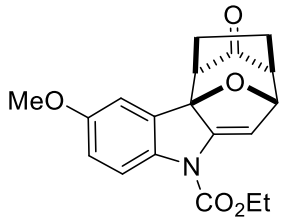
General procedure was followed using ethyl 7-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46f** (49.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) for 2 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5 to 9:1) yielded **147b** (52 mg, 80%) as an orange solid (m.p. 114-117° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.16 (bs, 1H), 7.07 (m, 1H), 6.85 (m, 1H), 5.53 (bs, 1H), 4.42 (dd, *J* = 4.2, 2.2 Hz, 1H), 3.84 (m, 2H), 2.31 – 2.13 (m, 2H), 2.04 (m, 1H), 1.93 (s, 3H), 1.75 (m, 1H), 1.54 – 1.34 (m, 2H), 0.81 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 205.5 (C), 150.98 (C), 143.5 (C), 133.4 (C), 130.7 (CH), 129.1 (C), 126.7 (C), 123.9 (CH), 116.0 (CH), 106.9 (CH), 91.8 (C), 87.0 (CH), 62.2 (CH_2), 56.5 (CH), 50.7 (CH), 22.3 (CH_2), 21.0(CH_2), 20.4 (CH_3), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 326 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found C, 69.92; H, 5.90; N, 4.29.

Ethyl 2-fluoro-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[*b*]indole-5(7*H*)-carboxylate (147c)



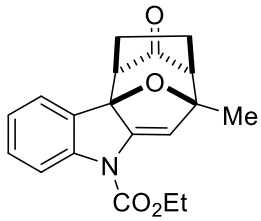
General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **46g** (50.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) for 2 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **147c** (46 mg, 70%) as a yellow solid (m.p. 136-140° C). **^{1}H NMR** (300 MHz, C_6D_6): 7.99 (bs, 1H), 6.88 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.66 (td, *J* = 9.0, 2.8 Hz, 1H), 5.45 (bs, 1H), 4.33 (dd, *J* = 4.3, 2.2 Hz, 1H), 3.81 (m, 2H), 2.19 (m, 1H), 2.04 (m, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.50 – 1.23 (m, 2H), 0.79 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 205.0 (C), 159.3 (d, *J* = 243.6 Hz, C), 150.8 (C), 150.6 (C), 141.4 (C), 130.3 (d, *J* = 7.7 Hz, C), 117.3 (d, *J* = 8.1 Hz, CH), 116.5 (d, *J* = 23.2 Hz, CH), 110.8 (d, *J* = 24.5 Hz, CH), 107.3 (CH), 91.19 (C), 87.0 (CH), 62.31 (CH_2), 56.1 (CH), 50.7 (CH), 22.2 (CH_2), 20.8 (CH_2), 13.7 (CH_3). **ESI(+)-MS**: m/z(%) = 328 (100) $[M-H]^-$. Anal. Calcd for $C_{18}H_{16}FNO_4$: C, 65.65; H, 4.90; N, 4.25. Found C, 65.82; H, 4.92; N, 4.24.

Ethyl 2-methoxy-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[*b*]indole-5(7*H*)-carboxylate (147d)



General procedure was followed using ethyl 7-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **46n** (52.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) for 2 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **147d** (50 mg, 73%) as a white solid (m.p. 118-122° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.86 (bs, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 6.90 (dd, *J* = 9.0, 2.7 Hz, 1H), 5.74 (bs, 1H), 4.96 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.36 (m, 2H), 3.80 (s, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 2.02 – 1.82 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 208.0 (C), 156.5 (C), 151.3 (C), 150.8 (C), 138.8 (C), 129.4 (C), 116.9 (CH), 115.4 (CH), 109.3 (CH), 106.9 (CH), 91.7 (C), 87.4 (CH), 62.7 (CH_2), 56.5 (CH_3), 55.7 (CH), 50.9 (CH), 22.3 (CH_2), 21.1 (CH_2), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 363 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found C, 66.76; H, 5.63; N, 4.11.

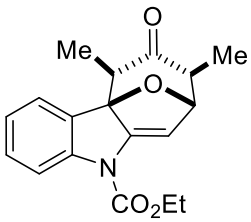
Ethyl 7-methyl-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[*b*]indole-5(7*H*)-carboxylate (147e)



General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **46b** (49.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) for 3 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **147e** (50 mg, 77%) as a white solid (m.p. 155-160° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.95

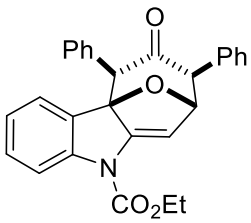
(bs, 1H), 7.43 (m, 1H), 7.37 (m, 1H), 7.10 (td, *J* = 7.5, 0.9 Hz, 1H), 5.63 (bs, 1H), 4.36 (m, 2H), 2.45 (m, 1H), 2.30 (m, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.95 – 1.80 (m, 2H), 1.50 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 208.6 (C), 151.3 (C), 150.0 (C), 145.0 (C), 130.5 (CH), 128.6 (C), 124.2 (CH), 123.2 (CH), 116.2 (CH), 110.6 (CH), 93.5 (C), 91.3 (C), 62.8 (CH_2), 55.4 (CH), 54.5 (CH), 21.3 (CH_2), 21.1 (CH_3), 19.8 (CH_2), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 348 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found C, 70.33; H, 5.88; N, 4.30.

Ethyl 8,10-dimethyl-9-oxo-7,8,9,10-tetrahydro-5*H*-7,10a-epoxycyclohepta[*b*]indole-5-carboxylate (147f)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46.0 mg, 0.2 mmol) and 2-bromopentan-3-one **110c** (46 mg, 0.28 mmol) for 24 at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **147f** (49 mg 78%) as an orange solid (m.p. 102-105° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.89 (d, *J* = 7.0 Hz, 1H), 7.52 – 7.33 (m, 2H), 7.17 (td, *J* = 7.5, 0.8 Hz, 1H), 5.83 (bs, 1H), 5.13 (dd, *J* = 4.8, 2.5 Hz, 1H), 4.37 (m, 2H), 3.28 – 2.86 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.62 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 207.8 (C), 151.3 (C), 150.3 (C), 145.9 (C), 130.4 (CH), 127.3 (C), 124.5 (CH), 123.8 (CH), 115.8 (CH), 107.6 (CH), 92.4 (C), 88.3 (CH), 62.9 (CH_2), 54.7 (CH), 49.9 (CH), 14.4 (CH_3), 11.0 (CH_3), 8.7 (CH_3). **ESI(+)-MS**: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found C, 68.86; H, 6.12; N, 4.45.

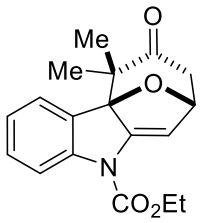
Ethyl 9-oxo-8,10-diphenyl-7,8,9,10-tetrahydro-5*H*-7,10a-epoxycyclohepta[*b*]indole-5-carboxylate 147g)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46.0 mg, 0.2 mmol) and 1-chloro-1,3-diphenylpropan-2-one **110d** (63 mg, 0.28 mmol) for 24 h at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **147g** (83 mg 95%) as a yellow solid (m.p. 202-204° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 7.50 (m, 1H), 7.45 – 7.28 (m, 6H), 7.19 – 6.95 (m, 5H), 6.85 – 6.75 (m, 2H), 5.97 (bs, 1H), 5.39 (dd, *J* = 4.9, 2.5 Hz, 1H), 4.44 (d, *J* = 4.9 Hz, 1H), 4.38 (qd, *J* = 7.1, 2.2 Hz, 2H), 4.24 (s, 1H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 205.3 (C), 150.7 (C), 150.1 (C), 145.1 (C), 135.4 (C), 133.3 (C), 130.3 (CH), 129.9 (2xCH), 129.8 (CH), 128.6 (2xCH), 127.6 (CH), 127.4 (2xCH), 127.1 (CH), 126.9 (C), 123.9 (CH), 123.9 (CH), 115.3 (CH), 108.9 (CH), 92.6 (C), 88.6 (CH), 65.8 (CH), 62.7 (CH_2), 61.5 (CH), 14.5 (CH_3). CH_{sp2} is

overlapped with another CH_{sp2}. **ESI(-)-MS**: m/z(%) = 436 (50) $[M-H]^-$. Anal. Calcd for $C_{28}H_{23}NO_4$: C, 76.87; H, 5.30; N, 3.20. Found C, 77.05; H, 5.31; N, 3.21.

Ethyl 10,10-dimethyl-9-oxo-7,8,9,10-tetrahydro-5*H*-7,10a-epoxycyclohepta[*b*]indole-5-carboxylate (147h)

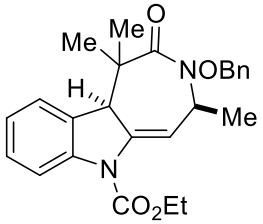


General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46.0 mg, 0.2 mmol) and 1-bromo-3-methylbutan-2-one **110e** (46 mg, 0.28 mmol) for 48 h at 40 °C. TFE (0.2 ml, 1 M) was used as solvent instead than toluene, while Na_2CO_3 (32 mg, 0.3 mmol) was used as base. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **147h** (36 mg 57%) as a thick yellow wax. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.94 (d, *J* = 7.9 Hz, 1H), 7.49 – 7.35 (m, 2H), 7.15 (td, *J* = 7.5, 0.6 Hz, 1H), 5.84 (s, 1H), 5.28 (m, 1H), 4.39 (m, 2H), 3.24 (dd, *J* = 16.2, 4.9 Hz, 1H), 2.58 (dd, *J* = 16.2, 0.8 Hz, 1H), 1.47 – 1.37 (m, 6H), 0.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 210.0 (C), 151.3 (C), 150.4 (C), 146.2 (C), 130.4 (CH), 126.0 (C), 124.8 (CH), 123.8 (CH), 115.6 (CH), 109.6 (CH), 92.8 (C), 83.2 (CH), 62.8 (CH_2), 56.5 (C), 44.2 (CH_2), 21.0 (CH_3), 17.4 (CH_3), 14.4 (CH_3). **ESI(+)-MS**: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found C, 68.87; H, 6.09; N, 4.47.

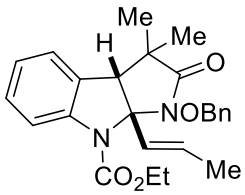
4.2.5.2.4 General procedure for the reaction between **4a** or **46a** and *N*- (benzyloxy)-2-bromo-2-methylpropanamide **124**.

To a stirring solution of 2-vinylindole **4a** or 4*H*-furo[3,2-*b*]indole **46a** (0.2 mmol, 1.0 equiv.) and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **7** (82 mg, 0.3 mmol, 1.5 equiv.) in HFIP (0.84 ml, 0.25 M), DIPEA (52.3 µl, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 1 at room temperature. Solvent was then removed and the crude was purified by column chromatography to yield the corresponding products **160-162.**

Ethyl 3-(benzyloxy)-1,1,4-trimethyl-2-oxo-2,3,4,10*b*-tetrahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (160) and ethyl (E)-1-(benzyloxy)-3,3-dimethyl-2-oxo-8a-(prop-1-en-1-yl)-2,3,3a,8*a*-tetrahydropyrrolo[2,3-*b*]indole-8(1*H*)-carboxylate (161)



158



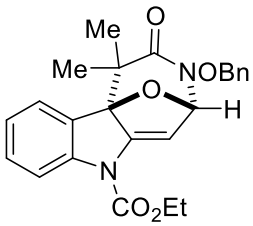
159

General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **4a** (46.0 mg, 0.2. mmol) and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124** (82.0 mg, 0.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded progressively **161** (34 mg, 40%) and **160** (35 mg, 42%) as

clear thick oils. **160: ^{1}H NMR** (300 MHz, C_6D_6): 8.08 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.32 – 7.18 (m, 4H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (dd, *J* = 4.6, 2.1 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.41 (m, 1H), 4.26 – 4.00 (m, 3H), 1.57 (s, 3H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.05 (dd, *J* = 8.9, 5.3 Hz, 6H). **^{13}C NMR** (75 MHz, C_6D_6): 179.3 (C), 152.2 (C), 143.5 (C), 143.2 (C) 136.8 (C), 129.4 (2xCH), 128.3 (C), 128.3 (CH), 128.3 (2xCH), 128.2 (CH), 126.5 (CH), 122.9 (CH), 116.0 (CH), 110.8 (CH), 76.2 (CH_2), 62.1 (CH_2), 57.6 (CH), 51.2 (C), 48.7 (CH), 26.2 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 13.9 (CH_3). **ESI(+)-MS**: m/z(%) = 421 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found C, 71.34; H, 6.73; N, 6.64.

161: ^{1}H NMR (300 MHz, C_6D_6): 8.29 (d, *J* = 8.2 Hz, 1H), 7.30 (m, 1H), 7.14 – 6.94 (m, 5H), 6.82 – 6.68 (m, 2H), 5.68 (dq, *J* = 15.5, 6.2 Hz, 1H), 5.56 (dd, *J* = 15.5, 1.2 Hz, 1H), 5.03 (d, *J* = 2.9 Hz, 2H), 4.15 – 3.86 (m, 2H), 3.14 (s, 1H), 1.35 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.19 (s, 3H), 0.99 – 0.85 (m, 6H). **^{13}C NMR** (75 MHz, C_6D_6): 162.5 (C), 152.4 (C), 142.8 (C), 138.7 (C), 131.0 (CH), 129.0 (CH), 127.2 (CH), 126.0 (CH), 126.0 (C), 125.5 (CH), 122.3 (CH), 115.3 (CH), 103.6 (C), 75.9 (CH_2), 61.2 (CH_2), 61.2 (CH), 43.4 (C), 29.5 (CH_3), 24.4 (CH_3), 16.8 (CH_3), 14.0 (CH_3). 4xCH_{sp2} are overlapped with C_6D_6. **ESI(+)-MS**: m/z(%) = 421 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found C, 71.68; H, 6.72; N, 6.67.

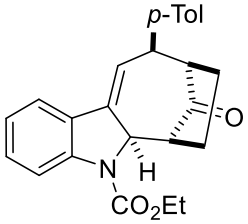
Ethyl 3-(benzyloxy)-1,1-dimethyl-2-oxo-1,2,3,4-tetrahydro-6*H*-4,10*b*-epoxyazepino[4,5-*b*]indole-6-carboxylate (162)



General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **46a** (46.0 mg, 0.2 mmol) and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124** (82.0 mg, 0.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 8:2) yielded **162** (53 mg, 63%) as a transparent oil. **^{1}H NMR** (300 MHz, C_6D_6): 8.27 (bs, 1H), 7.49 (m, 2H), 7.37 – 7.08 (m, 5H), 6.86 (td, *J* = 7.6, 0.8 Hz, 1H), 6.01 (bs, 1H), 5.54 (d, *J* = 1.8 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 4.97 (d, *J* = 10.6 Hz, 1H), 3.97 (m, 2H), 1.69 (s, 3H), 1.02 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 174.2 (C), 153.7 (C), 150.8 (C), 146.8 (C), 136.2 (C), 130.6 (CH), 129.6 (2xCH), 128.5 (CH), 128.4 (2xCH), 125.6 (CH), 125.3 (C), 123.6 (CH), 115.7 (CH), 110.5 (CH), 96.3 (CH), 94.7 (C), 77.8 (CH_2), 62.5 (CH_2), 52.4 (CH_2), 22.9 (CH_3), 18.7 (CH_3), 13.8 (CH_3). **ESI(+)-MS**: m/z(%) = 421 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found C, 68.38; H, 5.77; N, 6.68.

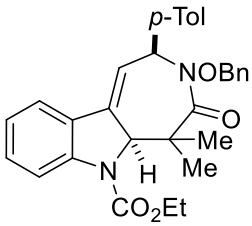
4.2.5.2.5 Reaction between 3-vinylindole **141** and **110a** or **124**.

Ethyl (12-oxo-10-(*p*-tolyl)-5a,6,7,8,9,10-hexahydro-5*H*-6,9-methanocycloocta[*b*]indole-5-carboxylate (163)



General procedure employed for the synthesis of **146a-m** was followed using ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **141** (61.1 mg, 0.2 mmol), and 2-bromocyclopentan-1-one **110a** (46.0 mg, 0.28 mmol) for 24 h at rt. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **163** (52 mg, 67%) as a white solid (m.p. 85-90° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.35 (bs, 1H), 7.25 – 7.16 (m, 2H), 7.15 – 7.10 (m, 4H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 3.5, 1H), 4.73 (s, 1H), 4.20 (m, 2H), 3.75 – 3.64 (m, 2H), 2.65 (m, 1H), 2.25 (s, 3H), 1.70 (m, 1H), 1.51 – 1.33 (m, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 217.0 (C), 152.8 (C), 144.9 (C), 142.4 (C), 138.1 (C), 136.2 (C), 129.6 (2xCH), 129.5 (CH), 129.3 (C), 127.6 (2xCH), 123.0 (CH), 121.2 (CH), 119.4 (CH), 116.1 (CH), 66.0 (CH), 61.8 (CH_2), 56.9 (CH), 50.3 (CH), 48.2 (CH), 21.3 (CH_2), 20.7 (CH), 20.2 (CH_2), 14.2 (CH_3). **ESI(+)-MS**: m/z(%) = 388 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61; found C, 77.24; H, 6.52; N, 3.60.

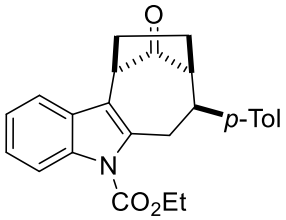
Ethyl -3-(benzyloxy)-5,5-dimethyl-4-oxo-2-(*p*-tolyl)-3,4,5,5*a*-tetrahydroazepino[4,5-*b*]indole-6(2*H*)-carboxylate (164)



General procedure employed for the synthesis of **158-160** was followed using ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **141** (61.1 mg, 0.2 mmol) and and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **124** (82.0 mg, 0.3 mmol) for 24 h. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **164** (48 mg, 48%) as a clear thick oil. **^{1}H NMR** (500 MHz, C_6D_6): 7.94 (bs, 1H), 7.37 – 7.30 (m, 2H), 7.15 (ddt, *J* = 10.1, 8.4, 1.8 Hz, 4H), 7.11 – 7.03 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.83 (dd, *J* = 4.1, 3.6 Hz, 1H), 6.73 (td, *J* = 7.5, 1.0 Hz, 1H), 5.75 (m, 1H), 5.63 (bs, 1H), 5.27 (t, *J* = 3.1 Hz, 1H), 4.64 (s, 2H), 4.03 (m, 2H), 2.06 (s, 3H), 1.65 (s, 3H), 1.11 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6): 181.7 (C), 154.2 (C), 145.6 (C), 137.8 (C), 137.7 (C), 137.2 (C), 136.9 (C), 129.6 (CH), 129.4 (2xCH), 129.1 (2xCH), 128.8 (C), 128.2 (2xCH), 128.0 (2xCH), 127.7 (CH), 123.3 (CH), 119.8 (CH), 117.4 (CH), 114.6 (CH), 74.9 (CH_2), 69.2 (CH), 64.9 (CH), 61.8 (CH_2), 54.3 (C), 26.6 (CH_3), 20.6 (CH_3), 19.0 (CH_3), 14.0 (CH_3). **ESI(+)-MS**: m/z(%) = 497 (100) $[M+H]^+$. Anal. Calcd for $C_{31}H_{32}N_2O_4$: C, 74.98; H, 6.50; N, 5.64; found C, 75.14; H, 6.51; N, 5.63.

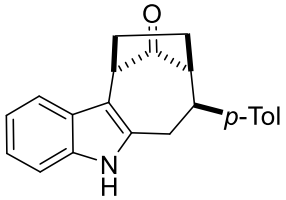
4.2.5.2.6 Preparation and characterization data for compounds 165-167

Ethyl 12-oxo-7-(*p*-tolyl)-6,7,8,9,10,11-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (165)



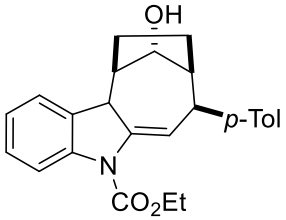
To a stirring solution of **146d** (38.7 mg, 0.1 mmol) in $CHCl_3$ (0.5 ml, 0.2 M), *p*-TSOH (1.90 mg, 0.01 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with $NaHCO_3$ saturated solution (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield **165** (37 mg, 96%) as a brownish solid (m.p. 177-180° C). **^{1}H NMR** (300 MHz, $CDCl_3$): 8.00 (m, 1H), 7.53 (m, 1H), 7.30 – 7.23 (m, 4H), 7.16 (m, 2H), 4.45 (q, *J* = 7.14, 2H), 4.11 (m, 1H), 3.69 – 3.51 (m, 3H), 2.85 (m, 1H), 2.50 (m, 1H), 2.35 (m, 4H), 2.23 – 2.11 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 216.8 (C), 152.2 (C), 141.5 (C), 136.4 (C), 135.4 (C), 135.4 (C), 129.3 (2xCH), 128.1 (C), 126.8 (2xCH), 124.4 (CH), 123.0 (CH), 119.8 (C), 117.8 (CH), 115.4 (CH), 63.3 (CH_2), 53.7 (CH), 49.0 (CH), 43.5 (CH), 28.4 (CH_2), 28.1 (CH_2), 21.0 (CH_3), 20.2 (CH_2), 14.3 (CH_3). **ESI(+)-MS**: m/z(%) = 388 (100) $[M+H]^+$. Anal. Calcd. for $C_{25}H_{25}NO_3$: calcd. for C, 77.49; H, 6.50; N, 3.61. Found C, 77.74; H, 6.52; N, 3.61.

7-(*p*-tolyl)-6,7,8,9,10,11-hexahydro-5*H*-8,11-methanocycloocta[*b*]indol-12-one (166).



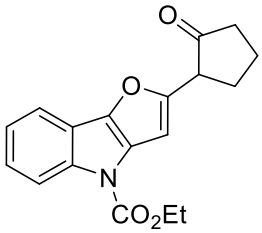
To a stirring solution of **146d** (50.0 mg, 0.13 mmol) in MeOH (1.4 ml, 0.01 M), K_2CO_3 (17.8 mg, 0.13 mmol) was added and the mixture was stirred for 5 h at 50°C. Solvent was then removed and the crude was diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 9:1) to yield **166** (32 mg, 78%) as a white solid (m.p. 186-190° C). **^{1}H NMR** (300 MHz, acetone-d_6): 10.04 (bs, 1H), 7.54 (m, 1H), 7.33 – 7.26 (m, 3H), 7.18 (m, 2H), 7.09 – 7.00 (m, 2H), 3.73 – 3.57 (m, 3H), 3.10 (m, 1H), 2.84 (s, 1H), 2.71 (m, 1H), 2.50 – 2.36 (m, 2H), 2.32 (s, 3H), 2.21 (m, 1H). **^{13}C NMR** (75 MHz, acetone-d_6): 215.7 (C), 142.0 (C), 136.0 (C), 134.8 (C), 133.5 (C), 129.2 (2xCH), 127.3 (C), 126.7 (2xCH), 121.1 (CH), 119.0 (CH), 117.3 (CH), 110.5 (CH), 110.5 (C), 52.8 (CH), 48.4 (CH), 44.0 (CH), 30.1 (CH_2), 29.0 (CH_2), 20.1 (CH_3) 19.5 (CH_2). **ESI(+)-MS**: m/z(%) = 316 (100) $[M+H]^+$. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found C, 83.53; H, 6.70; N, 4.46.

Ethyl 12-hydroxy-7-(*p*-tolyl)-7,8,9,10,11,11a-hexahydro-5*H*-8,11-methanocycloocta[*b*]indole-5-carboxylate (167)



To a stirring solution of **146d** (50.0 mg, 0.13 mmol) in EtOH (1.3 ml, 0.1 M), $NaBH_4$ (4.90 mg, 0.13 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with NH_4Cl saturated solution (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 9:1) to yield **167** (33 mg 65%) as a white solid (m.p. 135-139° C). **^{1}H NMR** (300 MHz, C_6D_6): 8.21 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 2H overlapped with C_6D_6), 7.16 – 7.04 (m, 4H), 4.73 (m, 1H), 4.53 (m 1H), 4.17 – 4.09 (m, 2H), 4.0o (t, *J* = 6.9 Hz, 1H) 2.50 (bs, 1H), 2.27 (m, 4H), 1.99 (m, 1H), 1.55 – 1.45 (m, 3H), 1.35 (bs, 1H), 1.04 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6): 152.9 (C), 145.8 (C), 143.6 (C), 142.5 (C), 135.0 (C), 132.8 (C), 129.3 (2xCH), 128.9 (CH), 127.9 (2xCH), 123.4 (CH), 122.9 (CH), 116.3 (CH), 115.4 (CH), 75.6 (CH), 61.7 (CH_2), 49.5 (CH), 44.0 (CH), 43.2 (CH), 40.3 (CH), 23.5 (CH_2), 23.4 (CH_2), 20.8 (CH_3), 14.0 (CH_3). **ESI(+)-MS**: m/z(%) = 390 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found C, 76.91; H, 7.01; N, 3.61.

Ethyl 2-(2-oxocyclopentyl)-4*H*-furo[3,2-*b*]indole-4-carboxylate (168)

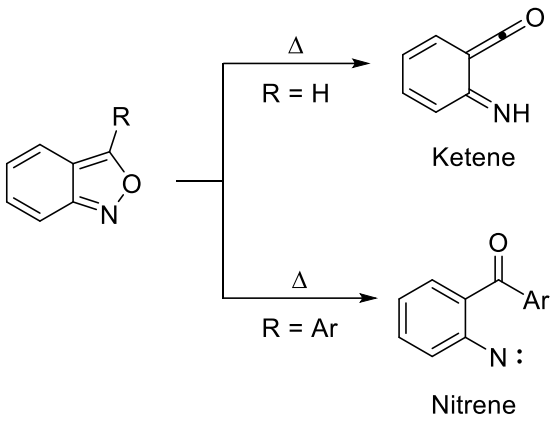


To a stirring solution of **147a** (47.0 mg, 0.15 mmol) in $CHCl_3$ (0.75 ml, 0.2 M), *p*TSOH (3.00 mg, 0.015 mmol) was added and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was concentrated, and the crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 8:2) to yield **168** (44 mg 94%) as a pink sold (117-119° C). **^{1}H NMR** (500 MHz, $CDCl_3$): 8.33 (bs, 1H), 7.63 (m, 1H), 7.34 – 7.25 (m, 2H), 6.68 (s, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 10.6, 8.5 Hz, 1H), 2.57 (m, 1H), 2.50 (ddd, *J* = 18.8, 8.5, 3.5 Hz, 1H), 2.44 (dd, *J* = 10.1, 8.5 Hz, 1H), 2.36 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.52 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): 214.8 (C), 155.3 (C), 151.0 (C), 142.7 (C), 138.2 (C), 129.7 (C), 123.6 (CH), 123.3 (CH), 118.1 (C), 116.3 (CH), 116.1 (CH), 100.8 (CH), 63.0 (CH_2), 49.8 (CH), 37.9 (CH_2), 29.6 (CH_2), 21.0 (CH_2), 14.5 (CH_3). **ESI(+)-MS**: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found C, 69.21; H, 5.52; N, 4.48.

Chapter 5. Synthesis of 2-hydrazineylisophthalaldehyde derivatives

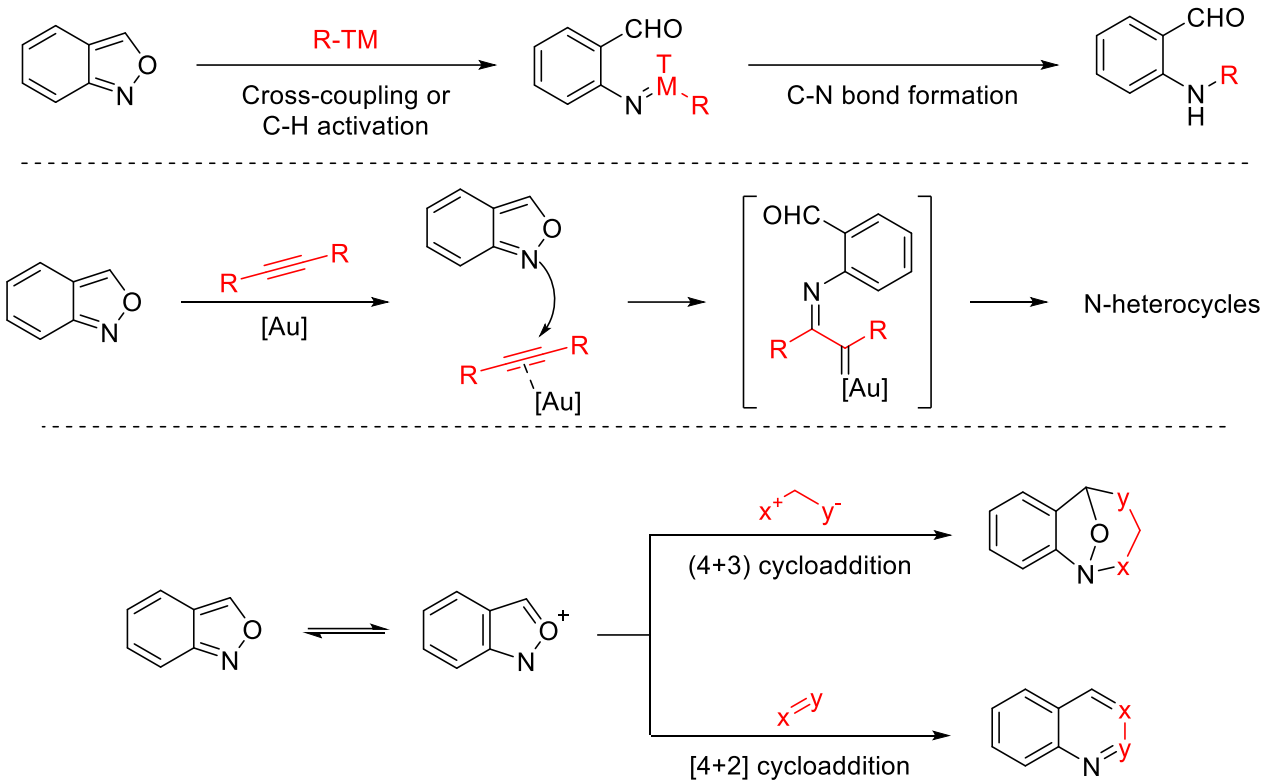
5.1 Reactivity of 2,1-benzisoxazoles

Anthranils, also known as 2,1-benzisoxazoles or benzo[*c*]isoxazoles, are versatile building blocks mainly employed for the construction of new C–N bonds.[223–225] They exhibit rich and tunable reactivities especially in transition metal-catalyzed processes. Thus, the thermolysis of anthranils can lead to the generation of reactive ketene or nitrene intermediates depending on the substitution pattern at the C3 position of the starting compounds (scheme 5.1).



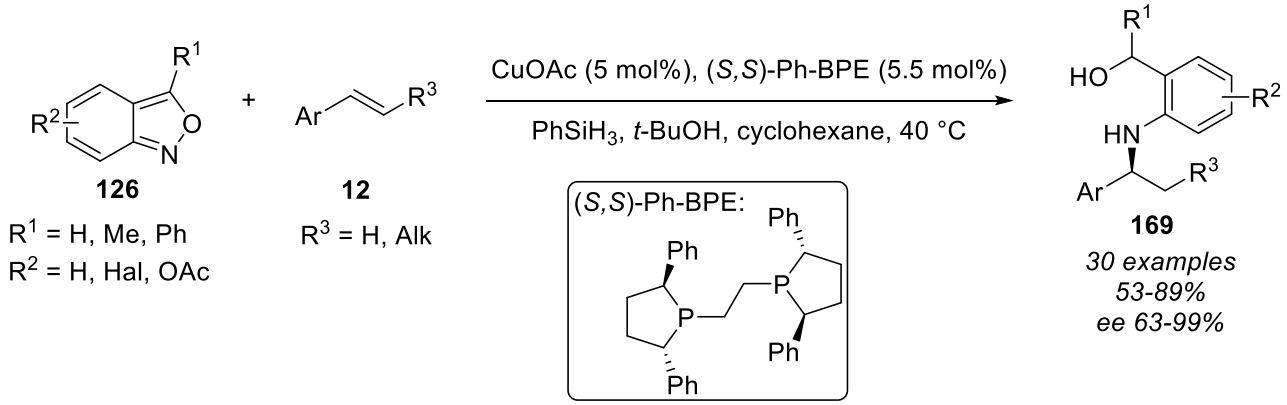
Scheme 5.1

More recently, the development of transition metal catalyzed reactions allowed for the activation of anthranils under milder reaction conditions, leading to the formation of metal reactive nitrene species able to act as electrophilic reagents with organometallic compounds or in C-H amination or as nucleophiles in reactions with gold activated π-systems (scheme 5.2). Finally, anthranils present a 1,3-dipolar structure and can be involved in (4+3) or [4+2] cyclization reactions.



Scheme 5.2

For example, the employment of organometallic reagents leads to the construction of new C-N bonds through a selective cleavage of the N-O bond of anthranils. Liu and co-workers reported one of the most recent development in this field. They proposed an asymmetric hydroamination of olefins **12** using anthranils **126** as electrophilic aminating reagents (scheme 5.3).[226] CuOAc and $PhSiH_3$ were used to generate the highly reactive CuH species that in the presence of chiral ligand (*S*,*S*)-Ph-BPE forms the corresponding chiral complex. This latter is responsible of the chiral induction in a catalytic cycle involving a chiral copper nitrene species as intermediate and resulting in the isolation of enantioenriched secondary arylamines **169** tethered to a benzylic alcohol.



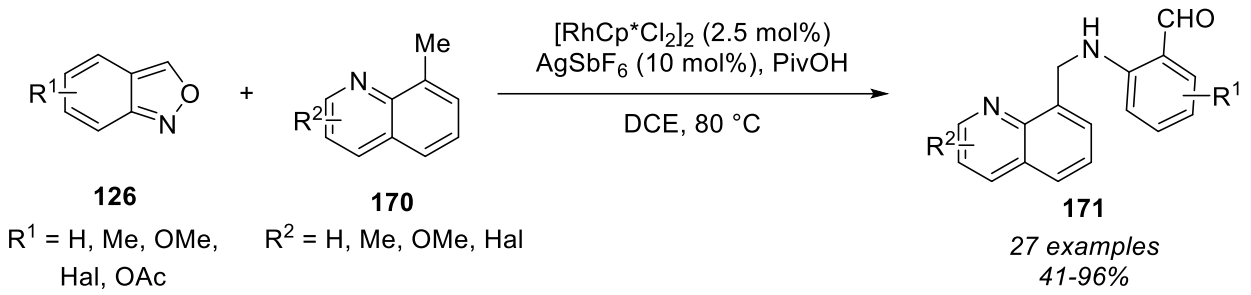
126
R^1 = H, Me, Ph
R^2 = H, Hal, OAc

12
R^3 = H, Alk

169
30 examples
53-89%
ee 63-99%

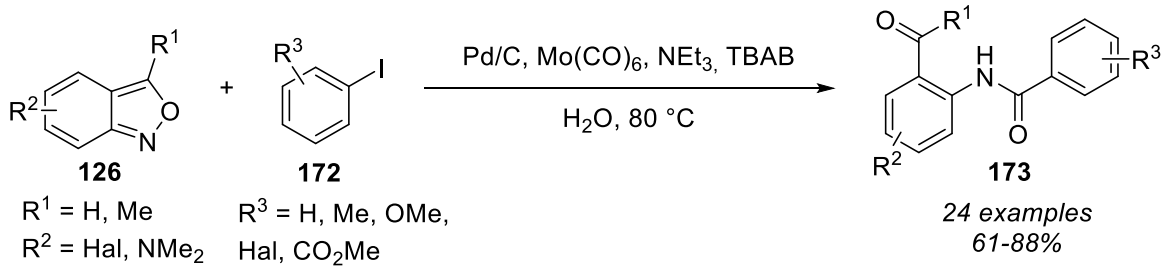
Scheme 5.3

Another interesting reaction involves anthranils in C-H amination reaction allowing for the formation of arylamine derivatives bearing an electrophilic formyl group able to undergo further functionalizations. In 2016, Jiao and co-workers proposed an innovative C(sp^3)-H amination of 8-methylquinolines **170** with anthranils **126** under rhodium catalysis. The transformation tolerated various functional groups giving rise to a variety of aminated products **171** presenting an additional formyl group (scheme 5.4).[227]



Scheme 5.4

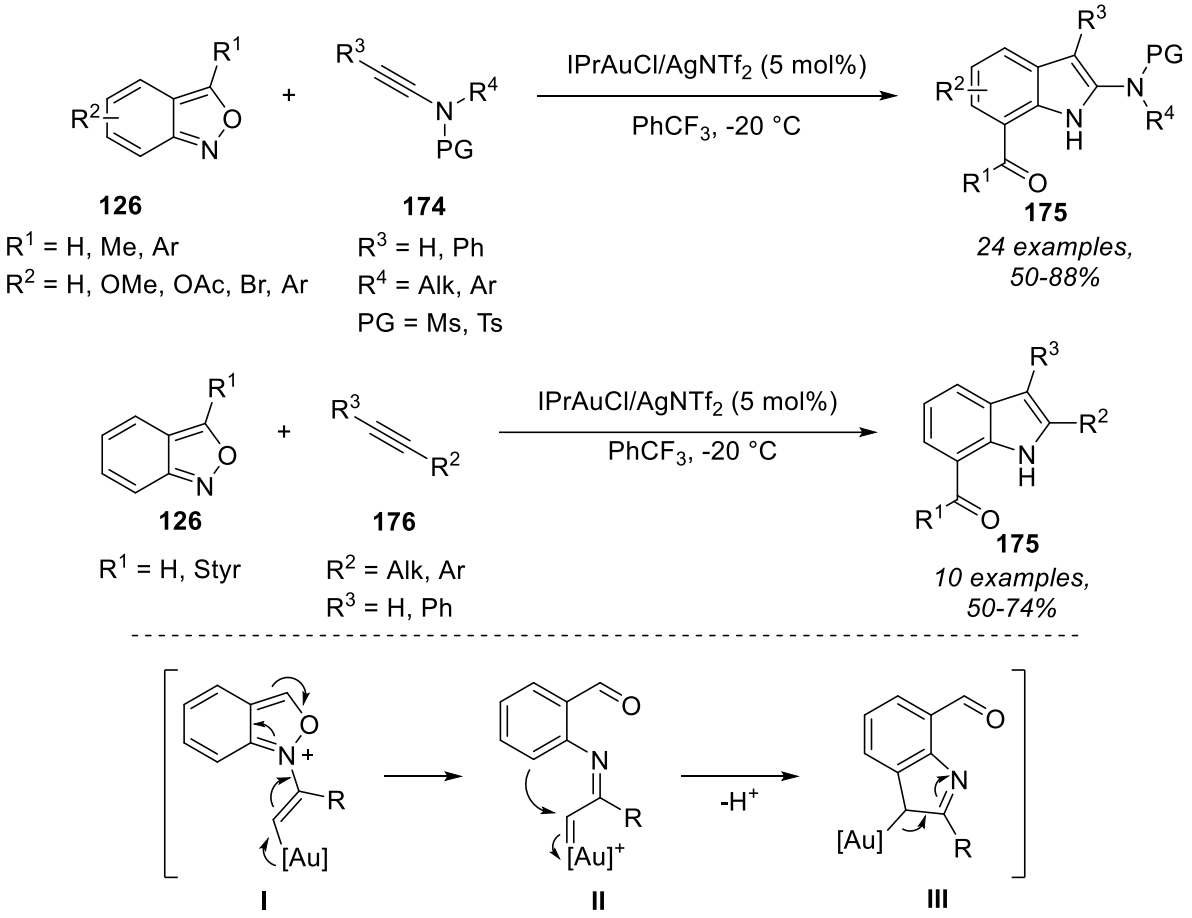
Furthermore, in 2017 the research group of Wu proposed an aminocarbonylation using anthranils **126** as nitrogen source in order to synthesize *N*-(2-carbonylaryl)-benzamides **173**.[228] The methodology exploits Pd on carbon as catalyst and the $Mo(CO)_6$ as solid and safe CO source in water media and in a process that involved the possibility of recycling the Pd/C catalyst. The reaction tolerated different hindered and functionalized aryl iodides **172** allowing the isolation of the desired compounds in good yields (scheme 5.5).



Scheme 5.5

Moreover, the treatment of anthranils with gold activated alkynes permitted the development of various novel annulation reactions involving an α-imino gold carbene intermediate.[224] In this context, Hashmi and co-workers developed a facile and efficient synthesis of unprotected 7-acylindoles **175**.[229] In particular, they employed a series of alkynes including ynamides **174**, non-

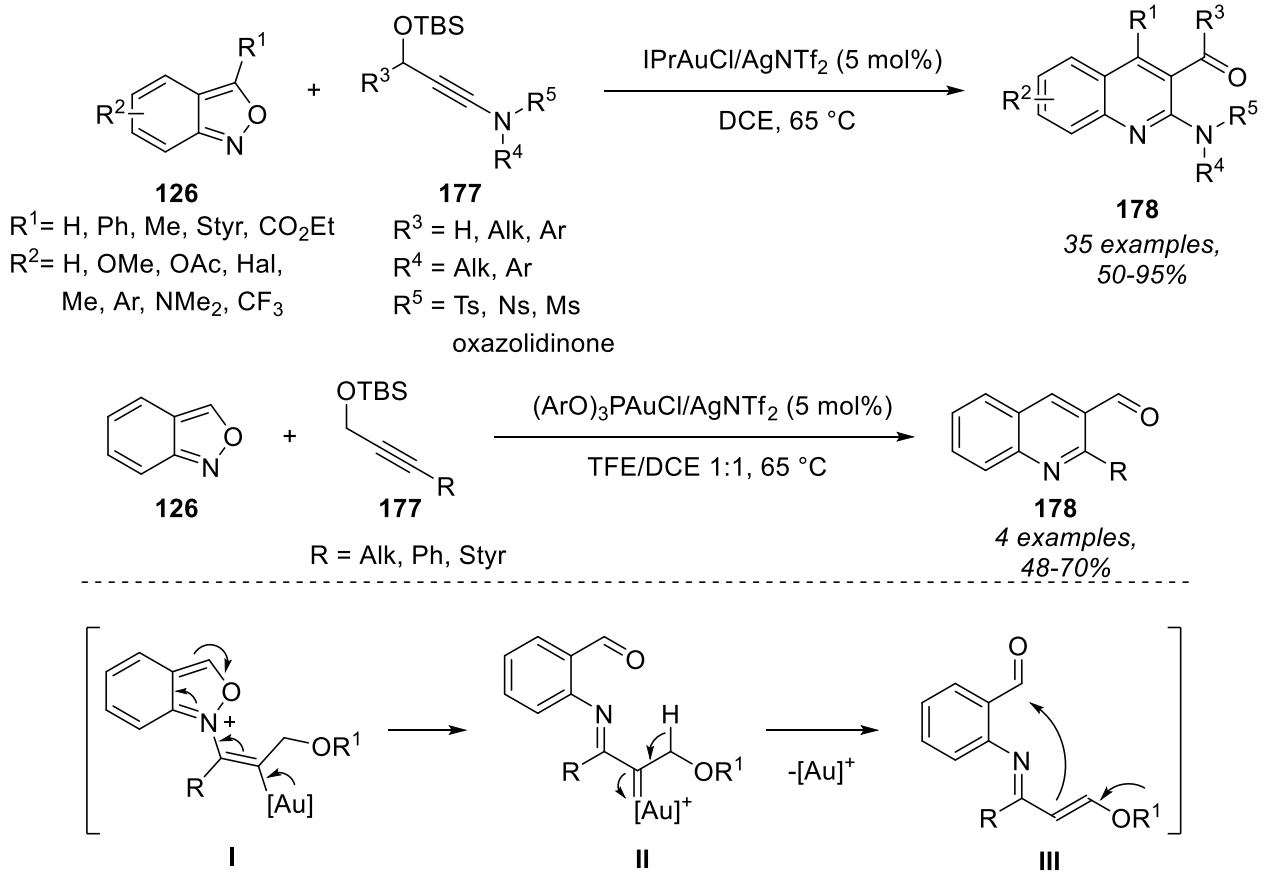
polarized alkynes **176** and internal alkynes **176** that reacted with anthranils affording 7-acylindoles **175** in good to excellent yields (scheme 5.6). The reaction occurred with the initial nucleophilic addition of the anthranil on the gold activated triple bond. Successively, the internal rearrangement of the anthranil moiety with the cleavage of N-O bond led to the formation of a highly electrophilic α-imino gold carbene **II** that promoted intramolecular *ortho*-aryl C-H insertion affording the 7-formyl indoles **175**.



Scheme 5.6

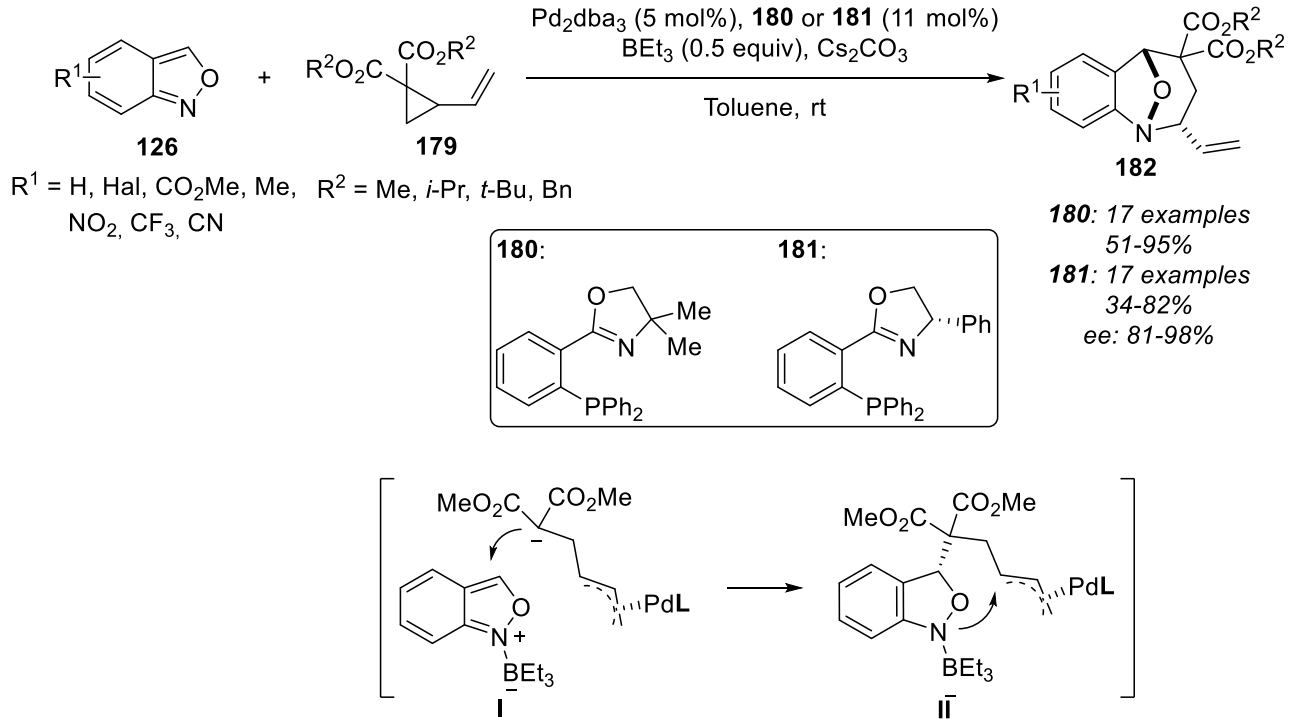
Subsequently, the reactivity of different type of alkynes with anthranils was tested in order to increase the molecular complexity. The same year, Hashmi and co-workers proposed a new synthesis of quinolines **178** from propargyl silyl ethers **177** and anthranils **126** through the umpolung of a gold carbene (scheme 5.7).[230] The transformation gave rise to a series of highly functionalized quinoline derivatives **178** performing the reaction under mild conditions. The reaction mechanism involves a cascade annulation comprising a sequential ring opening of the anthranil derivative with the cleavage of N-O bond, the subsequent 1,2 proton shift with protodeauration on the α-imino gold carbene **II**

that led to the formation of *N*-aryl-α,β-unsaturated imine **III** involved in the Mukaiyama aldol cyclization.



Scheme 5.7

Finally, one example of the employment of anthranils **126** as 1,3 dipole in palladium catalyzed (4+3) cyclization with vinylcyclopropanes **179** was reported by You and co-workers (scheme 5.8).[231] Due to the poor electrophilicity of anthranil an activator was required and they found that a borane compound could activate and direct the cyclization of the palladium activated vinylcyclopropane **179** for the stereoselective formation of the final cycloadduct. The reaction showed a good tolerance for different functional groups on the anthranil allowing for the isolation of the (4+3) products **182** in good to excellent yields. Furthermore, an enatioselective version of the reaction was proposed employing chiral ligand **181** for the palladium catalyst.

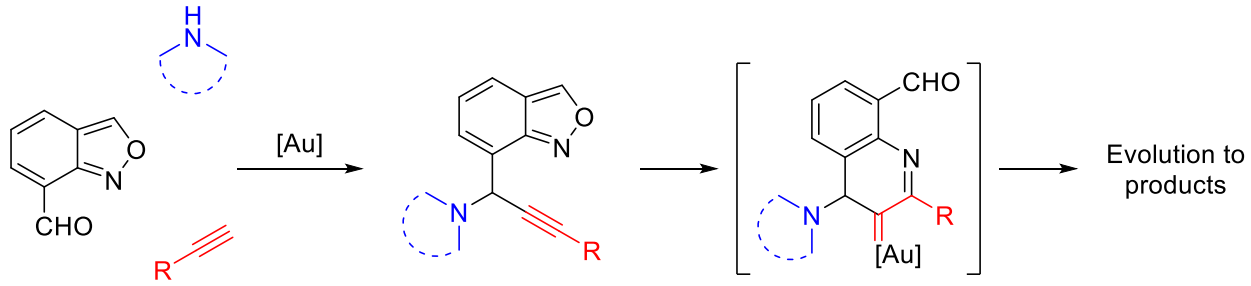

Pd2dba3 (5 mol%), 180 or 181 (11 mol%)
BEt3 (0.5 equiv), Cs2CO3
Toluene, rt
126
179
182
R1 = H, Hal, CO2Me, Me, NO2, CF3, CN
R2 = Me, i-Pr, t-Bu, Bn
180: 17 examples 51-95%
181: 17 examples 34-82%
ee: 81-98%
180:
181:
PPh2
PdL
BEt3

Scheme 5.8

5.2 Synthesis of 2-hydrazineylisophthalaldehyde derivatives from anthranil and secondary amines

5.2.1 Objectives

This part of my research was conducted at the University of Heidelberg under the supervision of Professor Hashmi. Starting from the expertise of the Hashmi's group in the gold functionalization of anthranils[229,230,232–234] and taking into account the reported literature on gold promoted A3 coupling reactions,[235] we decided to test the reactivity of a particular anthranil bearing an aldehyde group in 7-position with a terminal alkyne and a secondary amine in presence of a gold catalyst. The reaction should afford the corresponding A3 coupling product that in turn could undergo an intramolecular cyclization promoted by the same gold catalyst for the synthesis of more complex polycyclic compound (scheme 5.9)



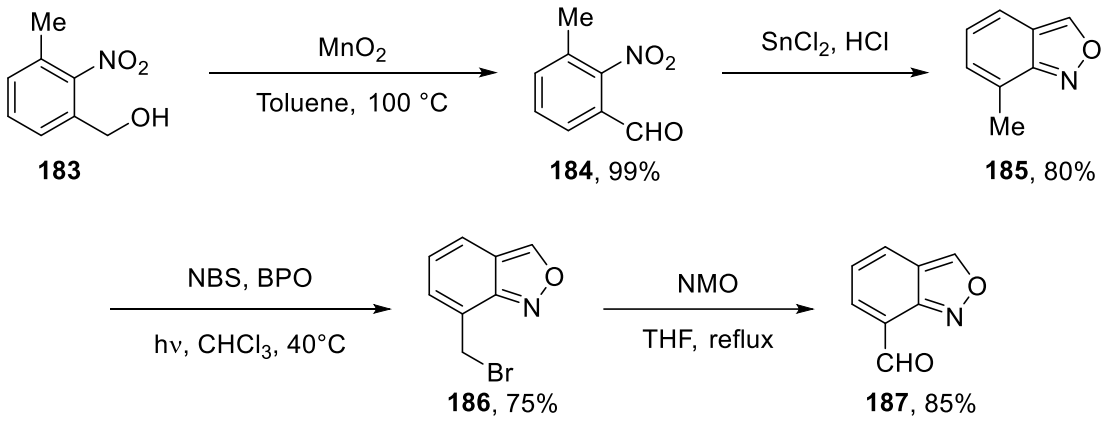
Scheme 5.9

5.2.2 Synthesis of starting material

In this work, benzo[*c*]isoxazole-7-carbaldehyde **187** has been synthetized and used.

*5.2.2.1 Synthesis of benzo[c]isoxazole-7-carbaldehyde **187***

Benzo[*c*]isoxazole-7-carbaldehyde **187** is a known compound and was synthetized following literature procedures. The synthesis started with the oxidation of (3-methyl-2-nitrophenyl)methanol **183** to the corresponding aldehyde **184** using MnO_2 in toluene.[236] Successively, the cyclization step was promoted by the treatment of **184** with tin chloride in HCl allowing for the isolation in good yield of the 7-methylbenzo[*c*]isoxazole **185**. The bromination of the methyl group was achieved *via* a radical process promoted by light with the radical initiator benzoyl peroxide (BPO) and in presence of NBS.[237] The last step was a second oxidation of the brominated derivative **186** induced by *N*-methylmorpholine *N*-oxide in THF giving rise to the desired benzo[*c*]isoxazole-7-carbaldehyde **187** (scheme 5.10).

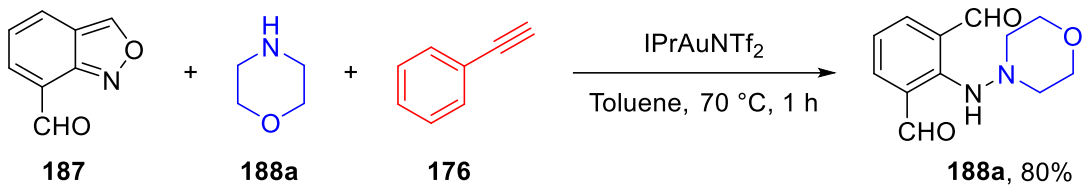


Scheme 5.10

5.2.3 Functionalization of anthranils for the synthesis of 2-hydrazineylisophthalaldehyde

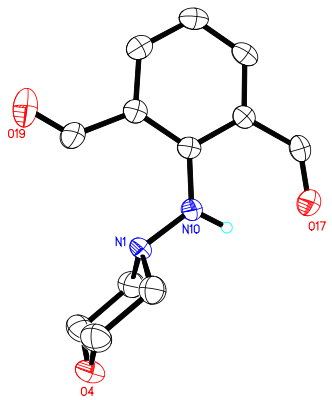
5.2.3.1 Initial studies

In order to obtain the A3 coupling product, benzo[*c*]isoxazole-7-carbaldehyde **187** was reacted with morpholine **188a** and phenylacetylene **176** in presence of $IPrAuNTf_2$ catalyst (scheme 5.11). Surprisingly, the product was a new symmetric hydrazine derivative **189a** bearing two *ortho*-formyl groups. This type of reactivity was completely unknown for anthranil derivatives and in literature there are no examples of this kind of isophthalaldehyde derivatives. Thus, we decided to investigate the new transformation.



Scheme 5.11

The structure of the product **189a** was confirmed by 2D-NMR and X-ray diffraction analysis on a single crystal (figure 5.1).



189a

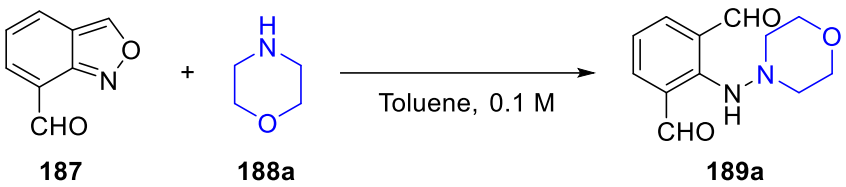
Figure 5.1

*5.2.3.2 Screening of the reaction condition for the synthesis of compound **189a***

Starting from the obtained result for this unknown reaction, the transformation was performed in presence of catalytic amount of gold, or *para*-toluensulfonic acid (*p*-TSOH) and without any catalyst

(table 1). Entry 1 shows that under gold catalysis at 70 °C the hydrazine derivative was obtained in good yield. Decreasing the reaction temperature and using *p*-TSOH in catalytic amount the yield increased (entry 2). Furthermore, the outcome of the reaction without the employment of catalysts allows for the isolation of compound **189a** in excellent yield (entry 3).

*Table 5.1 Optimization of the reaction conditions for the synthesis of **189a***



Entry	Cat	T, °C	Time, h	188a,[b] yield%
1	$IPrAuNTf_2$ (5 mol%)	70	1	80
2	*p*-TSA (5 mol%)	Rt	4	88
3	-	Rt	4	90

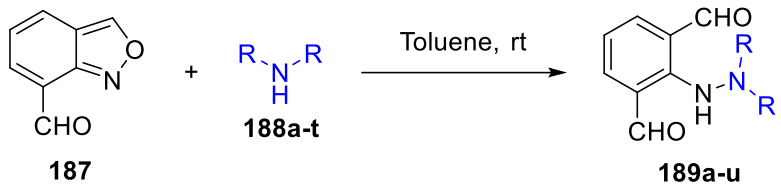
[a] All reactions were carried out using **187a** (0.2 mmol) and **188a** (0.24 mmol) in toluene (0.1 M). [b] Isolated yield.

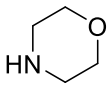
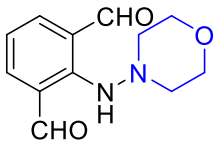
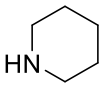
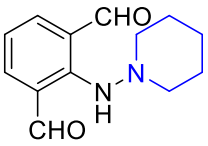
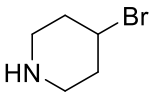
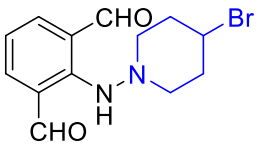
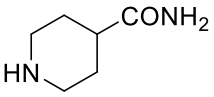
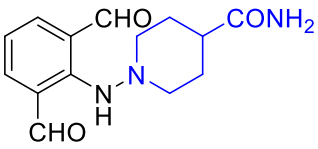
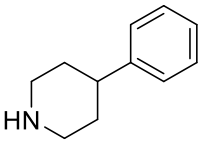
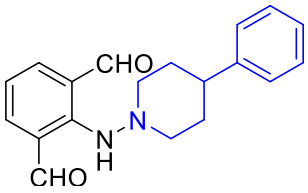
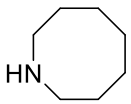
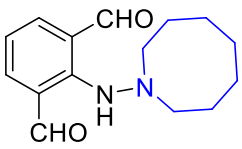
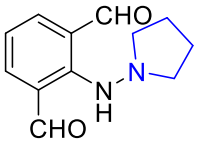
Thus, performing the reaction without the addition of any catalyst after four hours at room temperature we obtained the desired product **189a** in 90% yield after purification by column chromatography.

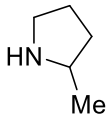
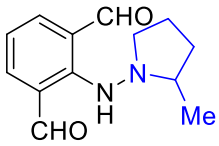
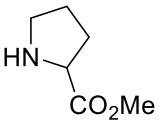
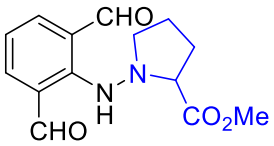
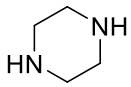
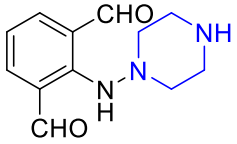
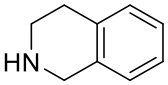
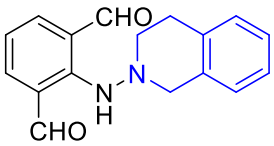
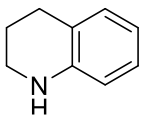
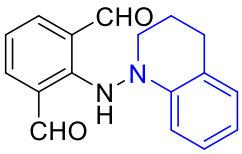
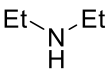
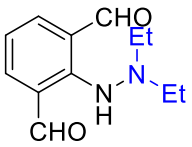
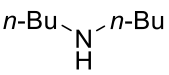
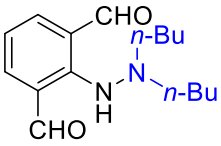
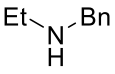
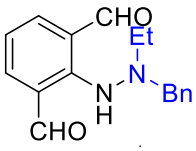
*5.2.3.3 Scope for the synthesis of 2-hydrazineylisophthalaldehyde derivatives **189***

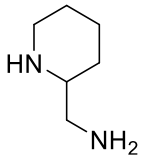
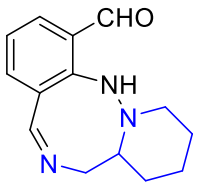
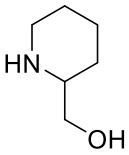
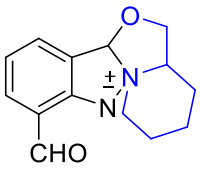
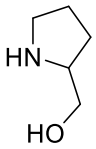
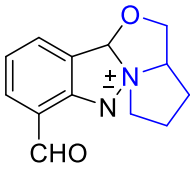
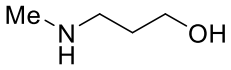
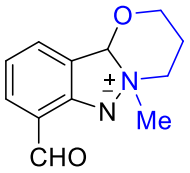
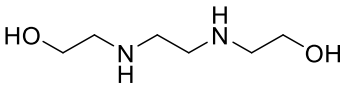
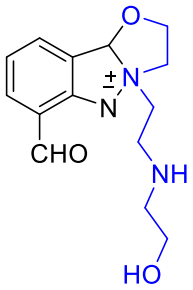
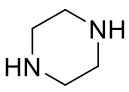
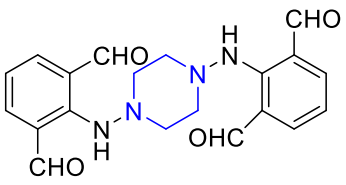
Having in hand the best reaction conditions (entry 3, table 5.1), we next explored the scope and the limitation of the reaction between anthranil **187** and secondary amines **188a-t**. The results are summarized in table 5.2

*Table 5.2 Scope for the synthesis of compound **189a-u***



Entry	188	Product	Yield,[b] %
1	 **188a**	 **189a**	90
2	 **188b**	 **189b**	80
3	 **188c**	 **189c**	64
4	 **188d**	 **189d**	93
5	 **188e**	 **189e**	86
6	 **188f**	 **189f**	52
7	 **188g**	 **189g**	87

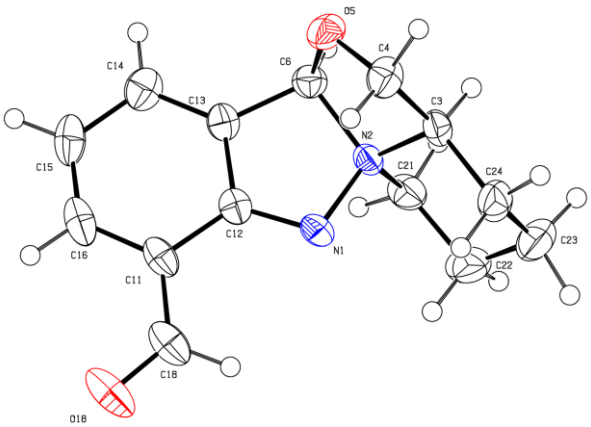
8	 **188h**	 **189h**	88
9	 **188i**	 **189i**	40
10	 **188j**	 **189j**	68
11	 **188k**	 **189k**	68[c]
12	 **188l**	 **189l**	20[c]
13	 **188m**	 **189m**	39[c]
14	 **188n**	 **189n**	36[c]
15	 **188o**	 **189o**	30[c]

16	 **188p**	 **189p**	57
17	 **188q**	 **189q**	72
18	 **188r**	 **189r**	74
19	 **188s**	 **189s**	68
20	 **188t**	 **189t**	72[d]
21	 **188j**	 **189u**	74[d]

[a]All reactions were carried out using **187** (0.2 mmol) and **188** (0.24 mmol) in toluene (0.1 M) at room temperature. [b]Isolated yields. [c]The reaction was heated at 50°C. [d]The reaction was conducted with **187** (0.2 mmol) and **188** (0.1 mmol) in toluene (0.1 M) at 50°C.

As reported before, employing **187** and morpholine **188** as secondary amine, the corresponding compound **189a** was obtained in excellent yield (entry 1). Successively, the evaluation focused on the influence of different cyclic amines on the outcome of the reaction. Firstly, six-member piperidine derivatives **188b-e** were employed yielding compounds **189b-e** in good to excellent yields. Using piperidine **188b**, the corresponding product **189b** was isolated in 80% yield, while changing **188b** to 4-bromo-piperidine **188c**, product **189c** was recovered in lower yield, probably due to the lower stability of this latter compound (entries 2 and 3). In fact, the NMR of the crude **189c** showed more impurities than that of previously synthesized compounds. Both amide and phenyl moieties at C4 position of piperidines **188d** and **188e** allowed for the formation of the corresponding products **189d** and **189e** in 93% and 86% yields, respectively (entries 4 and 5). Increasing the dimension of the ring (amine **188f**), the yield decreased, probably because of the use of a more sterically hindered base. Thus, compound **189f** was isolated in only 52% yield using heptamethyleneimine **188f** (entry 6). Subsequently, a series of pyrrolidine derivatives were tested and the simple pyrrolidine **188g** gave rise to hydrazine derivative **189g** in 87% yield (entry 7), comparable to the six-member piperidine. Moreover, increasing the dimension of the substituent in C2 position from methyl (**188h**) to carboxy ethyl (**188i**), the yields decreased significantly from compound **189h** to **189i** (88% and 40%, respectively, entries 8 and 9). Nevertheless, it is important to underline the possibility of using proline ethyl ester as base (compound **188i**, entry 9) for the formation of the corresponding hydrazine **189i**. Subsequently, other cyclic amines were examined: piperazine **188j** gave rise to the corresponding hydrazine derivative **189j**, in good 68% yield (entry 10); while the employment of the two isomeric 1,2,3,4-tetrahydroisoquinoline **188k** and 1,2,3,4-tetrahydroquinoline **188l** required heating at 50 °C and prolonged reaction time. In the first case, the yield for compound **189k** was 68%, while using the less nucleophilic amine **189l** the yield dropped to 20% for **189l** (entries 11 and 12). In fact, using less nucleophilic amine like diphenylamine, the reaction did not work at all and the starting material was recovered unaltered. The investigation continued with symmetric and non-symmetric linear amines. Firstly, the linear homologous of the pyrrolidine was used, diethylamine **188m**, and the product **189m** was obtained in modest yield under heating for a prolonged reaction time, probably due to the steric hindrance of the more flexible lateral chains (entry 13). The same trend was observed for symmetric *n*-dibutylamine **188n** and non-symmetric *N*-ethylbenzylamine **188o** (entries 14 and 15). Finally, more challenging cyclic secondary amines bearing another nucleophilic atom on a lateral chain were tested. Surprisingly, we obtained two different compounds using nitrogen or oxygen as second nucleophile. In the first case, the use of piperidin-2-ylmethanamine **188p** led to the formation of the triazocine derivatives **189p** in good yield (57%, entry 16), while using the amino alcohols **188q-t** we obtained

polycyclic compounds bearing a positive quaternary nitrogen (**189q-t**) in good yields (entries 17 to 20). The structure of compound **189q** was confirmed by NMR analysis and X-ray diffraction analysis on a single crystal (figure 5.2). As reported for compound **189b** and **189g**, between piperidine and pyrrolidine derivatives **188q** and **188r** we did not observe differences in terms of yields and compounds **189q** and **189r** were recovered both in good yield (entries 17 and 18). Moreover, the use of linear 3-(methylamino)propan-1-ol **188s** gave rise to the corresponding product **189s** in 68% yield (entry 19). Finally, the bidentate base **188t** was tested in the reaction with two molecules of anthranil (entry 20). Unfortunately, compound **189t**, arising from the addition of a single molecule of benzo[*c*]isoxazole, was the sole obtained compound, while using piperazine **188j** we obtained the desired double addition product **189u** in good yield (entry 21). However, because of the low solubility, compound **189u** was not completely characterized.

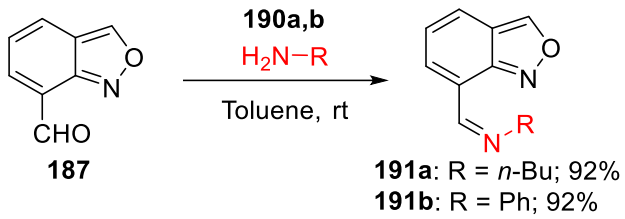


189q

Figure 5.2

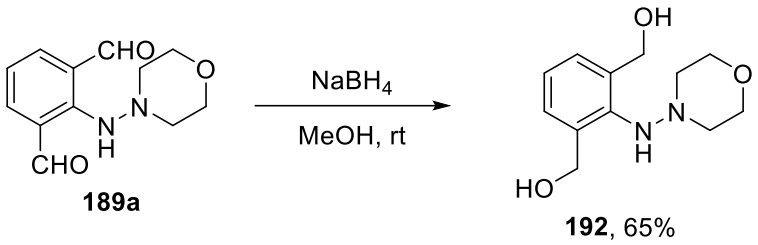
5.2.3.4 Additional experiments

We tested also primary amines **190a** and **191b** (scheme 5.12). Surprisingly, the reactions gave rise to the corresponding imine product **191a-b** bearing both alkyl or aryl amines in excellent yield. Thanks to the similar features of compound **191a** with benzo[*c*]isoxazole **187**, we tried to react **191a** with morpholine under the standard reaction conditions, however after prolonged heating the starting materials were recovered unreacted.



Scheme 5.12

Finally, some simple transformations were planned. Firstly, the 2-hydrazineylisophthalaldehyde derivative **189a** was tested in presence of $NaBH_4$ for the reduction of the aldehyde groups. The reaction resulted in the isolation of compound product **192** in 65% yield (scheme 5.13).



Scheme 5.13

5.2.3.5 Upcoming work

Unfortunately, I was not able to conclude this part of my work project because of my departure from Heidelberg University due to the pandemic COVID 19. However further investigations are ongoing in Hashmi laboratories in order to understand the mechanism of this transformation and to develop the chemistry of these interesting and unknown diformyl hydrazines.

5.2.4 Experimental data

5.2.4.1 Preface

5.2.4.1.1 General methods

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

5.2.4.1.2 Reagents

This study was carried out using benzo[c]isoxazole-7-carbaldehyde **187** which is known compound and it was prepared following the procedure described in section 5.2.2.1 according to literature procedure.[237,238]
The primary and secondary amines were purchased from commercial suppliers and used as received.

5.2.4.1.3 Solvents

Dry solvents were obtained from the solvent purification system MBraun MB SPS-800.

5.2.4.1.4 Chromatography/purification of compounds

The chromatographic column separations were conducted using silica gel 60 (70 – 230 mesh, 63 – 200 μm provided by SigmaAldrich).
For thin-layer chromatography (TLC), pre-coated TLC sheets (Macherey-Nagel ALUGRAM® Xtra SIL G/UV254) were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm).

5.2.4.1.5 NMR spectroscopy

^{1}H-NMR analyses were performed with Bruker Avance III 300; Bruker Avance III 500; Bruker Avance III 400 spectrometer. Chemical shifts δ are quoted in parts per million, whereas coupling constants J are quoted in Hertz (Hz).
For ^{1}H NMR, the multiplicity of the peaks are described as: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet), m (multiplet), bs (broad signal) as well as their combinations.

All ^{13}C NMR spectra were recorded with ^{1}H-decoupled and, when needed interpreted along with ^{13}C DEPT135, $^{1}H,^{1}H$ COSY, $^{1}H,^{13}C$ HSQC and $^{1}H,^{13}C$ HMBC. The peaks in the ^{13}C NMR spectra are addressed as: C (quarternary carbon), CH (tertiary carbon, CH), CH_2 (secondary carbon, CH_2) and CH_3 (primary carbon, CH_3).

5.2.4.1.6 Mass Spectroscopy

Mass spectra were measured at an Agilent 7890A Network GC System SSL gas chromatography system coupled with an Agilent 5975C VL MSD mass spectrometer. High resolution mass spectra (HR/MS) were measure on a JEOL AccuTOF GCx time-of-flight mass spectrometer, at the Institute of Organic Chemistry - Heidelberg University under the direction of Dr. J. Gross. The values are expressed as mass-charge ratio.

5.2.4.1.7 Melting points

The melting points of the solid products were measured in capillary tube with the device *StuarScientific* SMP3.

5.2.4.1.8 IR spettroscopy

Infrared spectroscopy was processed on an FT-IR Bruker (IF528), IR Perkin Elmer (283) or FTIR BrukerVektor 22 - wave numbers ν [cm-1] are reported for the most significant bands.

5.2.4.1.9 X-ray diffraction

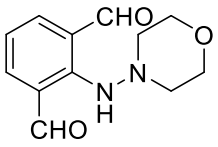
Single crystals suitable for X-ray diffraction were obtained by slow diffusion of hexane into a EtOAc solution of **189a** and an ethyl acetate solution of **189q** at ambient temperature.

5.2.4.2 Experimental data

5.2.4.2.1 General procedure for the reaction between benzo[c]isoxazole-7-carbaldehyde **187** and amines **188a-t** or **189a,b**

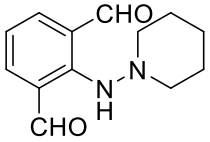
To a stirring solution of benzo[*c*]isoxazole-7-carbaldehyde **187** (0.2 mmol, 1equiv) in toluene (0.1 M), the secondary amine **188a-t** or the primary amines **190a,b** (0.24 mmol, 1.2 equiv) was added and the mixture was stirred at room temperature or 50°C until the consumption of the starting material. Then the reaction was concentrated under vacuum and the crude was purified by column chromatography to yield the desired product **189a-u** and **191a,b**.

2-(morpholinoamino)isophthalaldehyde (189a)



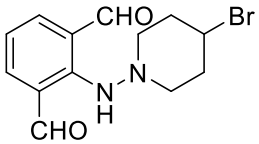
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), morpholine **188a** (20.9 mg, 0.24 mmol) in toluene (2 ml) for 4 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 3:1) yielded **189a** (42.0 mg, 90%) as a yellow solid (m.p. 153.3-155.0 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): 10.06 (s, 2H), 8.97 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 6.87 (t, *J* = 7.6 Hz, 1H), 3.67 (s, 4H), 2.85 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): 191.65 (2xCH), 150.04 (2xC), 137.89 (2xCH), 123.00 (C), 118.02 (CH), 66.12 (2xCH_2), 56.46 (2xCH_2). **IR** (ATR, cm-1): v = 3206, 3153, 3069, 2958, 2917, 2873, 2810, 1656, 1587, 1524, 1455, 1417, 1392, 1342, 1308, 1264, 1219, 1161, 1131, 1110, 1071, 1017, 971, 917, 871, 821, 786, 732, 656, 638. **HR-MS** (EI): m/z calcd for $C_{12}H_{14}N_2O_3$: 234.09989; found: 234.09881.

2-(piperidin-1-ylamino)isophthalaldehyde (189b)



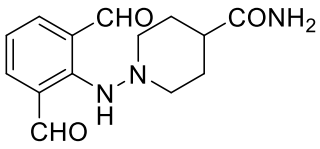
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), piperidine **188b** (20.4 mg, 0.24 mmol) in toluene (2 ml) for 2 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189b** (37.0 mg, 80%) as a orange thick oil. **^{1}H NMR** (400 MHz, $CDCl_3$): 10.04 (bs, 2H), 8.95 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 2.73 (bs, 4H), 1.70 – 1.35 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): 191.82 (2xCH), 150.38 (2xC), 137.73 2xCH), 122.35 (C), 117.13 (CH), 57.28 (2xCH_2), 25.04 (2xCH_2), 23.06 (2xCH_2). **IR** (ATR, cm-1): v = 3297, 3206, 3156, 3102, 2945, 2856, 2789, 1737, 1655, 1598, 1588, 1527, 1441, 1417, 1395, 1348, 1268, 1218, 1151, 1121, 1038, 969, 866, 803, 775, 731, 652, 616. **HR-MS** (EI): m/z calcd for $C_{13}H_{16}N_2O_2$: 232.12063; found: 232.11978.

2-((4-bromopiperidin-1-yl)amino)isophthalaldehyde (189c)



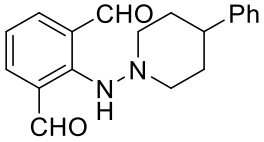
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), 4-bromopiperidine **188c** (39.4 mg, 0.24 mmol) in toluene (2 ml) for 7 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189c** (51.0 mg, 93%) as yellow solid (m.p. 126.0-127.7 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): 10.02 (s, 2H), 9.01 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 1H), 4.02 (m, 1H), 3.15 – 2.70 (m, 4H), 2.20 – 1.94 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): 191.78 (2xCH), 150.10 (2xC), 137.84 (2xCH), 122.99 (C), 117.86 (CH), 51.74 (CH), 47.61 (2xCH_2), 34.39 (2xCH_2). **IR** (ATR, cm-1): 3221, 2967, 2869, 2831, 1673, 1586, 1490, 1461, 1419, 1399, 1382, 1321, 1240, 1214, 1103, 1064, 1028, 1009, 977, 913, 883, 826, 806, 776, 739, 696, 654. **HR-MS** (EI): m/z calcd for $C_{13}H_{15}BrN_2O_2$: 310.03114; found: 310.03161.

1-((2,6-diformylphenyl)amino)piperidine-4-carboxamide (189d)



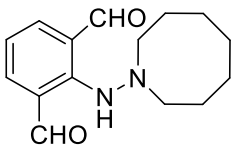
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **185** (29.4 mg, 0.2 mmol), piperidine-4-carboxamide **188d** (30.8 mg, 0.24 mmol) in toluene (2 ml) for 6 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 95:5) yielded **189d** (51.0 mg, 93%) as yellow solid (T>172 °C dec). **^{1}H NMR** (301 MHz, $CDCl_3$): 10.03 (s, 2H), 8.99 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 6.84 (t, *J* = 7.6 Hz, 1H), 5.68 (d, *J* = 25.1 Hz, 2H), 3.20 (d, *J* = 10.2 Hz, 2H), 2.54 (bs, 2H), 2.16 (bs, 1H), 2.02 – 1.70 (m, 4H). **^{13}C NMR** (76 MHz, $CDCl_3$): 191.42 (2xCH), 176.36 (C), 150.17 (2xC), 137.82 (2xCH), 117.68 (CH), 55.73 (2xCH_2), 45.88 (CH), 28.11 (2xCH_2). One quaternary carbon is missing, probably overlapped. **IR** (ATR, cm-1): v = 3387, 3160, 2955, 2939, 2925, 2795, 1658, 1582, 1514, 1419, 1392, 1209, 1106, 972, 805, 763, 731, 652. **HR-MS** (EI): m/z calcd for $C_{14}H_{16}N_2O_4$: 275.12644; found: 275.12551.

2-((4-phenylpiperidin-1-yl)amino)isophthalaldehyde (189e)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), 4-phenylpiperidine **188e** (38.7 mg, 0.24 mmol) in toluene (2 ml) for 4 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189e** (53.0 mg, 86%) as orange solid (m.p. 95.7-97.2 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 10.07 (bs, 2H), 9.01 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.28 – 7.17 (m, 2H), 7.16 – 7.09 (m, 3H), 6.81 (t, *J* = 7.6 Hz, 1H), 3.25 (d, *J* = 11.4 Hz, 2H), 2.64 – 2.52 (m, 2H), 2.45 (m, 1H), 1.87 – 1.73 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): 191.70 (2xCH), 150.37 (2xC), 144.91 (C), 137.81 (2xCH), 128.44 (2xCH), 126.71 (2xCH), 126.38 (CH), 117.33 (CH), 56.87 (2xCH_2), 41.30 (CH), 32.38 (2xCH_2). One quaternary carbon is missing, probably overlapped. **IR** (ATR, cm-1): v = 3244, 3061, 3028, 2943, 2909, 2832, 2733, 1673, 1652, 1580, 1485, 1458, 1419, 1395, 1369, 1329, 1255, 1209, 1145, 1104, 1068, 1028, 1011, 964, 887, 869, 834, 792, 773, 754, 697, 657. **HR-MS** (EI): m/z calcd for $C_{19}H_{20}N_2O_2$: 308.15193; found: 308.15175.

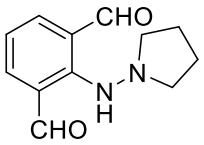
2-(azocan-1-ylamino)isophthalaldehyde (189f)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), heptamethyleneimine **188f** (27.1 mg, 0.24 mmol) in toluene (2 ml) for 20 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189f** (27.0 mg, 52%) as orange solid (m.p. 63.1-64.5 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 10.03 (s, 2H), 9.24 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 2H), 6.80 (t, *J* = 7.6 Hz, 1H), 2.97 (s, 4H), 1.70 – 1.45 (m, 10H). **^{13}C NMR** (75 MHz, $CDCl_3$): 191.53 (2xCH), 150.92 (2xC), 137.84 (2xCH), 117.23 (CH), 56.42 (2xCH_2), 26.21 (2xCH_2), 26.02 (CH_2), 25.12 (2xCH_2). One quaternary carbon is missing, probably overlapped. **IR** (ATR, cm-

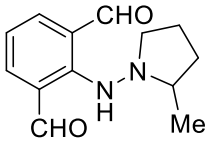
1): v = 3266, 2922, 2850, 1662, 1590, 1500, 1441, 1396, 1361, 1331, 1219, 1117, 978, 818, 766, 733, 656, 611. **HR-MS** (EI): m/z calcd for $C_{15}H_{20}N_2O_2$: 260.15193; found: 260.15068.

2-(pyrrolidin-1-ylamino)isophthalaldehyde (189g)



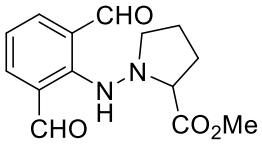
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), pyrrolidine **188g** (17.0 mg, 0.24 mmol) in toluene (2 ml) for 3.5 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 4:1) yielded **189g** (38.0 mg, 87%) as a yellow solid (m.p. 70.1-71.8 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 10.04 (s, 2H), 8.99 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 6.77 (t, *J* = 7.6 Hz, 1H), 2.88 (bs, 4H), 1.87 – 1.42 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): 190.53 (2xCH), 150.21 (2xC), 136.83 (2xCH), 121.42 (C), 115.83 (CH), 54.81 (2xCH_2), 20.96 (2xCH_2). **IR** (ATR, cm-1): v = 3206, 2920, 2846, 2808, 1657, 1582, 1520, 1460, 1388, 1339, 1217, 1124, 996, 979, 886, 773, 732, 659. **HR-MS** (EI): m/z calcd for $C_{12}H_{14}N_2O_2$: 218.10498; found: 218.10510.

2-((2-methylpyrrolidin-1-yl)amino)isophthalaldehyde (189h)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), 2-methylpyrrolidine **188h** (20.4 mg, 0.24 mmol) in toluene (2 ml) for 24 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189h** (41.0 mg, 88%) as yellow solid (m.p. 126.4-128.0 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 10.10 (bs, 2H), 9.05 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 6.74 (t, *J* = 7.6 Hz, 1H), 3.25 (s, 1H), 2.84 – 2.60 (m, 2H), 1.91 (m, 1H), 1.82 – 1.68 (m, 2H), 1.40 (m, 1H), 0.95 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 192.06 (2xCH), 151.94 (2xC), 136.47 (2xCH), 116.30 (CH), 64.03 (CH), 55.98 (CH_2), 30.05 (CH_2), 19.84 (CH_2), 17.48 (CH_3). One quaternary carbon is missing, probably overlapped. **IR** (ATR, cm-1): v = 3202, 3155, 2968, 2926, 2799, 1655, 1584, 1514, 1459, 1417, 1392, 1338, 1268, 1243, 1218, 1141, 1081, 1040, 999, 969, 893, 827, 769, 731, 656. **HR-MS** (EI): m/z calcd for $C_{13}H_{16}N_2O_2$: 232.12063; found: 232.12140.

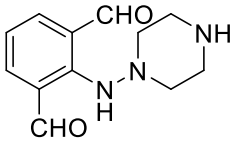
Methyl ((2,6-diformylphenyl)amino)prolinate (189i)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), methyl prolinate **188i** (31.0 mg, 0.24 mmol) in toluene (2 ml) for 48 hours at room temperature. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 4:1) yielded **189i** (23.0 mg, 42%) as yellow thick wax. **^{1}H NMR** (301 MHz, $CDCl_3$): 10.10 (s, 2H), 9.56 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 4.00 – 3.45 (m, 4H), 3.27 (d, *J* = 6.6 Hz, 1H), 3.02 (bs, 1H), 2.28 – 2.06 (m,

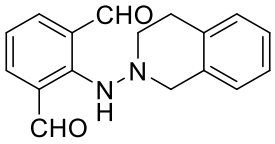
1H), 1.99 – 1.72 (m, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$): 191.99 (2xCH), 172.51 (C), 151.04 (2xC), 137.90 (2xCH), 117.16 (CH), 51.91 (CH_3), 27.27 (2xCH_2), 21.16 (CH_2). One quaternary carbon and one secondary carbon are missing, probably overlapped. **IR** (ATR, cm-1): v = 3243, 2955, 2903, 2874, 1721, 1661, 1595, 1578, 1498, 1427, 1399, 1283, 1214, 1093, 1038, 1001, 981, 903, 859, 775, 750, 720, 654. **HR-MS** (EI): m/z calcd for $C_{14}H_{16}N_2O_4$: 276.11046; found: 276.10949.

2-(piperazin-1-ylamino)isophthalaldehyde (189j)



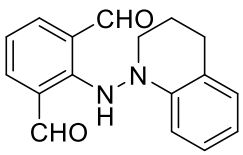
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), piperazine **188j** (20.7 mg, 0.24 mmol) in toluene (2 ml) for 20 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 9:1 + 0.5% trienthylamine) yielded **189j** (38.0 mg, 68%) as yellow solid (dec T>145 °C). **^{1}H NMR** (301 MHz, $CDCl_3$): 10.05 (s, 2H), 9.00 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 1H), 2.93 (bs, 8H). **^{13}C NMR** problem of solubility, spectrum is not correct. Need another measurement. **IR** (ATR, cm-1): v = 3249, 2923, 2825, 2726, 2693, 2627, 2600, 2512, 1656, 1583, 1504, 1454, 1386, 1324, 1272, 1213, 1115, 1084, 1045, 1010, 981, 862, 776, 734, 691, 654. **HR-MS** (EI): m/z calcd for $C_{12}H_{15}N_3O_2$: 233.11588; found: 233.11522.

2-((3,4-dihydroisoquinolin-2(1*H*)-yl)amino)isophthalaldehyde (189k)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), 1,2,3,4-tetrahydroisoquinoline **188k** (31.9 mg, 0.24 mmol) in toluene (2 ml) for 19 hours at 50°C. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189k** (38.0 mg, 68%) as orange solid (m.p. 143.9-145.8 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): 10.08 (s, 2H), 9.25 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.13 – 7.01 (m, 3H), 6.96 – 6.90 (m, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 4.16 – 3.72 (m, 2H), 3.30 – 2.80 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): 191.79 (2xCH), 150.44 (2xC), 138.05 (2xCH), 132.77 (C), 132.42 (C), 128.64 (CH), 126.88 (CH), 126.67 (CH), 126.16 (CH), 117.68 (CH), 58.13 (CH_2), 53.66 (CH_2), 28.20 (CH_2). One quaternary carbon is missing, probably overlapped. **IR** (ATR, cm-1): v = 3218, 2924, 2899, 2855, 2790, 1663, 1586, 1495, 1454, 1421, 1389, 1323, 1267, 1215, 1121, 1068, 1009, 977, 967, 936, 858, 828, 774, 754, 742, 657, 643. **HR-MS** (EI): m/z calcd for $C_{17}H_{16}N_2O_2$: 280.12063; found: 280.12028.

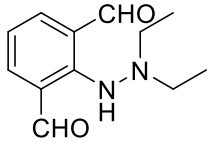
2-((3,4-dihydroquinolin-1(2*H*)-yl)amino)isophthalaldehyde (189l)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), 1,2,3,4-tetrahydroquinoline **188l** (31.9 mg, 0.24 mmol) in toluene (2 ml) for 19 hours at 50°C. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189l** (11.0 mg, 20%) as

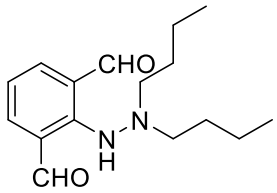
yellowish thick oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 10.12 (s, 1H), 9.87 (s, 1H), 9.62 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.81 (td, *J* = 7.4, 1.1 Hz, 1H), 3.45 – 3.05 (m, 2H), 2.88 – 2.55 (m, 2H), 2.12 – 1.80 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): 193.96 (CH), 191.34 (CH), 151.42 (C), 145.95 (C), 140.53 (CH), 136.04 (CH), 129.61 (CH), 127.17 (CH), 125.19 (C), 125.22 (C), 121.58 (CH), 120.25 (C), 117.92 (CH), 113.82 (CH), 52.27 (CH_2), 26.59 (CH_2), 21.84 (CH_2). **IR** (ATR, cm-1): v = 3266, 2928, 2865, 2836, 2744, 1681, 1657, 1596, 1581, 1502, 1455, 1408, 1381, 1331, 1302, 1279, 1217, 1189, 1119, 1025, 1004, 974, 932, 861, 800, 757, 721, 656, 609. **HR-MS** (EI): m/z calcd for $C_{17}H_{16}N_2O_2$: 280.12063; found: 280.12001.

2-(2,2-diethylhydrazineyl)isophthalaldehyde (189m)



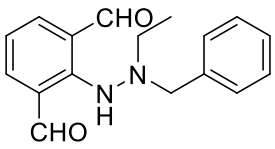
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), diethylamine **188m** (17.5 mg, 0.24 mmol) in toluene (2 ml) for 24 hours at 50°C. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189m** (17.0 mg, 39%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 10.58 (bs, 1H), 9.85 (s, 1H), 9.16 (s, 1H), 7.89 – 7.44 (m, 2H), 6.74 (t, *J* = 7.6 Hz, 1H), 2.78 (d, *J* = 31.1 Hz, 4H), 0.99 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): 193.30 (2xCH), 151.85 (2xC), 142.90 (2xCH) 120.02 (C), 116.28 (CH), 51.98 (2xCH_2), 10.95 (2xCH_3). **IR** (ATR, cm-1): v = 3430, 3318, 3230, 3069, 2975, 2935, 2848, 2747, 1660, 1585, 1509, 1464, 1380, 1339, 1273, 1213, 1181, 1125, 1055, 1012, 964, 936, 869, 773, 735, 656. **HR-MS** (EI): m/z calcd for $C_{12}H_{16}N_2O_2$: 220.12063; found: 220.12017.

2-(2,2-dibutylhydrazineyl)isophthalaldehyde (189n)



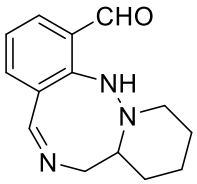
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), dibutylamine **188n** (31.0 mg, 0.24 mmol) in toluene (2 ml) for 16 hours at 50°C. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189n** (20.0 mg, 36%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 10.58 (bs, 1H), 9.81 (bs, 1H), 9.21 (s, 1H), 7.65 (bs, 2H), 6.74 (t, *J* = 7.6 Hz, 1H), 2.70 (d, *J* = 30.9 Hz, 4H), 1.54 – 1.29 (m, 4H), 1.27 – 1.13 (m, 4H), 0.79 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): 190.92 (2xCH), 151.59 (2xC), 140.95 (2xCH), 116.16 (CH), 58.41(2xCH_2), 27.92 (2xCH_2), 20.46 (2xCH_2), 13.80 (2xCH_3). One quaternary carbon is missing, probably overlapped. **IR** (ATR, cm-1): v = 3429, 3317, 3228, 3159, 3069, 2959, 2933, 2865, 2741, 1681, 1594, 1515, 1462, 1415, 1378, 1331, 1215, 1108, 1083, 1000, 981, 877, 777, 737, 656, 615. **HR-MS** (EI): m/z calcd for $C_{16}H_{24}N_2O_2$: 276.18323; found: 276.18303.

2-(2-benzyl-2-ethylhydrazineyl)isophthalaldehyde (189o)



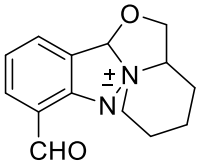
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), *N*-benzylethanamine **188o** (32.5 mg, 0.24 mmol) in toluene (2 ml) for 24 hours at 50°C. The purification of the crude by column chromatography (SiO_2, petroleum ether/ethyl acetate 9:1) yielded **189o** (17.0 mg, 30%) as a yellow thick oil. **^{1}H NMR** (300 MHz, $CDCl_3$): 10.53 (bs, 1H), 9.84 (s, 1H), 9.15 (s, 1H), 7.79 – 7.46 (m, 2H), 7.26 – 7.05 (m, 5H), 6.70 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 2H), 2.79 (bs, 2H), 1.05 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 193.30 (2xCH), 151.71 (2xC), 142.91 (2xCH), 134.96 (C), 129.84 (2xCH), 128.35 (2xCH), 127.85 (CH), 120.03 (C), 116.73 (CH), 62.40 (CH_2), 51.99 (CH_2), 11.11 (CH_3). **IR** (ATR, cm-1): v = 3430, 3317, 3229, 3064, 3030, 2974, 2929, 2845, 2746, 1954, 1888, 1813, 1663, 1586, 1496, 1455, 1416, 1393, 1340, 1269, 1213, 1120, 1102, 1003, 936, 875, 825, 776, 748, 700, 682, 656, 624. **HR-MS** (EI): m/z calcd for $C_{17}H_{18}N_2O_2$: 282.13628; found: 282.13595.

(*Z*)-2,3,4,4a,5,12-hexahydro-1*H*-benzo[*g*]pyrido[1,2-*b*][1,2,5]triazocine-11-carbaldehyde (189p)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), piperidin-2-ylmethanamine **188p** (27.4 mg, 0.24 mmol) in toluene (2 ml) for 4 hours at room temperature. The purification of the crude by column chromatography (SiO_2, ethyl acetate/dichloromethane 9:1+1% triethylamine) yielded **189p** (28.0 mg, 57%) as yellow thick wax. **^{1}H NMR** (301 MHz, $CDCl_3$): 9.73 (s, 1H), 9.21 (bs, 1H), 8.37 (s, 1H), 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.32 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.68 (td, *J* = 7.5, 2.9 Hz, 1H), 3.73 – 3.38 (m, 2H), 3.15 (dd, *J* = 6.1, 4.0 Hz, 1H), 2.94 (m, 1H), 2.60 (m, 1H), 2.31 (m, 1H), 1.79 (m, 1H), 1.64 (m, 1H), 1.50 – 1.31 (m, 2H), 1.19 (m, 1H). **^{13}C NMR** (76 MHz, $CDCl_3$): 193.37 (CH), 162.39 (CH), 149.68 (C), 139.48 (CH), 139.23 (CH), 118.72 (C), 117.96 (C), 115.15 (CH), 57.85 (CH), 56.76 (CH_2), 53.84 (CH_2), 29.95 (CH_2), 25.57 (CH_2), 23.83 (CH_2). **IR** (ATR, cm-1): v = 2932, 2853, 1657, 1631, 1584, 1518, 1458, 1442, 1383, 1340, 1266, 1214, 1081, 1014, 973, 914, 773, 729, 657, 614. **HR-MS** (EI): m/z calcd for $C_{14}H_{17}N_3O$: 243.13661; found: 243.13677.

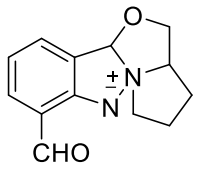
10-formyl-1,2,3,4,4a,5-hexahydro-6a*H*-pyrido[1',2':3,4]oxazolo[3,2-*b*]indazol-12-ium-11-ide (189q)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), piperidin-2-ylmethanol **188q** (27.6 mg, 0.24 mmol) in toluene (2 ml) for 20 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 98:2 + 1% triethylamine) yielded **189q** (35.0 mg, 72%) as orange solid (T>133.0 °C dec). **^{1}H NMR** (301 MHz, CD_2Cl_2): 9.83 (s, 1H), 7.30 (dd, *J* =

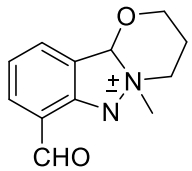
7.9, 1.3 Hz, 1H), 7.04 (dd, *J* = 6.9, 1.0 Hz, 1H), 6.01 (dd, *J* = 12.7, 5.3 Hz, 1H), 5.67 (s, 1H), 4.09 (m, 1H), 3.67 – 3.55 (m, 2H), 3.29 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.0 (m, 1H), 2.64 (m, 1H), 2.29 (m, 1H), 1.96 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.47 (m, 1H). **^{13}C NMR** (76 MHz, CD_2Cl_2): 187.75 (CH), 133.40 (CH), 129.31 (CH), 123.11 (C), 101.31 (CH), 71.54 (CH), 70.47 (CH_2), 60.81 (CH_2), 22.13 (CH_2), 21.36 (CH_2), 20.96 (CH_2). Two quaternary carbon and one CH is missing, probably overlapped. **IR** (ATR, cm-1): v = 2966, 2947, 2929, 2817, 1636, 1619, 1546, 1467, 1441, 1375, 1256, 1233, 1198, 1180, 1146, 1085, 1017, 990, 939, 896, 867, 840, 799, 768, 745, 655, 620. **HR-MS** (EI): m/z calcd for $C_{14}H_{16}N_2O_2$: 244.12063; found: 244.11890.

9-formyl-2,3,3a,4-tetrahydro-1*H*,5a*H*-pyrrolo[1',2':3,4]oxazolo[3,2-*b*]indazol-11-ium-10-ide (189r)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), D-prolinol **188r** (24.4 mg, 0.24 mmol) in toluene (2 ml) for 2 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 9:1 + 1% triethylamine) yielded **189r** (34.0 mg, 74%) as orange solid (m.p. 74.0-76.1). **^{1}H NMR** (300 MHz, CD_2Cl_2): 9.76 (s, 1H), 7.48 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.24 (d, *J* = 7.1 Hz, 1H), 6.52 (t, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 4.82 (m, 1H), 4.19 – 4.06 (m, 2H), 3.96 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.85 (m, 1H), 2.65 (m, 1H), 2.31 (m, 1H), 2.17 (m, 1H), 1.86 (m, 1H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 188.64 (CH), 153.37 (C), 135.11 (CH), 129.52 (CH), 119.32 (C), 115.48 (C), 115.19 (CH), 107.10 (CH), 78.71 (CH), 71.27 (CH_2), 65.40 (CH_2), 29.19 (CH_2), 24.27 (CH_2). **IR** (ATR, cm-1): v = 3393, 2956, 2924, 2882, 2850, 2741, 1679, 1637, 1613, 1603, 1533, 1466, 1442, 1396, 1375, 1236, 1207, 1118, 1049, 987, 878, 788, 739, 661. **HR-MS** (EI): m/z calcd for $C_{13}H_{14}N_2O_2$: 230.10; found: 244.11890.

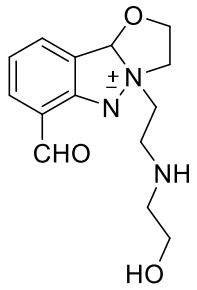
7-formyl-5-methyl-3,4,5,10b-tetrahydro-2*H*-[1,3]oxazino[3,2-*b*]indazol-5-ium-6-ide (189s)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), 3-(methylamino)propan-1-ol **188s** (21.4 mg, 0.24 mmol) in toluene (2 ml) for 24 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 9:1 + 1% triethylamine) yielded **189s** (30.0 mg, 69%) as orange thick wax. **^{1}H NMR** (300 MHz, CD_2Cl_2): 9.87 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 6.65 (t, J = 7.5 Hz, 1H), 6.23 (s, 1H), 4.20 – 4.00 (m, 3H), 3.92 – 3.81 (m, 1H), 3.47 (s, 3H), 2.17 (m, 1H), 1.92 (m, 1H). **^{13}C NMR** (75 MHz, CD_2Cl_2): 188.93 (CH), 151.65 (C), 134.47 (CH), 130.01 (CH), 121.10 (C), 117.34 (C), 116.73 (CH), 99.77 (CH), 61.43 (CH_2), 57.45 (CH_2), 51.47 (CH_3), 19.06 (CH_2). **IR** (ATR, cm-1): v = 3353, 2925, 1685,

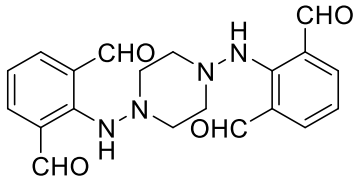
1641, 1612, 1537, 1445, 1370, 1241, 1222, 1058, 898, 794, 735, 665. **HR-MS** (EI): m/z calcd for $C_{12}H_{14}N_2O_2$: 218.10498; found: 218.10444.

6-formyl-4-(2-((2-hydroxyethyl)amino)ethyl)-2,3,4,9b-tetrahydrooxazolo[3,2-*b*]indazol-4-ium-5-ide (189t)



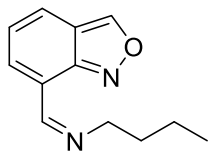
General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), *N*,*N*′-bis(2-hydroxyethyl)ethylenediamine **188t** (14.8 mg, 0.1 mmol) in toluene (2 ml) for 48 hours at 50 °C. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 9:1 + 0.5% triethylamine) yielded **189t** (20.0 mg, 72%) as orange thick wax. **^{1}H NMR** (500 MHz, MeOD): 9.93 (s, 1H), 8.89 (s, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 4.08 (dd, *J* = 13.6, 4.3 Hz, 1H), 4.00 – 3.92 (m, 4H), 3.80 (m, 1H), 3.74 – 3.66 (m, 2H), 3.33 (m, 1H), 3.31 – 3.27 (m, 2H), 3.24 (m, 1H), 3.13 (td, *J* = 12.3, 4.5 Hz, 1H). **^{13}C NMR** (126 MHz, MeOD): 193.11 (CH), 164.25 (C), 150.59 (C), 143.35 (CH), 140.54 (CH), 119.36 (C), 116.68 (CH), 112.13 (CH), 65.52 (CH_2), 61.67 (CH_2), 59.90 (CH_2), 58.35 (CH_2), 58.29 (CH_2), 50.56 (CH_2). **HR-MS** (EI): m/z calcd for $C_{14}H_{19}N_3O_3$: 277.14209; found: 218.14005.

2,2'-(piperazine-1,4-diylbis(azanediyl))diisophthalaldehyde (189u)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), piperazine **188j** (8.6 mg, 0.1 mmol) in toluene (2 ml) for 30 hours at 50 °C. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 99:1) yielded **189u** (28.0 mg, 74%) as yellow solid (dec T>200 °C). **HR-MS** (EI): m/z calcd for $C_{20}H_{20}N_4O_4$: 380.14791; found: 380.14666.

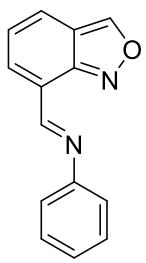
(*Z*)-1-(benzo[*c*]isoxazol-7-yl)-*N*-butylmethanimine (191a)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), butan-1-amine **190a** (17.5 mg, 0.24 mmol) in toluene (2 ml) for 2 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane + 0.5 % triethylamine) yielded **191a** (37.0 mg, 92%) as yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): 10.43 (s, 1H), 7.99 (s, 1H), 7.88 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.78 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.14 (dd, *J* = 8.3, 7.0 Hz, 1H), 4.43 (t, *J* = 7.3 Hz, 2H), 1.95 (m, 2H), 1.30 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 190.87 (CH), 145.70 (C), 131.86, (CH) 127.60 (CH), 125.40 (C), 123.64 (CH), 123.44 (C), 120.89 (CH), 53.89 (CH_2), 32.62 (CH_2), 19.88 (CH_2), 13.55 (CH_3). **IR** (ATR, cm-1): v = 3359, 3116, 2959, 2933, 2873, 2722, 1689,

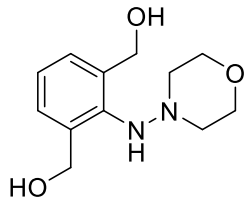
1618, 1556, 1519, 1466, 1399, 1365, 1312, 1251, 1153, 1111, 1072, 1024, 997, 890, 876, 809, 753, 681, 652. **HR-MS** (EI): m/z calcd for $C_{12}H_{14}N_2O$: 202.11006; found: 202.11096.

(*E*)-1-(benzo[*c*]isoxazol-7-yl)-*N*-phenylmethanimine (191b)



General procedure was followed using of benzo[*c*]isoxazole-7-carbaldehyde **187** (29.4 mg, 0.2 mmol), aniline **190b** (22.4 mg, 0.24 mmol) in toluene (2 ml) for 2 hours at room temperature. The purification of the crude by column chromatography (SiO_2, dichloromethane/ethanol 99:1) yielded **191b** (41.0 mg, 92%) as yellow solid (m.p. 113.2-115.0 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): 10.60 (s, 1H), 8.47 (s, 1H), 7.93 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.87 (ddd, *J* = 8.9, 5.1, 1.1 Hz, 3H), 7.49 – 7.43 (m, 2H), 7.35 (m, 1H), 7.18 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): 190.46 (CH), 147.14 (C), 140.18 (C), 131.17 (CH), 129.66 (2xCH), 128.52 (CH), 127.69 (CH), 125.71 (C), 124.27 (C), 121.89 (CH), 121.57 (CH), 121.36 (2xCH). **IR** (ATR, cm-1): v = 3119, 3082, 3062, 2858, 2774, 1873, 1823, 1684, 1622, 1595, 1555, 1521, 1499, 1453, 1412, 1380, 1347, 1326, 1305, 1257, 1223, 1057, 1033, 1021, 955, 907, 868, 812, 792, 757, 747, 703, 683. **HR-MS** (EI): m/z calcd for $C_{14}H_{10}N_2O$: 222.07876; found: 222.07805.

(2-(morpholinoamino)-1,3-phenylene)dimethanol (192)



To a stirring solution of **189a** (30.0 mg, 0.13 mmol) in ethanol (1.3 mL) $NaBH_4$ was added and the mixture was stirred at room temperature for 2 hours. Then the reaction was quenched with water and extracted with ethyl acetate. The organic layers were dried with Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography (SiO_2, dichloromethane/ethanol 98:2) to yield **192** (20.0 mg, 65%) as a beige sold (m.p. 121.8-124.0 °C). **^{1}H NMR** (301 MHz, $CDCl_3$): 7.11 (d, *J* = 7.5 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 4.53 (s, 4H), 3.62 (s, 4H), 2.83 (s, 4H). **^{13}C NMR** (76 MHz, $CDCl_3$): 144.78 (C), 132.90 (2xC), 130.43 (2xCH), 123.17 (CH), 66.82 (2xCH_2), 64.07 (2xCH_2), 56.87 (2xCH_2). **IR** (ATR, cm-1): v = 3339.07, 3270.84, 2948.24, 2922.96, 2856.51, 2813.76, 1595.68, 1453.62, 1363.86, 1265.44, 1201.75, 1165.16, 1132.71, 1107.39, 1070.38, 1018.99, 1004.54, 989.03, 962.22, 918.18, 861.62, 828.48, 771.34, 645.68, 620.74. **HR-MS** (EI): m/z calcd for $C_{12}H_{18}N_2O_3$: 238.13119; found: 238.13149.

Chapter 6. Bibliographic references

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