Università degli Studi di Urbino Carlo Bo

Department of Pure and Applied Sciences

Ph.D. in Research Methods in Science and Technology – Curriculum: Chemistry

Cycle XXXV

ACCESS TO *N*-BASED HETEROCYCLES *VIA* SUSTAINABLE APPROACHES

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CHAPTER 1

General Introduction

1.1 *N*-heterocycles in green chemistry

1.1.1 Overview

An analysis of all U.S. FDA approved small-molecule pharmaceuticals revealed that the majority of them (59%) comprises at least one nitrogen-containing heterocycle within their structures.[1] Both aromatic and non-aromatic nitrogen-based heterocycles are often recurring in approved drugs. Among them, piperidine and piperazine represent the most frequent saturated scaffolds, while the pyridine and the thiazole ring are the most common aromatic *N*-heterocycles. Given the high percentage of azaheterocycles in the U.S. FDA drugs database, it is not surprising that lots of efforts in organic chemistry are directed towards the development of new synthetic methods, aiming to access this extremely broad class of compounds.

Novel and innovative procedures for the synthesis of *N*-heterocycles are published in chemistry journals on a daily basis, highlighting the great interest cultivated in this field by research groups all over the world. The constant need for new methods goes at the same pace with the rapid discovery of interesting pharmacological profiles of newly investigated heterocycles. Thus, the research for versatile, general, scalable and efficient synthetic procedures is fundamental in academia as well as in industry.

In these years, however, everyone is able to recognize that scientific, technological and commercial advances come with concerns related to environmental issues at a global level. While it is true that the progress brings welfare and deep knowledge of our surroundings, on the other hand it is equally true that neglecting its impact on nature poses the risk for an irreversible deterioration of the planet's health status (and, consequently, of our own health). Thus, in industry and academia, it is of absolute importance to take these considerations into account when developing new protocols or technologies, in order to avoid a potential boomerang effect.

With these observations in mind, it is clear that chemistry, a discipline that deals with the transformation of substances and with hazardous procedures, has a pivotal role in the advancement of sustainable approaches. Traditional routes involve the use of pollutant and toxic compounds (especially solvents, e.g. chlorinated ones which still are widely employed), as well as energy-intensive techniques such as heating at high temperatures. The great improvement in the field of catalysis, that has been witnessed during the past decades, brought enormous advantages in terms of processes sustainability, since catalysts allow to lower the activation energy for a reaction. However, many catalysts are based on noble and rare metals such as palladium, rhodium, ruthenium and gold. Intensive mining of natural sources is required to collect even small amounts of these metals, and this results in a significant environmental impact.

In 1998, Paul Anastas and John Warner introduced the 12 principles of green chemistry (figure **1**),[2] which still today constitute the foundations for the research of new ecologically friendly procedures.

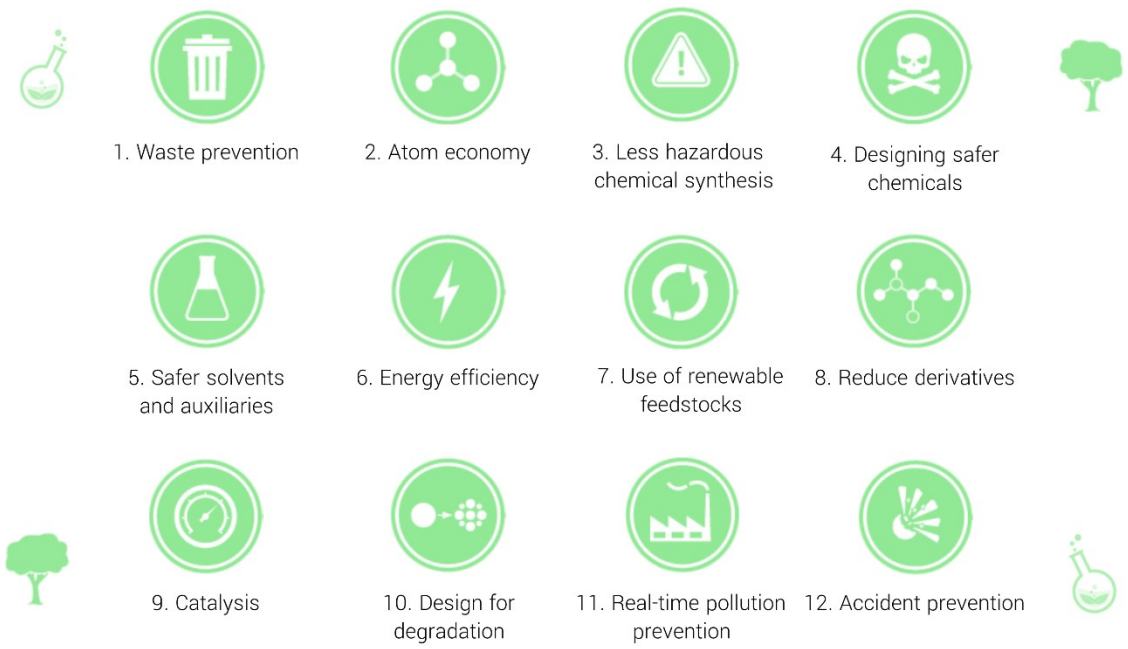


Figure 1. The 12 principles of green chemistry

Since the chemistry of *N*-heterocyclic compounds is of great interest, this field has also been deeply influenced by the concepts of green chemistry. As a result, a large number of sustainable methods for the synthesis of nitrogen compounds can be found in the literature today. To this end, a plethora of different approaches can be pursued. For the purpose of this PhD thesis, only a small selection of them will be introduced.

1.1.2 Non-noble metals in the synthesis of N-heterocycles

The use of non-noble transition metals (TMs) as catalysts for chemical transformations is highly attractive for several reasons. First row TMs (copper, iron, zinc, nickel, manganese, …) are considerably less expensive when compared to other widely employed transition metals, such as palladium, rhodium, ruthenium or iridium. Furthermore, being common in Earth's crust, their extraction is much less invasive and impactful and this translates in a benefit from the environmental point of view. Moreover, they usually are less pollutant and less toxic, also because they have important biological roles and are naturally occurring in water and in the environment. Because of these reasons, novel methods based on the use of abundant metals rather than noble ones are of extremely high value.

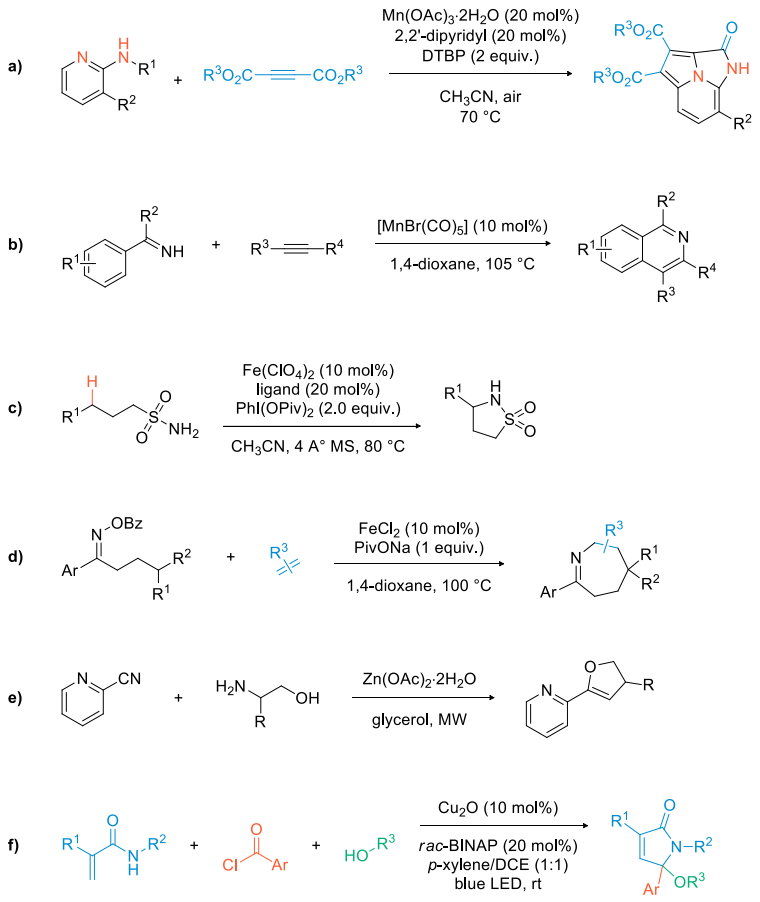
The interest towards the employment of such TMs based-catalysts in the synthesis of *N*-heterocycles has been rising in the past years. Yu and colleagues reported a method for the preparation of azacycl[3,2,2]azines *via* a Mn(III)-catalyzed three-component cascade of C–H/N–H functionalizations, using 2-aminopyridines and 2 equivalents of dialkyl butyndioates (scheme **1a**).[3] Another nice example regarding the use of manganese in the construction of azaheterocycles was reported by He. In their work, the authors employed [$MnBr(CO)_5$] as the catalyst for a [4 + 2] dehydrogenative cyclization between imines and alkynes (scheme **1b**).[4]

Iron, being the second most abundant metal on Earth, is highly attractive as a catalyst and a large number of

methods that make use of its salts and complexes for the synthesis of *N*-heterocycles have been disclosed in recent years. For instance, sultams have been prepared by Liu's group starting from linear sulfonamides. These substrates, under $Fe(ClO_4)_2$ catalysis in the presence of an appropriate ligand and of $PhI(OPiv)_2$ as the oxidant, undergo intramolecular amidation (scheme **1c**).[5] Many intermolecular methods that involve an iron catalyst have also been reported. Ye et al. showed that oxime can undergo [5 + 2] annulation when treated with alkenes in the presence of $FeCl_2$, affording azepine products (scheme **1d**).[6]

Zinc acetate was used as catalyst by Dos Santos's group for the synthesis of 2-pyridil-2-oxazolines from 2-cyanopyridines (scheme **1e**).[7] Apart from the use of a Zn catalyst, other green aspects of this method are represented by the use of glycerol as the solvent and by the microwave irradiation as the heating source.

In a photochemical setup, copper (I) oxide was employed for the three-component synthesis of α,β-unsaturated-γ-lactams by Sarkar and colleagues (scheme **1f**).[8]



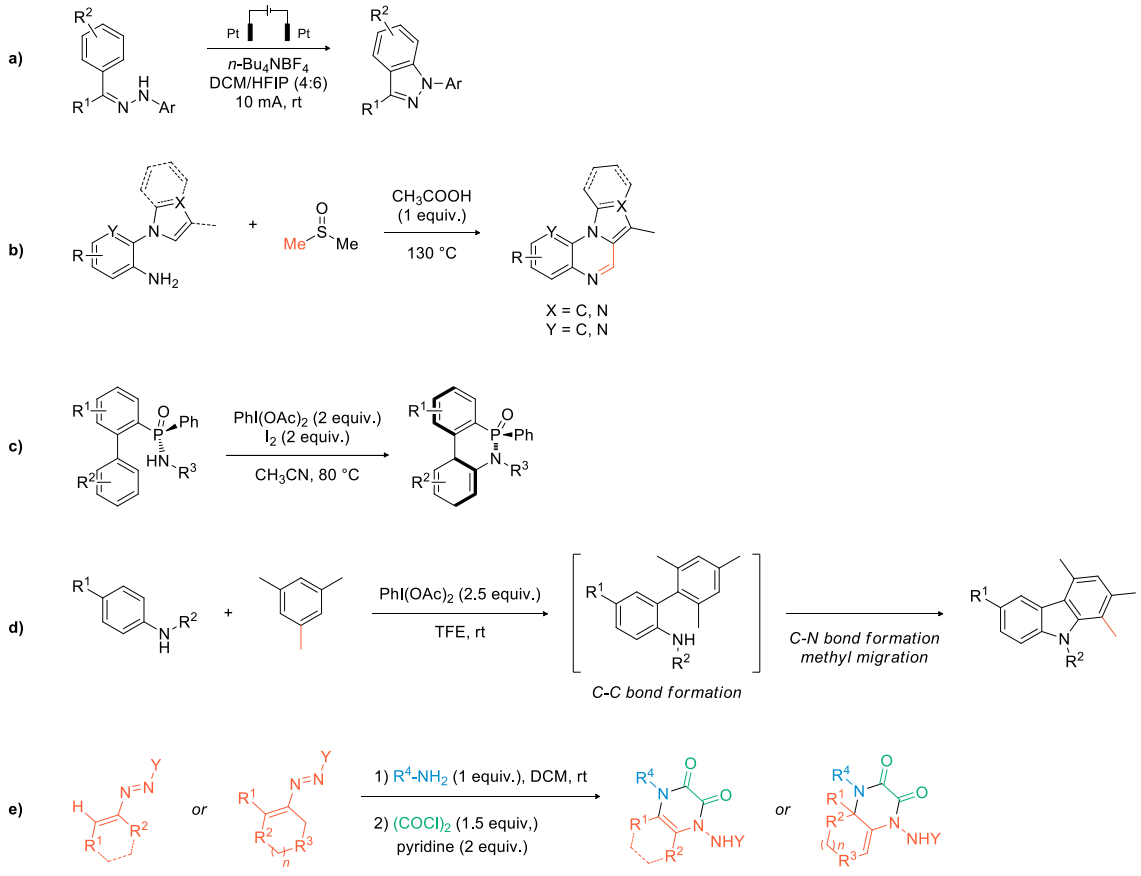
Scheme 1. First-row TMs catalysis for the synthesis of *N*-heterocycles

1.1.3 Metal-free synthesis of N-heterocycles

A large number of methods for the synthesis of nitrogen-containing heterocycles do not rely on the use of catalysts. This represents a clear advantage in terms of costs, environmental impact and waste reduction. Electrochemistry is a powerful tool for this aim, and was exploited for the synthesis of indazoles by Wan and colleagues (scheme **2a**).[9] In another work, Ma's group developed a protocol for the simple preparation of

quinoxalines, using DMSO as a one carbon source with the addition of an equimolar amount of acetic acid (scheme **2b**).[10] A very useful class of reagents, broadly exploited for the synthesis of a plethora of nitrogen-containing heterocycles, is represented by hypervalent iodine reagents (HIRs). To mention just two examples among countless works, Ma et al. reported the use of $PhI(OAc)_2$ (PIDA) for the cyclization of phosphinamides to atropoisomeric N–P tricyclic compounds (scheme **2c**),[11] while Maiti and Mal achieved the synthesis of substituted carbazoles in an intermolecular fashion (scheme **2d**) using the same reagent.[12]

1,2-diaza-1,3-butadienes (azoalkenes) are very useful building blocks for the synthesis of azaheterocycles. Their versatility is highlighted by the great number of works published, during the last decades, by the group in which this PhD course was carried out.[13] A very recent example is represented by the three-component approach for the preparation of pyrazine-(2,3)-diones, which employs azoalkenes, primary amines and oxalyl chloride (scheme **2e**).[14]



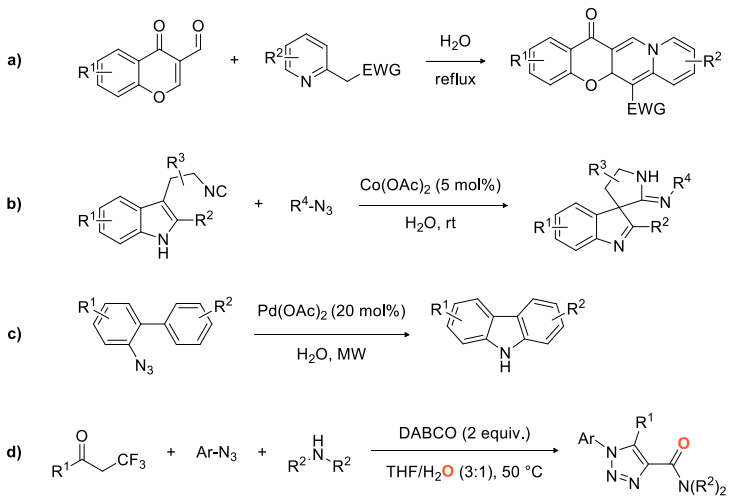
Scheme 2. Metal-free approaches to the synthesis of *N*-heterocycles

1.1.4 Water as solvent for the synthesis of N-heterocycles

One of the most challenging goals in green chemistry is the development of reactions that run in water as the sole solvent. This is particularly intriguing, since water is one of the cleanest substances that chemists can find on their benches, and it is the solvent of choice in nature. In addition to this, water is extremely cheap, totally safe and readily available.

Traditionally, the use of water has long been overlooked, mainly because it is not able to dissolve most organic compounds. However, as first pointed out by Professor Sharpless,[15] reactions can happen not only when reagents are solubilized in the aqueous medium, but also "on water", that is, the reaction mixture is heterogeneous. Not only compounds can easily react in water despite being undissolved, but the presence of heterogeneous mixtures is often beneficial for the reactions outcome, thanks to the so-called "on water effect", which arises from the interactions at the solid-liquid interface.[16,17] Therefore, chemists have no longer excuses for not investigating their reactions in aqueous media, even when chemical incompatibilities between water, reagents, functional groups and/or products seem to make this impossible. For example, in fact, Capriati's group managed to use organolithium and Grignard reagents,[18] as well as organozinc compounds[19] in "on water" reactions.

The synthesis of *N*-heterocycles using water as the sole solvent has seen great advances in recent years. As an example, Chen and colleagues developed a protocol for the synthesis of quinolizines by simply reacting chromone-3-carboxaldehydes with ethyl 2-(pyridine-2-yl)acetate derivatives in refluxing water, with no need for catalysts or additives (scheme **3a**).[20] Spiroindolenines have been synthesized by Jiang and coworkers, by treating 3-(2-isocyanoethyl)indoles with $Co(OAc)_2$ as the catalyst and water as the solvent (scheme **3b**).[21] Another intramolecular example is given by the work of Lu's group. The authors used palladium acetate as the catalyst for the intramolecular C–H amination of 2-azidobiphenyls, which are transformed into a variety of carbazoles, including several natural products (scheme **3c**).[22] Moreover, there are also examples in which water plays the double role of cosolvent and reactant. For instance, Gao and colleagues synthesized 1,2,3-triazoles in water following a three-component approach. Here, the products are functionalized with a carbonyl moiety, whose oxygen atom derives from water (scheme **3d**).[23]



Scheme 3. Examples of *N*-heterocycles synthesized in water

1.2 Purpose of this thesis

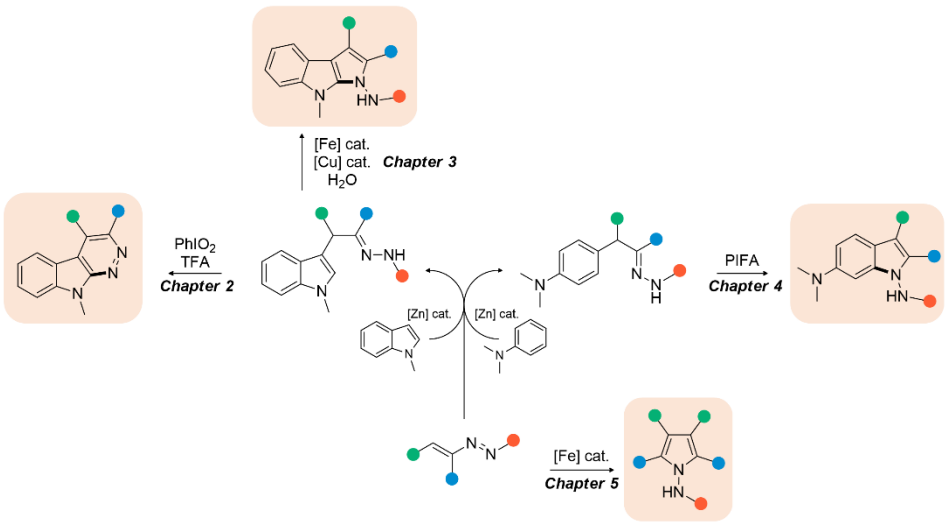
With all the aforementioned concepts in mind, this PhD work was conducted with the aim of developing novel sustainable methods for the synthesis of nitrogen heterocycles. As regards chapters **2**, **3** and **4**, the synthesis of all substrates was based on the chemistry of azoalkenes, that has always been the main research area of this group. Azoalkenes were instead directly used for the work described in chapter **5**.

In chapter **2**, the synthesis of azacarbolines *via* an oxidative cyclization of α-indolyl-hydrazones is described. This transformation occurs through an intramolecular C–H amination promoted by iodylbenzene ($PhIO_2$), a hypervalent iodine (V) reagent that, similarly to other reagents in which the iodine center is pentavalent, very rarely can be seen in the literature as a promoter of cyclization or C–H amination reactions. Besides the novelty in this sense, the main advantage lies in the fact that iodylbenzene is a green, safe, easily synthesizable and non-toxic alternative to the much more traditional transition metals.

While chapter **2** reports a six-membered ring annulation of α-indolyl-hydrazones, the work described in chapter **3** concerns a complementary five-membered cyclization carried out on the same starting materials, affording pyrrolo[2,3-*b*]indoles. Here, the green features of the process are immediately recognized in the use of water as the sole solvent for this transformation, as well as in the employment of a combination of two catalysts based on copper and iron, which are among the most abundant metal on this planet.

Chapter **4** contains data from a work that, at the time this thesis was written, was not completed yet but close to the submission to a journal. Herein, α-aryl-hydrazones bearing a *para*-*N*,*N*-dialkyl group undergo cyclization in the presence of bis(trifluoroacetoxy)iodobenzene (PIFA, an hypervalent iodine (III) reagent), to furnish interesting 1-aminoindoles as products. The metal-free and sustainable access to such an important scaffold is the feature of this chapter.

Finally, the practical and easy synthesis of 1-aminopyrroles from azoalkenes is described in chapter 5. In this work, azoalkenes react with themselves *via* a formal [3 + 2] cyclodimerization, affording symmetrical and fully substituted pyrrolic products. The main advantage of this procedure is represented by the use of iron (III) chloride, an extremely cheap and common compound, as the catalyst.



1.3 Indole: a privileged scaffold

Among heterocyclic compounds, those bearing an indole ring (figure **2**) are probably the most recurring in nature. Plants and trees,[24] as well as marine organisms,[25] fungi[26] and bacteria[27] represent rich sources from which indole-based alkaloids can be isolated.

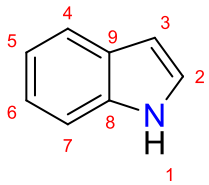


Figure 2. Indole structure

Due to the extremely wide structural diversification of indole alkaloids, these compounds exhibit a broad spectrum of biological properties, including (but not limited to) anti-inflammatory, antiviral, antibacterial, antidepressant, anticancer, antihypertensive and antidiabetic activities (figure **3**).[28]

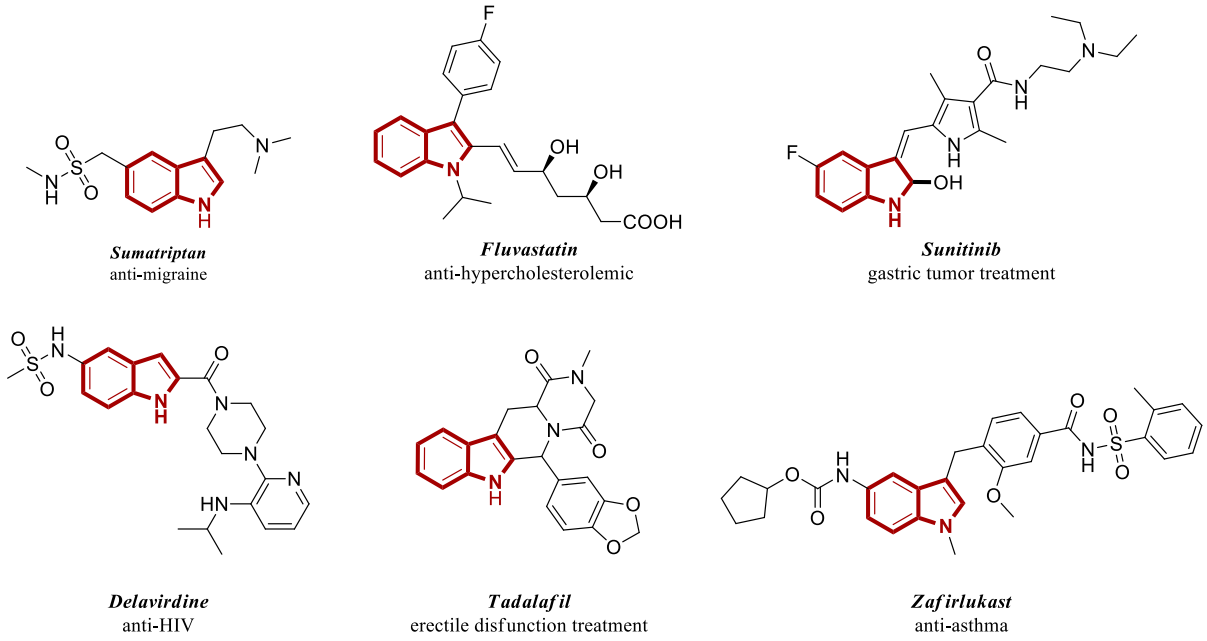


Figure 3. Examples of bioactive indoles

Because of this reason, for more than a century chemists have been fascinated by indole synthesis. Countless efforts have been made to conceive efficient and versatile methods for the preparation of highly functionalized indoles. Since their potential biological activity, new indole system-bearing substances might be evaluated as leads in pharmaceutical development at the industrial level. Thus, it is of great importance to investigate important features of novel procedures, e.g. scalability, easiness of the purification step and overall efficiency of the process (atom economy of reactions, financial costs, etc.).

An important subclass of indole compounds is represented by polycyclic indoles. Polycyclic indoles are substances that include at least one additional ring aside from the benzopyrrole (indole) system. The added ring(s) can be either aromatic or non-aromatic hetero- or carbocycles; they can be fused to the indole ring in

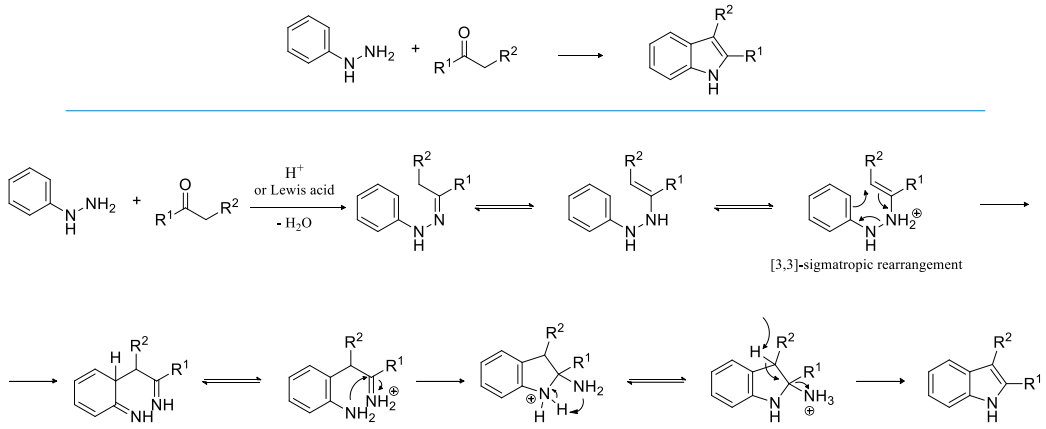
any position, or they can form spiro compounds. The following subchapters cover a selection of both traditional and modern reactions that have been developed in the field of indoles and polycyclic indoles synthesis.

1.3.1 Traditional methods for the indole synthesis

Fischer indole synthesis

In 1883, after his studies on phenylhydrazine, Emil Fischer discovered the first efficient method for the synthesis of indoles.[29,30] Although indole had been known since 1866 thanks to Adolf Baeyer's discovery,[31] very few organic chemists showed interest in indole, mainly because of the lack of known procedures for its production in acceptable yields. Owing to Fischer's work, indole quickly began to be among the most studied compounds.

Fischer indole synthesis (scheme **4**) is the reaction between phenylhydrazines and aldehydes or ketones, in the presence of a Brønsted or Lewis acid, and requires high temperatures (up to 200 °C).

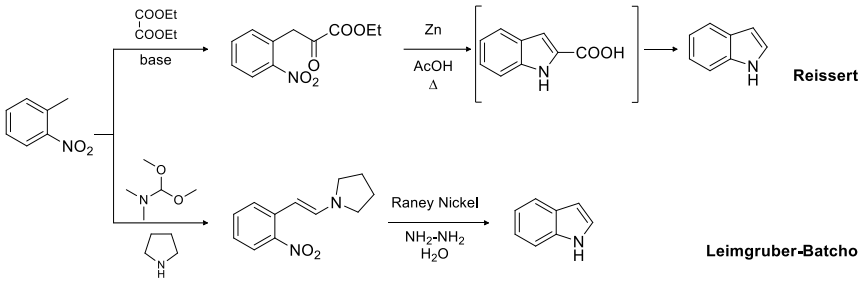


Scheme 4. Fischer indole synthesis with mechanism

This is a highly efficient procedure, since it affords indoles in high yields, and the scope is considerably broad. Interestingly, products are often obtained with significant C-2/C-3 regioselectivity when unsymmetrical carbonyl compounds are employed, depending on the pH of the reaction medium and on the steric properties of the hydrazine intermediate.

Reissert and Leimgruber-Batcho indole synthesis

Two classical methods for the synthesis of indoles starting from 2-nitrotoluenes are represented by Reissert reaction[32] and Leimgruber-Batcho reaction (scheme **5**),[33] disclosed in 1897 and 1973, respectively.

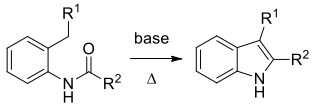


Scheme 5. Reissert and Leimgruber-Batcho synthesis

These represent valuable alternatives to Fischer indolization, and the main advantage consists in milder conditions needed. In fact, no intense heating needs to be applied to the reaction mixture.

Madelung indole synthesis

An extensively explored reaction is the Madelung synthesis of indoles, published in 1912.[34] It is carried out on *ortho*-alkylamides, which react with strong bases (usually alkoxy salts) at high temperatures (scheme **6**).

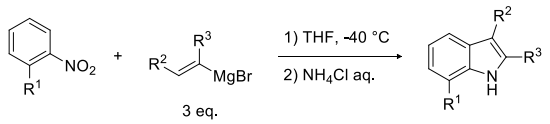


Scheme 6. Madelung synthesis

This procedure represents one of the few traditional indole syntheses in which a base is used rather than an acid, thus allowing the presence of unprotected acid-labile moieties. Furthermore, indoles that are not substituted on the carbocycle and/or on the C-3 can be produced. On the other hand, a major drawback is the need for drastic temperatures, often within the 250–350 °C range. However, later modifications have been made in the following decades, and milder variants are known. An interesting and modern application of Madelung reaction is the indolization step of (–)-penitrem D total synthesis, reported by Smith and co-workers.[35]

Bartoli indole synthesis

The synthesis of indoles starting from nitroarenes and vinyl Grignard reagents was disclosed by Giuseppe Bartoli in 1989 (scheme **7**).[36]

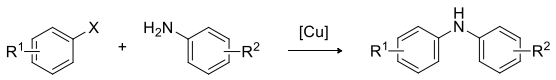


Scheme 7. Bartoli indole synthesis

The main advantage of this reaction is the possibility to synthesize highly functionalized indoles in very short times, with multiple substituents on both the five and the six membered ring. In addition to this, the procedure is particularly efficient at the industrial level, and the starting materials are readily available. However, Bartoli indole synthesis also suffers from several drawbacks: first, the nitroarene always needs to be substituted at the position *ortho* to the -NO_2 group. Secondly, the use of Grignard reagents rules out electrophilic and acidic functions (although it is noteworthy the fact that ketones are not attacked by R–MgBr in these conditions). During the following years, Bartoli and coworkers further developed this reaction to a broader extent.[37]

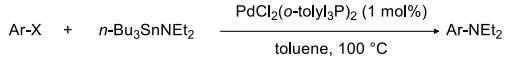
1.3.2 Metal-catalyzed synthesis of indoles

The use of metal catalysts for the C–N bond formation can be traced back to the first years of 1900, owing to the seminal work of Ullmann (1903)[38] and Goldberg (1906),[39] who developed complementary methods for the coupling of aryl amines to aryl halides by copper catalysis. The reaction has been further developed during the following years, and the general approach is known as Ullmann-Goldberg reaction. This protocol involves the presence of a base and catalytic amounts of copper salts (scheme **8**).



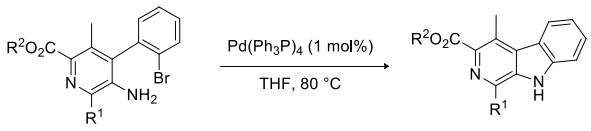
Scheme 8. Ullmann-Golberg reaction

In 1983, following their interest on organotin compounds, Migita and coworkers published the first palladium-catalyzed C–N bond construction on aromatic substrates.[40] In this work, a Pd complex in 1 mol% loading allows to couple *N*,*N*-diethylamino-tributyltin to aryl bromides (scheme **9**).



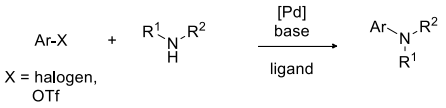
Scheme 9. Migita cross-coupling

The following year, the first Pd-catalyzed intramolecular amination of aryl bromides was reported by Boger, who accomplished the construction of the β-carboline system, which comprises an indole portion fused to a pyridine ring (scheme **10**).[41]



Scheme 10. Boger Pd-catalyzed cyclization

A highly versatile and general method has been independently disclosed in 1995 by Buchwald[42] and Hartwig.[43] The Buchwald-Hartwig reaction is the palladium catalyzed coupling of amines with aryl halides or triflates, in the presence of a base and of a ligand, needed for the activation of the catalyst (scheme **11**).



Scheme 11. Buchwald-Hartwig amination

The reaction has been further developed by a great number of research groups. In particular, investigations have been mainly focused on the development of newer class of phosphine ligands.[44] The most important features of this protocol are the scope, which is much more extended (especially in the presence of newer ligands) with respect to previous Pd-catalyzed methods, and the fact that no unstable and hazardous organotin reagents need to be utilized.

The above-mentioned works paved the way for extensive research on the chemistry of TM-based catalysis, and countless methods for the synthesis of the indole ring can be found in the literature. This field is still very active and fruitful, and the following schemes show a selection of just a small part of modern TM-catalyzed reactions capable of promoting the formation of indole systems, including polycyclic fused ones.

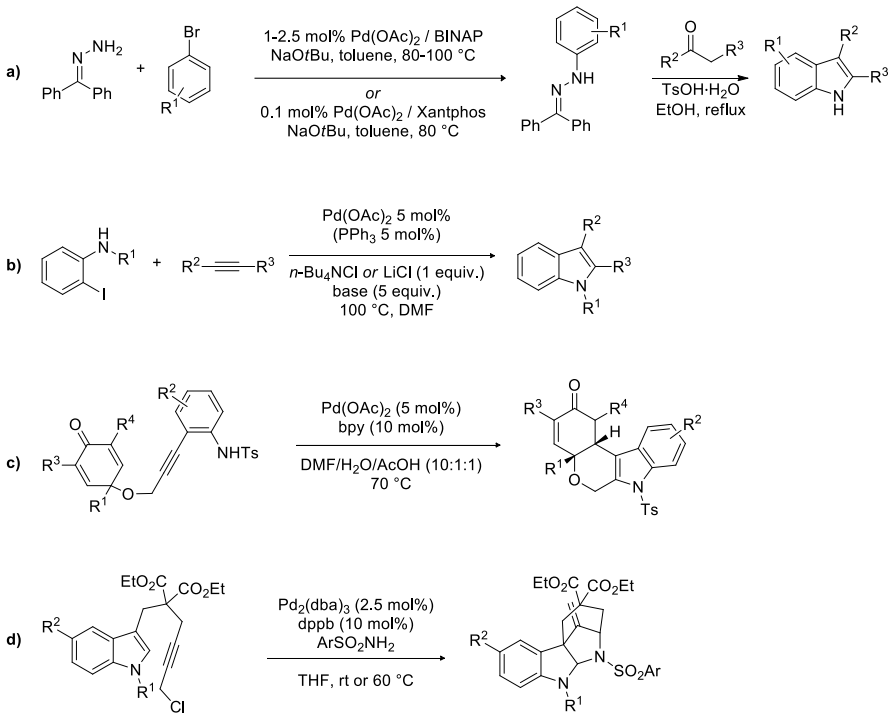
Palladium catalysis

Initial efforts consisted in TMs-promoted variants of the Fischer indole synthesis, i.e., *via* the formation of aryl hydrazone intermediates. Such methodologies overcome the unavailability of a variety of substituted aryl hydrazones to be employed in the traditional conditions. Additionally, lower reaction temperatures are usually required. As an example, Buchwald published a palladium-catalyzed *in situ* formation of *N*-aryl-hydrazones. Refluxing the mixture in ethanol in the presence of *p*-toluenesulfonic acid affords indoles with a Fischer cyclization mechanism (scheme **12a**).[45]

Internal alkynes undergo heteroannulation when they react with *o*-iodoanilines in the presence of palladium acetate, a base and a chloride (LiCl or *n*-Bu_4NCl). Some substates also required the use of triphenyl phosphine as ligand (scheme **12b**).[46] This reaction is known as Larock heteroannulation, or Larock indole synthesis. 2,3-disubstituted indoles can be prepared with this method, in a highly regioselectivity which is determined during the carbopalladated intermediate formation, depending on the electronic nature of the alkyne.[47]

Tetrahydropyrano[3,4-*b*]indoles were prepared in an enantioselective manner by Chen and colleagues. The authors used $Pd(OAc)_2$ and a chiral bipyridine ligand to accomplish a tandem intramolecular aminopalladation/1,4-addition sequence on aniline-tethered alkynyl cyclohexadienones (scheme **12c**).[48]

As an example of Pd-promoted construction of rings fused to the indole system, Ohno's group developed a cascade cyclisation that affords interesting tetracyclic spiroindoles in mild conditions.[49] In this work, indoles functionalized at C-3 with a chain bearing a propargyl chloride are treated with bis(dibenzylideneacetone)palladium ($Pd(dba)_2$), a diphenylphosphine ligand, cesium carbonate and an aryl sulfonamide (scheme **12d**).



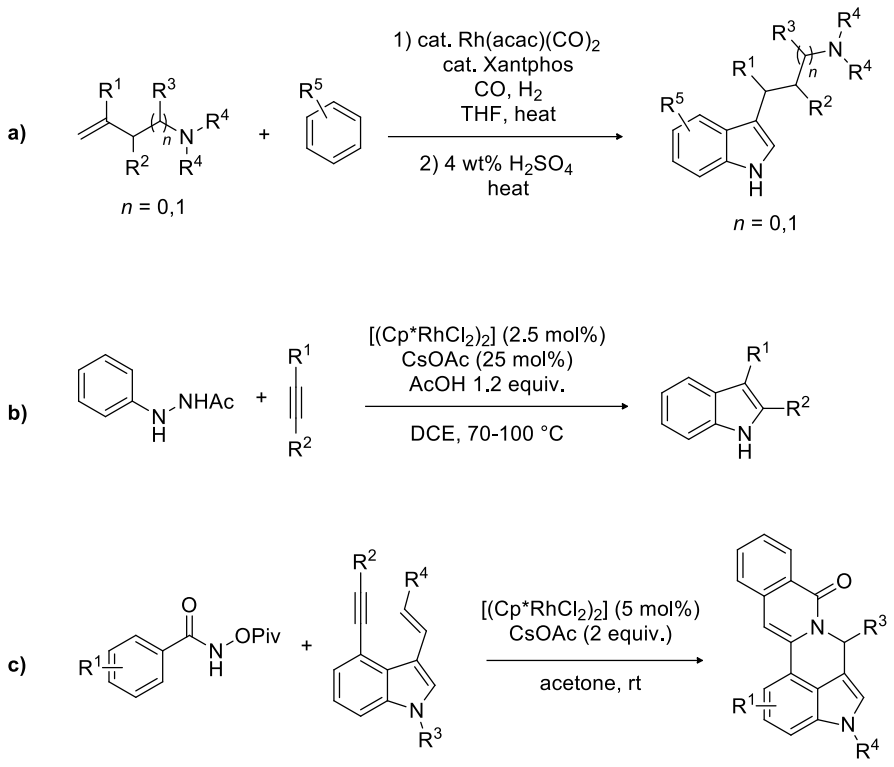
Scheme 12. Palladium catalysis in indole derivatives synthesis

Rhodium catalysis

A variety of procedures rely on the use of arylhydrazines and on a Fischer cyclization step. For instance, an elegant work published by Eilbracht and Schmidt reports a tandem hydroformylation/Fischer indolyzation catalyzed by $Rh(acac)(CO)_2$, that yields linear and branched (homo)tryptamines (scheme **13a**).[50] Despite long reaction times (1–3 days), highly diversified products (including migraine drug candidates) are afforded in excellent yields and high purity.

Glorius's group disclosed an intermolecular redox-neutral annulation between acetyl arylhydrazines and alkynes, in the presence of $[RhCp^*Cl_2]_2$ and CsOAc and acetic acid as additives (scheme **13b**).[51] The method permits the synthesis of 2,3-aryl/alkyl disubstituted indoles, with the possibility to achieve regioselectivity when certain unsymmetrical alkynes are used.

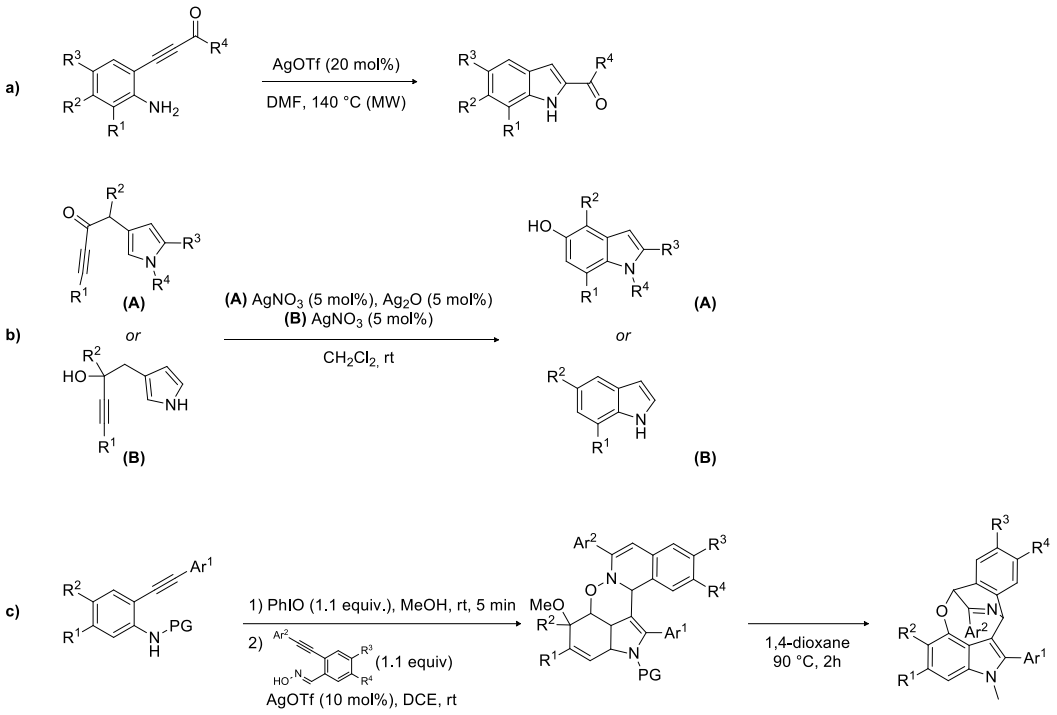
To further demonstrate the potential of rhodium (III) in the indole chemistry, Reddy and co-authors developed a protocol for the construction of a tricyclic isoquinolinone skeleton fused to the indole C-3,4 (scheme **13c**).[52]



Scheme 13. Rhodium catalysis in indole derivatives synthesis

Silver catalysis

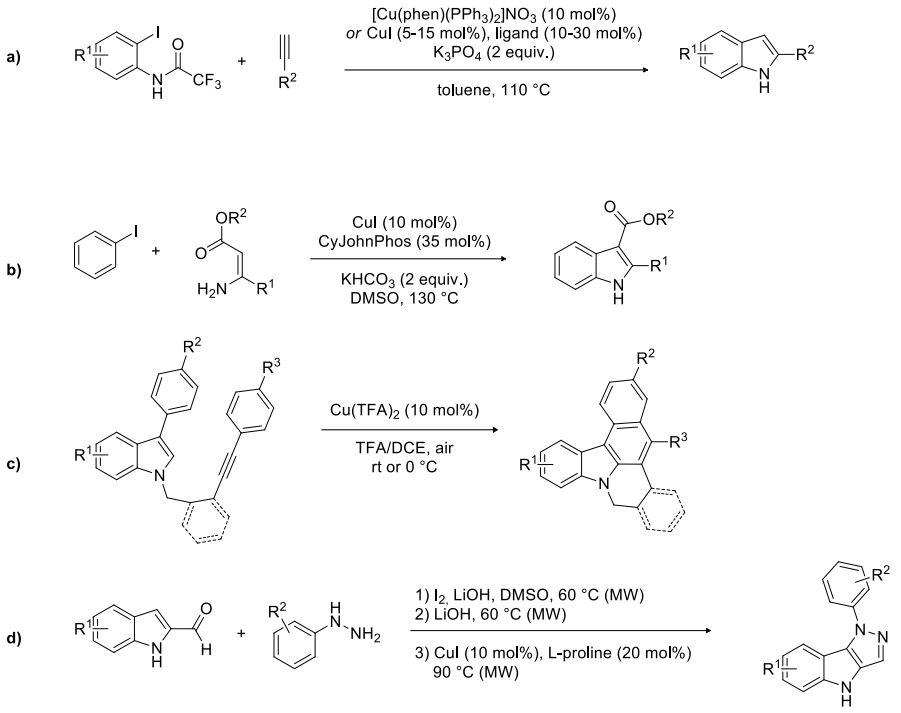
Many authors demonstrated that also silver catalysts can be versatile tools in the construction of indole products. Rode and coworkers described a method that makes use of AgOTf to prepare 2-acyl indoles *via* an anti-Michael hydroamination of (2-aminophenyl)-ynones in very short times (15-20 minutes) under microwave heating (scheme **14a**).[53] An interesting example is the procedure published by Clarke and colleagues: while the vast majority of methods focus on the use of benzene precursors, here the starting materials are pyrroles bearing ynol or ynone functionalizations, which under Ag(I) catalysis bring to the construction of the six-membered ring of the indole (scheme **14b**).[54] Structurally complex polycyclic fused indoles can be obtained with Ag catalysts. For example, an article published by Han reports a reaction mediated by PhIO (iodosobenzene) and Ag (I) with 2-alkynylanilines and 2-alkynylbenzaldoximes (scheme **14c**).[55] This reaction proceeds *via* a cascade of an oxidative dearomatization of the anilines followed by a [3 + 3] cycloaddition. Furthermore, the products can undergo a thermal rearrangement that leads to aromatization with formation of oxocino[4,3,2-*cd*]indoles.



Scheme 14. Silver catalysis in indole derivatives synthesis

Copper catalysis

Since copper is among the most abundant metal on the Earth, its employment in catalysis is of particular interest. A method developed by Cacchi and coworkers involves the use of terminal alkynes for the synthesis of 3-unsubstituted 2-(hetero)aryl indoles, starting from *o*-iodotrifluoroacetanilide and with copper iodide or copper complexes (scheme **15a**).[56] Copper iodide is also the catalyst of choice in the synthesis of 2-aryl indoles bearing an ester substituent on the C-3 position, published by Li.[57] The Cu salt has a double role: at first, it allows an Ullmann-type C–N coupling between iodobenzene/4-iodotoluene, then a copper-catalyzed cross-dehydrogenative coupling takes place, affording the final product. (scheme **15b**) A recent copper-catalyzed [4 + 2] annulation of 3-arylindoles, *N*-substituted with chains bearing an alkyne moiety, leads to a series of penta- or hexacyclic derivatives (scheme **15c**).[58] An easy access to pyrazolo[4,3-*b*]indoles has been reported by Liu's group (scheme **15d**).[59] In their work, the authors accomplished the formation of an unprecedented indole-based scaffold, starting from indole-2-carbaldehydes and alkyl- or arylhydrazines. The method consists of a sequence of three steps that can take place in one pot: activation of the indole by a C-3 iodination, formation of the hydrazone on the aldehyde moiety and the final, CuI-catalyzed, intramolecular coupling.

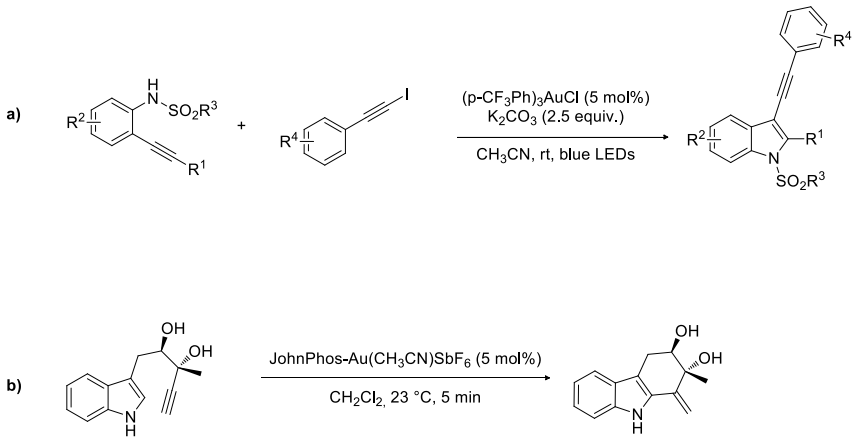


Scheme 15. Copper catalysis in indole derivatives synthesis

Gold catalysis

Au catalysts also are broadly exploited in the field of indole chemistry. A nice example has been reported by Zhao very recently. In this work, (p-$CF_3Ph)_3PAuCl$ catalyzes the cross-coupling between iodoalkynes and 2-alkynyl anilines under photochemical conditions (scheme **16a**).[60]

Gold was also used in the final step of the total synthesis of the alkaloid sorazolon B, by Nair and coworkers, highlighting the synthetic potential of Au catalysis in the preparation of complex molecules (scheme **16b**).[61]



Scheme 16. Gold catalysis in indole derivatives synthesis

Other transition metals

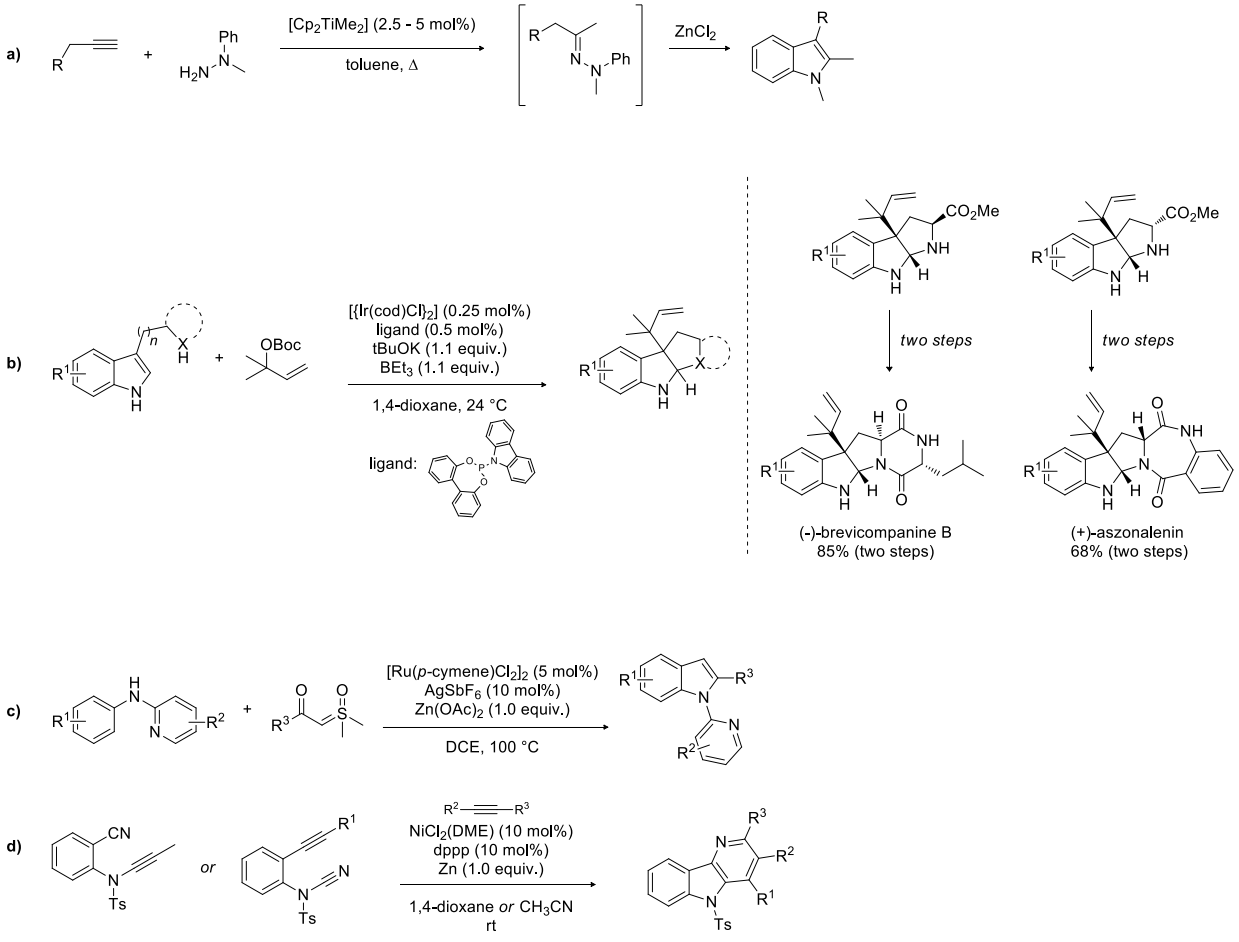
Beller's group developed a titanium-catalyzed synthesis of indoles, including a tryptamine analogue, that makes use of alkynes and *N*-methyl-*N*-phenylhydrazine (scheme **17a**).[62] Here, the key step is the Markovnikov hydroamination of the alkyne, that occurs with an unprecedented regioselectivity. The subsequent one-pot

addition of excess $ZnCl_2$ allows the indolization step.

An iridium (I) catalyst was employed by Carreira for the prenylation of 3-substituted indoles. Here, the catalyst allows the intramolecular cyclization of (*S)*-tryptophan methyl ester, yielding a pyrroloindoline. Furthermore, some products could be further transformed into two natural bioactive alkaloids in just few steps, (+)-aszonalenin (a NK_1 receptor inhibitor, for the treatment of nausea during anticancer therapy) and (–)-brevicompanine B (a plant growth regulator) (scheme **17b**).[63]

Many examples regarding the use of ruthenium as a catalyst in the synthesis of indoles can be found in the literature. For an example, *N*-aryl-2-aminopyridines can react with sulfoxonium ylides, affording products bearing a pyridine substituent on the indole nitrogen (scheme **17c**).[64]

A procedure for the synthesis of both δ- and α-carbolines was developed by Wang (scheme **17d**).[65] Here, the catalyst employed is $NiCl_2$(DME) ($NiCl_2$ ethylene glycol dimethyl ether complex) that, in the presence of a phosphine ligand and Zn, leads to the [2 + 2 + 2] cycloaddition of ynamide-nitriles or alkynyl cyanamides with alkynes.

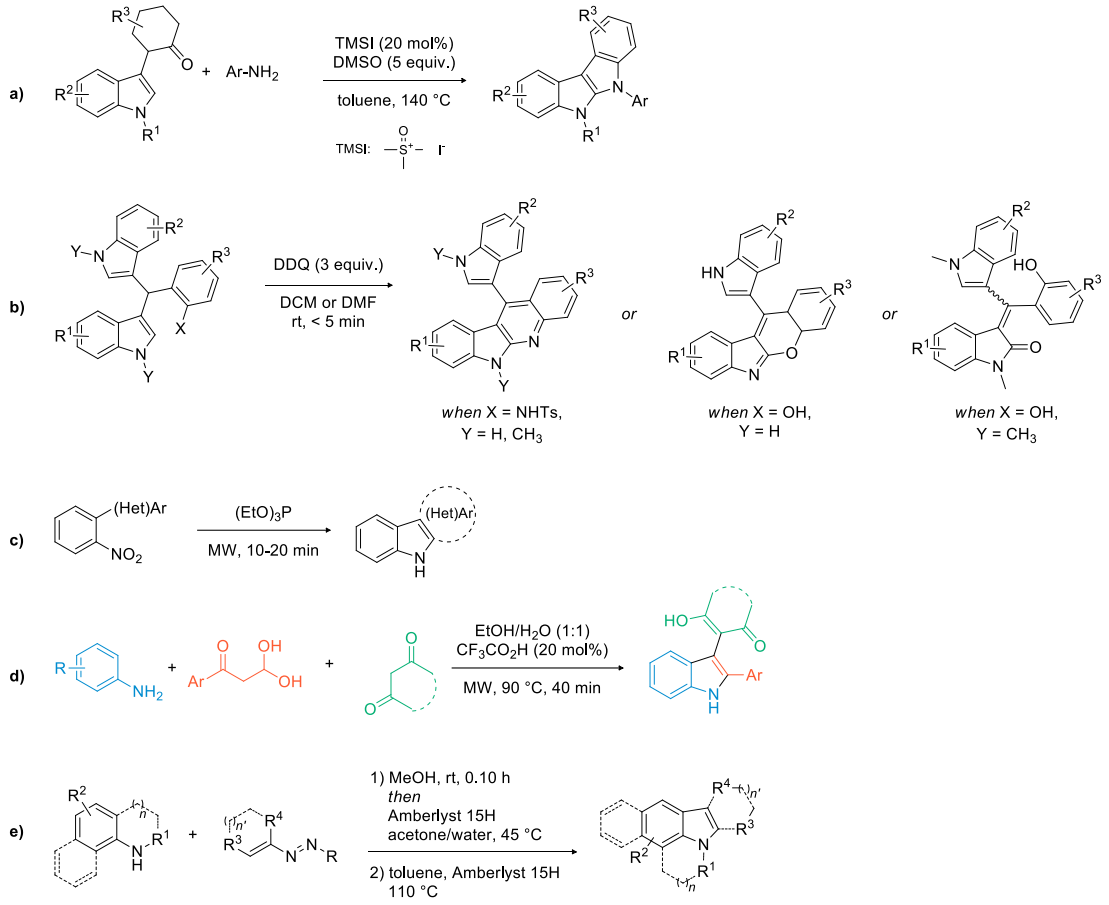


Scheme 17. Nickel catalysis in the synthesis of indole derivatives

1.3.3 Metal-free approaches to the synthesis of indoles

Modern methodologies for the synthesis of indoles, as well as for the construction of additional rings on the indole core do not exclusively rely on transition metals. On the contrary, plenty of metal-free approaches are available, and this research area is being intensively investigated. A recent contribution from Deng's group revealed that unsymmetrical indolo[2,3-*b*]indoles can be synthesized by reacting anilines with indoles bearing cyclohexanone substituents at the C-3, in the presence of a catalytic trimethylsulfoxonium iodide (TMSI)/DMSO system (scheme **18a**) for the *in situ* I_2 generation.[66] Easy access to indolo[2,3-*b*]quinolines, chromeno[2,3-*b*]indoles and 3-alkenyl-oxindoles is permitted by the reaction of certain diindolylmethanes by an oxidative annulation promoted by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (scheme **18b**).[67] Microwave heating represent a useful tool in synthetic chemistry. The main advantage of this approach lies in the fact that, usually, microwave-assisted reactions are complete within few minutes or even seconds. An example is the preparation of a library of carbazoles and fused poly(hetero)cyclic indoles starting from nitrobiaryls which, when irradiated with microwaves in the presence of $(EtO)_3P$, undergo a Cadogan reductive cyclization (scheme **18c**).[68] Another example is represented by an article published Lin and colleagues, which describes the formation of highly functionalized 2-aryl indoles *via* a three-component domino sequence (scheme **18d**).[69]

Recently, a metal-free approach was also pursued by the group in which this PhD work was carried out. In this work, variously substituted anilines undergo reaction with 1,2-diaza-1,3-dienes in the presence of Amberlyst 15H (an acidic resin) to afford a variety of indoles (scheme **18e**).[70]



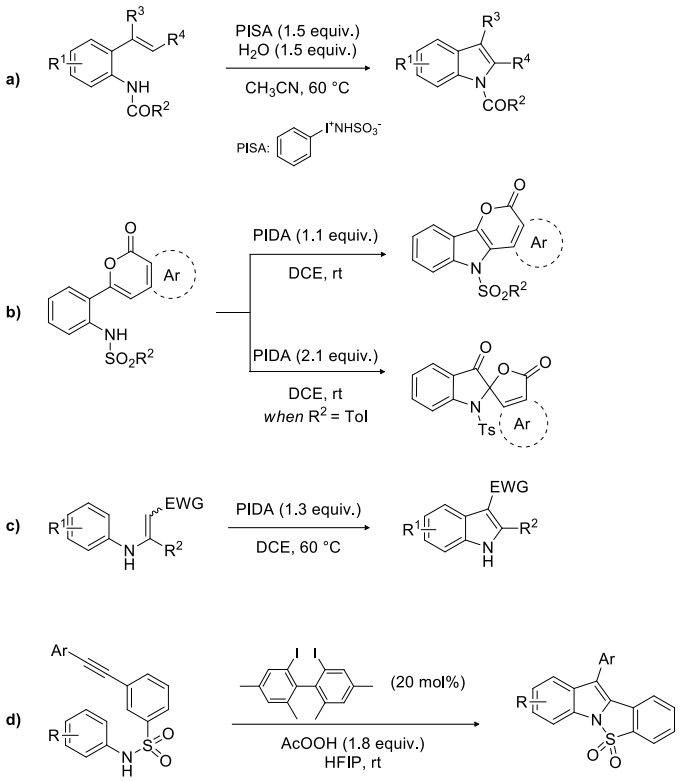
Scheme 18. Metal-free approaches

In the past years, the use of hypervalent iodine reagents (HIRs) for the synthesis of indole-based compounds has been extensively reported. The particularity of these reagents lies in the electronic properties of the iodine center, which resemble those of transition metals. Thus, it has been widely demonstrated how HIRs can be powerful tools in the construction of C–X bonds. Very recently Zhang's group, for example, described the use of (phenyliodonio)sulfamate (PISA) as a novel water-soluble reagent for the formation of *N*-acyl indoles (scheme **19a**).[71] In another work, diarylalkynes underwent aminocarboxylation and oxoaminocarboxylation promoted by (diacetoxyiodo)benzene (PIDA) (scheme **19b**).[72] The particularity of this method relies in its divergent nature. In fact, depending on the amount of iodine (III) used, products can be polycyclic 3-oxindoles or spiro derivatives of 3-oxindoles.

As described by Yu, readily available *N*-aryl enamines undergo cyclization through the PIDA-promoted formation of a new carbon-carbon bond, affording indoles in mild conditions (scheme **19c**).[73]

Interestingly, it is also possible to employ HIRs as organocatalysts. For instance, Muñiz disclosed a protocol that involves the *in situ* formation of an iodine (III) species by reacting a 2,2'-diiodobiphenyl catalyst with peracetic acid. The formed HIR promotes the cyclization of sulfonamides bearing an alkyne portion, forming indole products in which a 2-aryl substituent is tethered to the indole nitrogen through a sulfonyl group (scheme

19d).[74] A large number of other methodologies based on hypervalent iodine organocatalysis have been developed during the past years.[75]

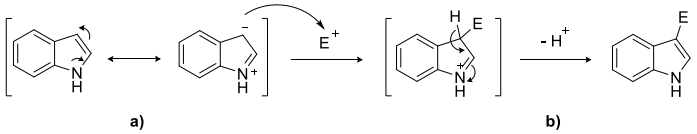


Scheme 19. HIRs-promoted synthesis of indoles

1.3.4 Reactivity of the indole ring

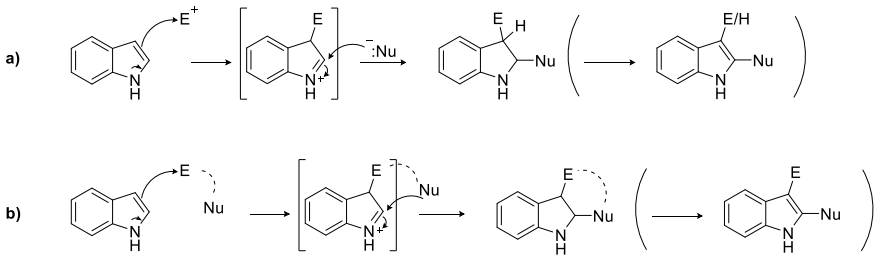
General reactivity

The indole ring is an electron-rich system, owing to the nitrogen electron pair participating to the aromaticity of this heterocycle (scheme **20a**). Thus, the most common reactivity of indole is towards electrophiles, which are preferably attacked by the C-3 (scheme **20b**).



Scheme 20

Another reactive position is the C-2, especially when the 3-position is substituted. In this case, it is possible to consider electrophiles as activators of the 2-position, as depicted in scheme **21a**. The transition state after the electrophilic substitution can react with a nucleophile, which will lead to the neutralization of the positive charge on the nitrogen atom. After that, either the electrophile or a proton may be eliminated to furnish an aromatic system. When the nucleophile is tethered to the indole, intramolecular nucleophilic attack can occur, leading to the formation of a new cycle fused to the C-2/C-3 bond (scheme **21b**). Furthermore, umpolung strategies can be adopted for the nucleophilic attack on the C-3 or for the electrophilic attack on the C-2, depending on the nature of substituents installed on the indole ring.[76]



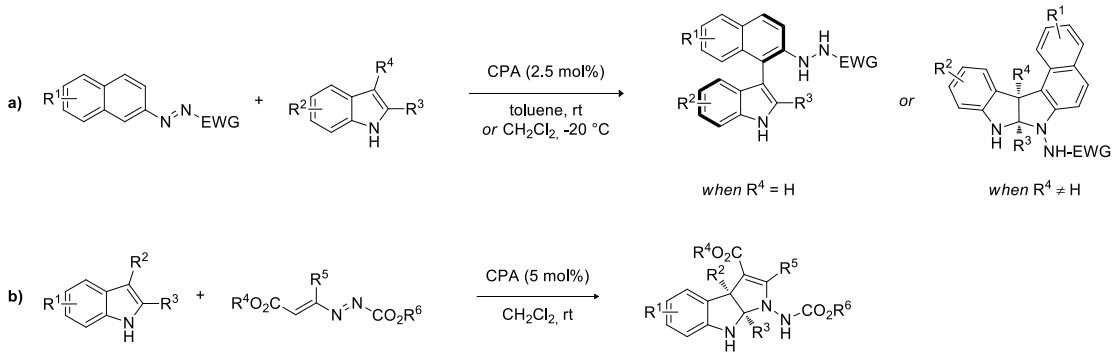
Scheme 21

The C-2 functionalization can also be achieved, especially in metal-catalyzed reactions, when directing groups are installed on the C-3 position or as *N*-substituents.[77] As regards the latter type of substitution, electrophiles can be easily linked to the nitrogen, usually *via* an S_N2 mechanism when bases are used for the N-H deprotonation.

Although the five-membered ring of the indole system is the one that is most commonly involved in reactions, a plethora of methods have been developed, particularly in the last decade, in order to functionalize the benzene ring rather than the pyrrole one.[78]

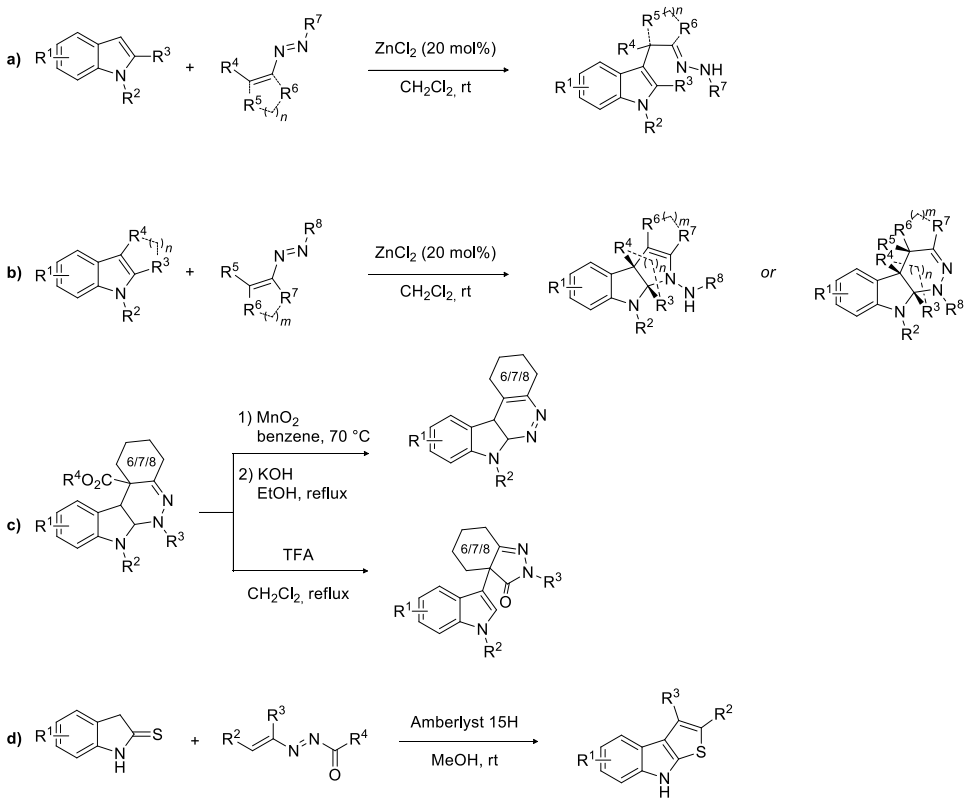
Reactivity towards conjugated diaza compounds

An interesting field of exploration consists in the reactivity of indole towards azo-compounds in which the N–N double bond is conjugated with a C–C double bond. In particular, azanapthalenes and 1,2-diaza-1,3-dienes have been broadly examined as reaction partners for indole-based compounds. For instance, Tan's group published a paper regarding the addition of 2-substituted indoles to 2-diazanapthalenyl substrates in an atroposelective way, by using a chiral phosphoric acid (CPA) as the catalyst (scheme **22a**). In the same work, when indoles are also substituted on the C-3, pyrroloindolines are formed.[79] The use of a chiral phosphoric acid has also been reported by Lu's group, which reported the reaction of 3-substituted *N*-H indoles with azoalkenes. In this work, the nucleophilic attack of the indole by the C-3 is followed by a subsequent asymmetric dearomatizative cyclization on the C-2. Therefore, this is a formal [3 + 2] cycloaddition of 1,2-diaza-1,3-dienes to indole systems that leads to an enantioselective dearomatization (scheme **22b**).[80]



Scheme 22

The research area of the group in which this PhD work was conducted is focused on the chemistry of azoalkenes, and in the past years their reactivity with indoles was tested as well. In a paper published in 2019, the Michael-type addition of indoles as C-3 carbon nucleophiles (among other types of nucleophiles) to various azoalkenes was reported (scheme **23a**) and indolyl-hydrazone products were obtained.[81] Later, it was demonstrated that, by tuning the substituents on the indole and/or on the diazadiene, it is also possible to obtain [3 + 2] and [4 + 2] annulation products (scheme **23b**).[82] Moreover, these cycloadducts can be further manipulated and, as depicted in scheme **23c** a divergent strategy allows their transformation in fused indolopyridazines or in indole-tethered pyrazol-5-ones. In another recent work, 2,3-disubstituted thieno[2,3-*b*]indoles were synthesized by the acid-catalyzed reaction between azoalkenes and indoline-2-thiones (scheme **23d**).[83]



Scheme 23

The linear, open hydrazone adducts that can be prepared by the $ZnCl_2$-catalyzed reaction of indoles and azoalkenes were employed as substrates in two works conducted during this PhD course. Two classes of products, azacarbolines and pyrrolo[2,3-*b*]indoles were obtained, and the results will be discussed in chapters 2 and 3.

1.4 Pyrrole

Indole structure cannot be drawn without drawing a pyrrole ring. Pyrrole is another heterocycle of high value in numerous branches of chemistry. Chlorophylls, hemes, vitamin B_{12}, as well as a number of commercial drugs, innovative materials e natural products bring a pyrrole system within their structure.

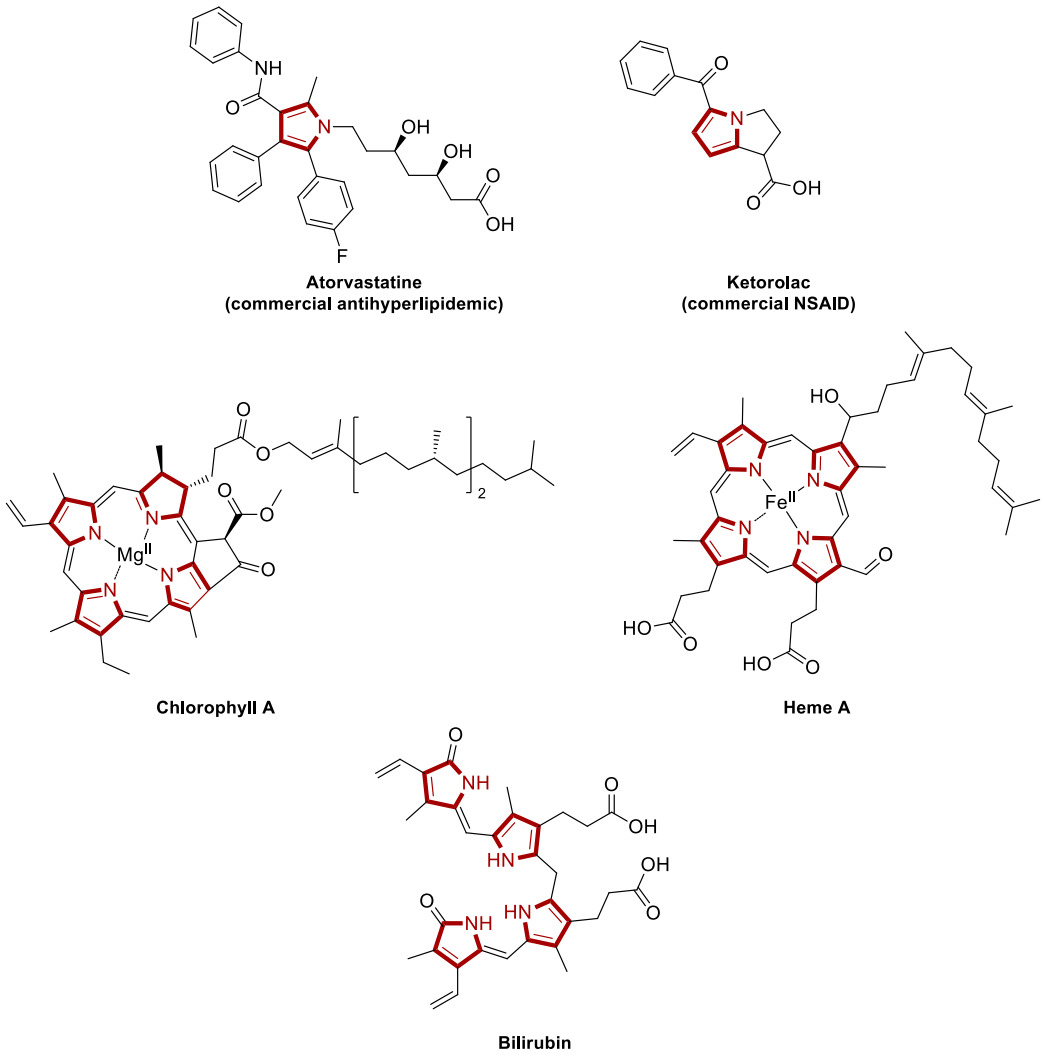
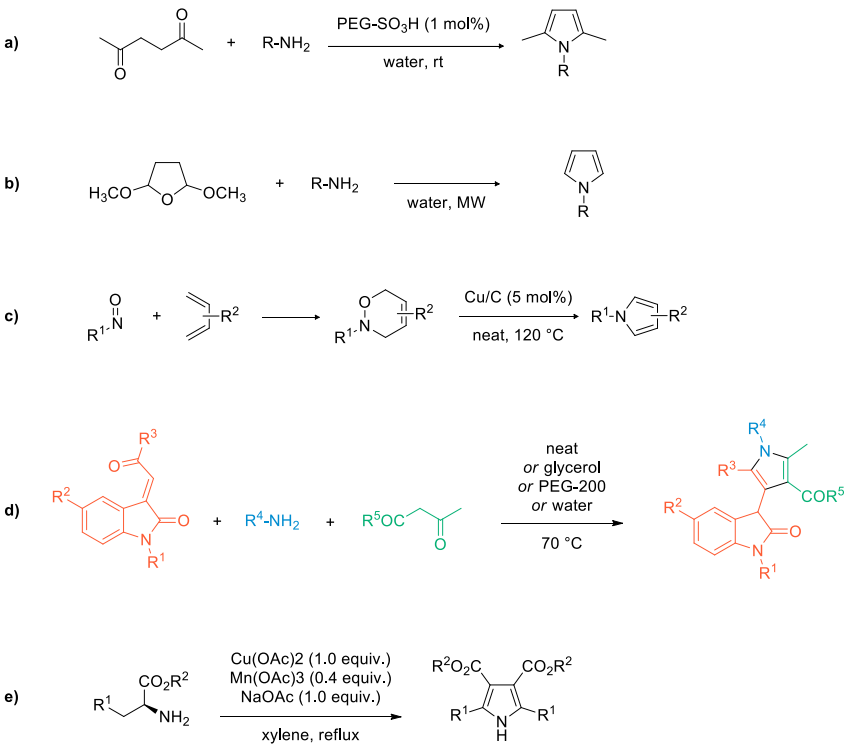


Figure 4. Some important pyrrole-containing compounds

Given its importance, the chemistry of pyrrole is extensive and its derivatives are accessible through a very large number of synthetic procedures. For the purpose of this thesis, a selection of sustainable and green methods for the preparation of pyrroles is depicted in scheme **24**. To begin with, a green version of the classical Paal-Knorr synthesis of pyrrole has been reported by Jafari and coworkers. The authors used poly(ethylene glycol)-bounded sulfonic acid (PEG-SO_3H) as the catalyst for the condensation between 2,5-hexanedione and aromatic or aliphatic amines (scheme **24a**).[84] The role of the polymer is not only to catalyze the reaction as a Brønsted acid, but it also acts as a surfactant, allowing to run the reaction in water at room temperature. Furthermore, this polymer is biodegradable and not corrosive. Another variant in water of the Paal-Knorr reaction has been developed by Welmaker's group (scheme **24b**).[85] Here, *N*-phenyl and *N*-arylsulfonyl pyrroles are obtained by treating 2,5-dimethoxytetrahydrofuran in water under microwave irradiation, and without

catalyst. Reaction times are short, and most products are purified simply by filtration.

Aside from the Paal-Knorr-type reaction, many other strategies are known. For instance, Yasukawa and colleagues reported that functionalized pyrroles can be obtained by treating 3,6-dihydro-1,2-oxazines with copper on carbon, in solvent-free conditions (scheme **24c**).[86] Interestingly, under the same conditions, the authors also successfully achieved the one-pot synthesis of several pyrroles starting from nitrosoarenes and dienes. The solvent can also be avoided, or replaced with green solvents such as glycerol, PEG-200 or water, when preparing pyrroles according to a method reported by Vivekanand et al. The authors developed a three-component reaction that involves the use of isatin derivatives, aliphatic or aromatic amines and 1,3-dicarbonyl compounds. These components react in the absence of any catalyst, and allow the construction of fully substituted pyrrole rings on indolin-2-ones scaffolds (scheme **24d**).[87] The atom economy of the process is very high, and the only waste product is water. Xie's group disclosed an interesting approach that involves the transformation of amino acid esters to highly substituted pyrroles (scheme **24e**).[88] Here, the substrates are treated with $Cu(OAc)_2$, $Mn(OAc)_3$ and NaOAc in refluxing xylene to accomplish tandem dehydrogenations, deamination, and oxidative cyclizations. This protocol was further exploited for a biomimetic synthetic access to lycogarubin C and chromopyrrolic acid.



Scheme 24. Sustainable procedures for the synthesis of pyrroles

CHAPTER 2

Synthesis of Azacarbolines via $PhIO_2$-Promoted Intramolecular Oxidative Cyclization of α-Indolylhydrazones

JOC The Journal of Organic Chemistry

Corrieri, M., Crescentini, L. De, Mantellini, F., Mari, G., Santeusanio, S., Favi, G. *J. Org. Chem.* **2021**, *86*, 17918–17929.

2.1 Introduction

The ubiquity of azaheterocycles in natural sources, fine chemicals and materials is a driving force for the development of efficient carbon-nitrogen bond formation methods. Since the pioneering work of Ullmann-Golberg,[38,39,89,90] Chan-Evans-Lam[91–94] and Buchwald-Hartwig,[42,43,95,96] transition metal (TM)-catalyzed amination reactions have been extensively explored.

The use of TMs, including palladium,[95,97] rhodium,[98,99] iridium,[100–102] ruthenium[103,104] and gold[105,106] as catalysts for the formation of new C–N bonds allows for a high degree of versatility and efficiency in heterocycles construction, especially when there is no need for a preactivated substrate (e.g., (pseudo)halides or boronic acids/esters). In recent years, the rapid progress (including in the fields of photochemistry,[107–110] flow chemistry[111–114] and electrochemistry[115–118]) has greatly contributed to the development of metal-catalyzed direct C–H amination strategies. However, despite them being powerful tools in synthetic chemistry, TMs also come with drawbacks. Aside from their high prices, reactions often require elevated temperatures and the employment of external metal-based oxidants such as silver and copper salts. In addition to this, TMs complexes are very frequently unstable to air and/or moisture, meaning that they need to be carefully handled taking precautions (such as the use of inert gas atmosphere, freshly dried solvents, gloveboxes, Schlenk techniques, specialized glassware, etc.), which add extra costs to synthetic protocols. Moreover, TMs-based catalysts usually display human toxicity, thus their use in late-stage functionalization at the pharmaceutical industry is limited.

Because of these reasons, there is a high demand for the development of efficient C–N bond formation procedures in metal-free, mild and safe conditions. Hypervalent iodine reagents (HIRs) play an important role in this context. In recent years, this class of compounds has been intensively investigated as surrogates of TMs since the electronic properties of the iodine center resembles that of a transition metal. Thus, numerous examples of HIRs-promoted C–H activation/C–N bond formation have been reported in the literature,[119–124] and a great plethora of azaheterocycles can be constructed with the aid of iodine (III) compounds. Despite this progress, a limited number of cyclization reactions involving hydrazone substrates is known. Few examples include the independent work of Tanimori[125] and Zhu,[126] who reported the HIRs-mediated cyclization of compounds bearing a vinyl or aryl hydrazone moiety (figure **1a**). Chen and colleagues also reported an intramolecular amination allowed by the use of $PhI(OAc)_2$ (PIDA) on allyl hydrazones, resulting in the formation of highly functionalized dihydropyrazole structures (figure **1b**).[127] On the other hand, the synthesis of pyridazine rings from hydrazone substrates in a metal-free fashion remains elusive.

In the past years, the research group in which this PhD work was carried on has been interested in the synthesis of polycyclic nitrogen-containing substance.[128–130] Following this path, we envisaged that HIRs could promote an oxidative intramolecular cyclization of α-indolyl-hydrazones via a $C(sp^2)$–H bond activation and a subsequent amination involving the NH portion of the substrate (figure **1c**).

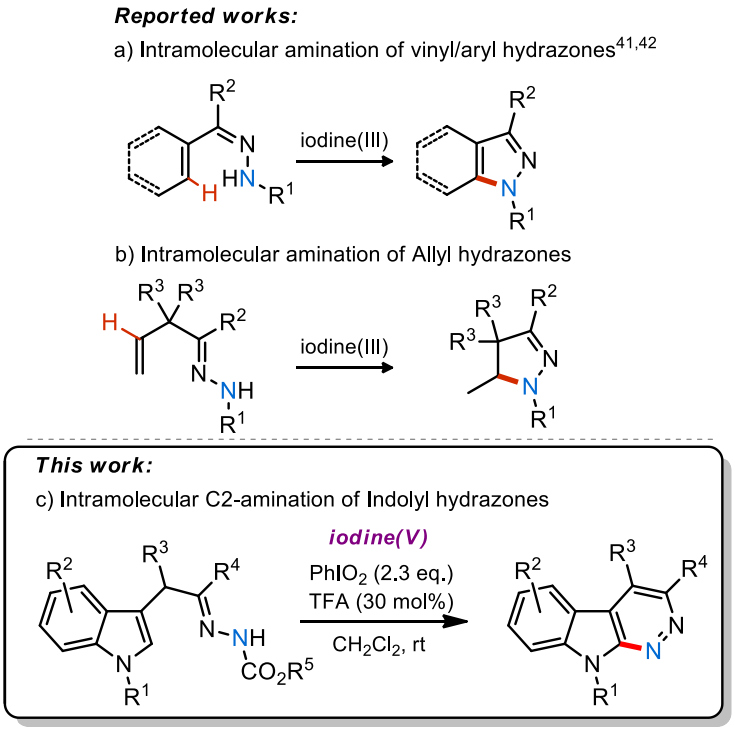


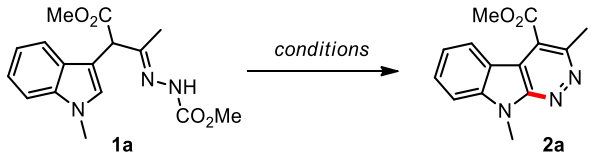
Figure 1

In this work, we report the use of $PhIO_2$ (iodylbenzene) as the source of hypervalent iodine for the construction of a functionalized pyridazine ring on the indole system. Notably, iodylbenzene belongs to the group of iodine (V) compounds, a class of HIRs that have rarely been employed in intramolecular amination reactions,[131–134] differently from the widely exploited iodine (III) compounds.

This protocol allows for the synthesis of a series of compounds comprising the indole and the pyridazine nuclei, both being of high pharmaceutical interest. These structures might be useful for the development of new biologically active molecules.

2.2 Results and discussion

Starting materials **1** were readily prepared by the $ZnCl_2$-catalyzed conjugate addition of indoles to 1,2-diaza-1,3-dienes.[52,81,135] Compound **1a** was chosen as the model substrate for our investigation, and we started by applying Reddy's conditions.[136] Using a combination of 2.3 equivalents of PIDA and 0.3 equivalents of trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature led us to the isolation of the desired product **2a** with an encouraging yield of 56% (Table **1**, entry 1). Lowering the temperature to 0 °C was detrimental for the reaction outcome, in terms of both product yield and conversion rate of the starting material (entry 2). Diphenyl phosphoric acid (DPP) was used instead of TFA, resulting in a lower yield as well (entry 3). Additives such as I_2 (entry 4) and $Cu(OTf)_2$ (entries 5, 8)[137] were added to the reaction medium, however poor yields were observed. Low product yields were also obtained when organic or inorganic bases, such as DBU and K_2CO_3, (entries 6, 7) were tested as additives. Increasing the amount of TFA, from 30 mol% to 1.0 equivalent, resulted in a shorter time needed for the complete conversion of **1a**, although the yield of **2a** decreased to 41% (entry 9).



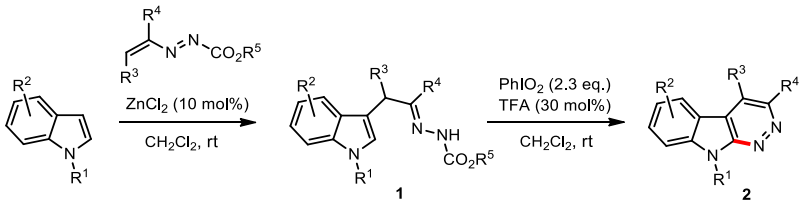
Entry	Oxidant (equiv.)	Additive (equiv.)	Solvent (2 mL)	Time (h)[a]	Yield (%)[b]
1	PIDA (2.3)	TFA (0.3)	CH_2Cl_2	0.5	56
2[c]	PIDA (2.3)	TFA (0.3)	CH_2Cl_2	4	43
3	PIDA (2.3)	DPP (0.3)	CH_2Cl_2	3	44
4	PIDA (2.3)	I_2 (1.5)	CH_2Cl_2	1	< 5
5	PIDA (2.3)	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	>24	17
6	PIDA (2.3)	DBU (1.2)	CH_2Cl_2	12	25
7	PIDA (2.3)	K_2CO_3 (1.2)	CH_2Cl_2	12	35[d]
8[e]	PIDA (2.3)	TFA (0.3)	CH_2Cl_2	0.5	51
9	PIDA (2.3)	TFA (1.0)	CH_2Cl_2	0.2	41
10	PIDA (2.3)	TFA (0.3)	$CHCl_3$	0.5	55
11	PIDA (2.3)	TFA (0.3)	CH_3OH	0.5	35
12	PIDA (2.3)	TFA (0.3)	CH_3CN	0.5	40
13	PIDA (2.3)	TFA (0.3)	THF	1	43
14	PIFA (2.3)	TFA (0.3)	CH_2Cl_2	0.3	46
15	HTIB (2.3)	TFA (0.3)	CH_2Cl_2	5	< 5
16	PhIO (2.3)	TFA (0.3)	CH_2Cl_2	3	37
17	IBX (2.3)	TFA (0.3)	CH_2Cl_2	4	79
18	DMP (2.3)	TFA (0.3)	CH_2Cl_2	12	64
19	**$PhIO_2$ (2.3)**	**TFA (0.3)**	**CH_2Cl_2**	**5**	**82**
20[f]	$PhIO_2$ (2.3)	TFA (0.3)	DCE	2.5	70
21	$PhIO_2$ (2.3)	TFA (0.3)	THF	6	68
22	$PhIO_2$ (2.3)	TFA (0.3)	CH_3CN	6	65 (16)[g]
23	$PhIO_2$ (2.3)	TFA (0.3)	HFIP	3	38
24	$PhIO_2$ (2.3)	–	AcOH	1	47
25	$PhIO_2$ (1.5)	TFA (0.3)	CH_2Cl_2	12	73 (9)[g]
26	–	TFA (0.3→1)	CH_2Cl_2	24	0[h]
27	$PhIO_2$ (2.3)	–	CH_2Cl_2	24[i]	0 (5)[g]

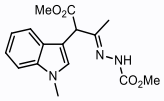
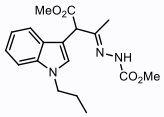
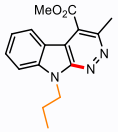
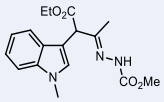
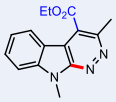
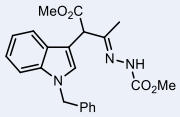
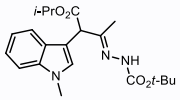
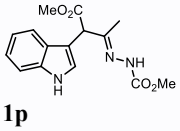
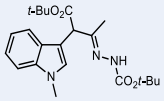
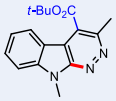
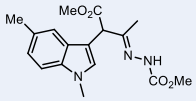
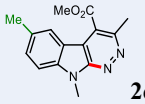
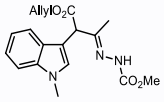
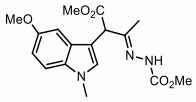
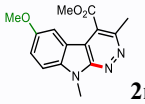
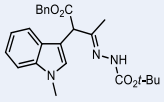
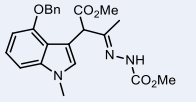
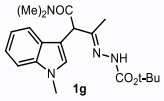
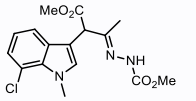
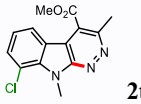
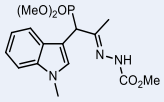
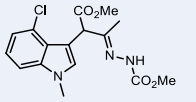
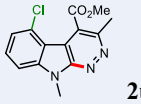
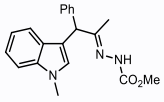
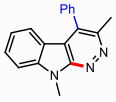
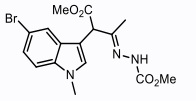
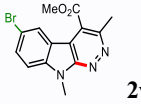
Table 1. Screening of the conditions - All reactions were performed on 0.2 mmol scale. [a] Denotes complete consumption of **1a** unless otherwise noted. [b] Isolated yields. [c] Performed at 0 °C. [d] 1-Methyl-1*H*-indole-2,3-dione was also isolated as a byproduct in 12% yield. [e] $Cu(OTf)_2$ (5 mol%) was added. [f] Performed at 50 °C. [g] Five-membered cross-coupled product **C** was also observed. [h] Denotes unreacted starting material. Abbreviations used: PIDA = phenyliodine diacetate, PIFA = phenyliodine bis(trifluoroacetate), HTIB = hydroxy(tosyloxy)iodo]benzene, IBX = *o*-iodoxybenzoic acid [1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide], DMP = Dess–Martin periodinane, DPP = diphenyl phosphoric acid, TFA = trifluoroacetic acid, AcOH = glacial acetic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE = 1,2-dicloroethane, THF = tetrahydrofuran, HFIP = hexafluoroisopropanol.

Different solvents ($CHCl_3$, CH_3OH, CH_3CN, THF) were screened, however no improvement in terms of product yields was observed (entries 10–13). Next, a screening of various hypervalent iodine sources was conducted. While trivalent iodine compounds, namely PIFA (bis(trifluoroacetoxy)iodo benzene), HTIB (Koser's reagent) and PhIO (iodosylbenzene) were less effective than PIDA (entries 14–16), switching to iodine (V) reagents such as IBX (2-iodoxybenzoic acid), DMP (Dess-Martin periodinane) and $PhIO_2$ was beneficial to the reaction outcome (entries 17–19). In particular, the combination of 2.3 equivalents of $PhIO_2$ and 30 mol% of TFA resulted in a satisfying yield of 82% for **2a** (entry 19).

Having found the most suitable reagent for this transformation, the solvent effect was re-screened confirming CH_2Cl_2 as the favored solvent (entries 20–24). Increasing the reaction temperature (entry 20) or lowering the amount of $PhIO_2$ led to no improvement (entry 25). Entries 26 and 27 show that both $PhIO_2$ and TFA are required.

The optimized conditions were applied to a series of α-indolyl-hydrazone substrates (**1a–y**), and variously functionalized azacarbolines **2a–y** were obtained in good to excellent yields. Modifications on each of the position of the azacarboline scaffold were possible, as depicted in table **2**. A variety of ester groups (**2b–f**) and phosphonate groups (**2h**) were tolerated as R^3, while an amide (**2g**) or a phenyl substituent (**2i**) showed a lower yield of the product. The insertion of a second indole moiety on this position was also well tolerated, and the bis-indole product **2j** was obtained in 67% yield. Different R^4 appendages could be installed in products **2k-m**). Longer alkyl chains as substituents of the indole nitrogen (**2n,o**), including a three carbons chain linking the nitrogen to the benzofused ring (**2y**), are tolerated for this transformation, while the use of a NH substrate results in a poor yield (**2p**). As regards the indole benzofused portion, electron-donating substituents such as Me, OMe and OBn (**2q–s**), as well as electron-withdrawing functions groups including Cl, Br, F and COOMe (**2t–x**) are all well tolerated.



Substrate	Product	Yield[a] (%)	Substrate	Product	Yield[b] (%)
 **1a**	 **2a**	82 (79)[b]	 **1n**	 **2n**	78
 **1b**	 **2b**	75	 **1o**	 **2o**	76
 **1c**	 **2c**	67	 **1p**	 **2p**	21
 **1d**	 **2d**	56	 **1q**	 **2q**	79
 **1e**	 **2e**	71	 **1r**	 **2r**	81
 **1f**	 **2f**	59	 **1s**	 **2s**	80
 **1g**	 **2g**	46	 **1t**	 **2t**	79
 **1h**	 **2h**	77	 **1u**	 **2u**	65
 **1i**	 **2i**	46	 **1v**	 **2v**	80

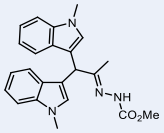
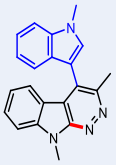
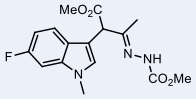
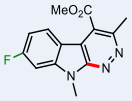
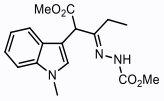
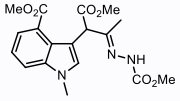
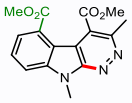
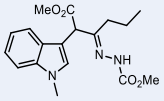
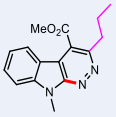
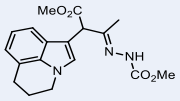
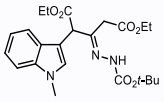
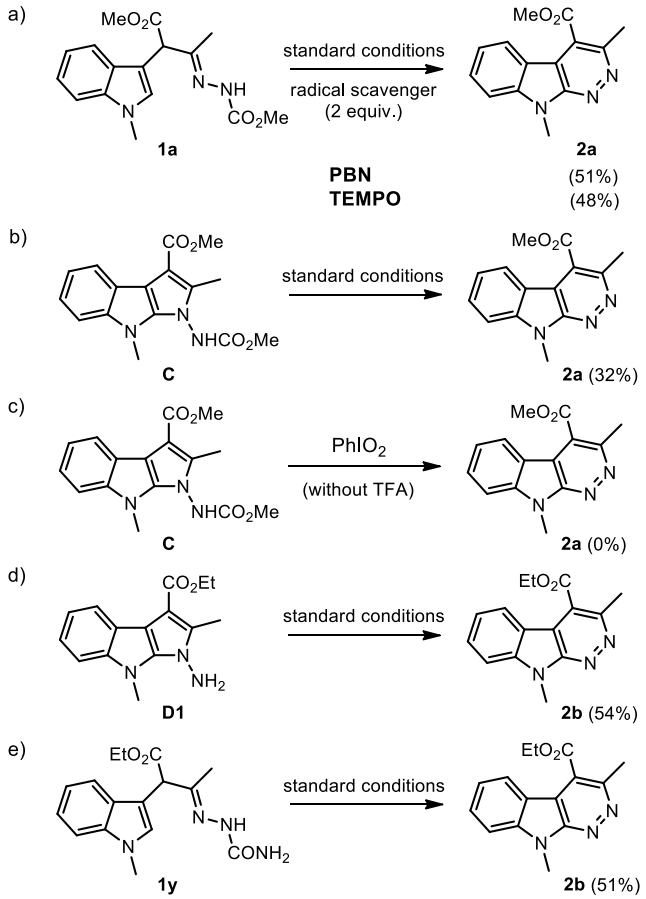
Substrate	Product	Yield[a] (%)	Substrate	Product	Yield[b] (%)
 **1j**	 **2j**	67	 **1w**	 **2w**	80
 **1k**	 **2k**	80	 **1x**[d]	 **2x**	73
 **1l**	 **2l**	76	 **1y**	 **2y**	67
 **1m**[c]	 **2m**	60			

Table 2. Substrate scope - Reactions were conducted on 0.2 mmol scale in 2.0 mL of solvent. [a] Isolated yields. [b] 3.0 mmol scale reaction (0.605 g). [c] Hydrazine tautomeric form.

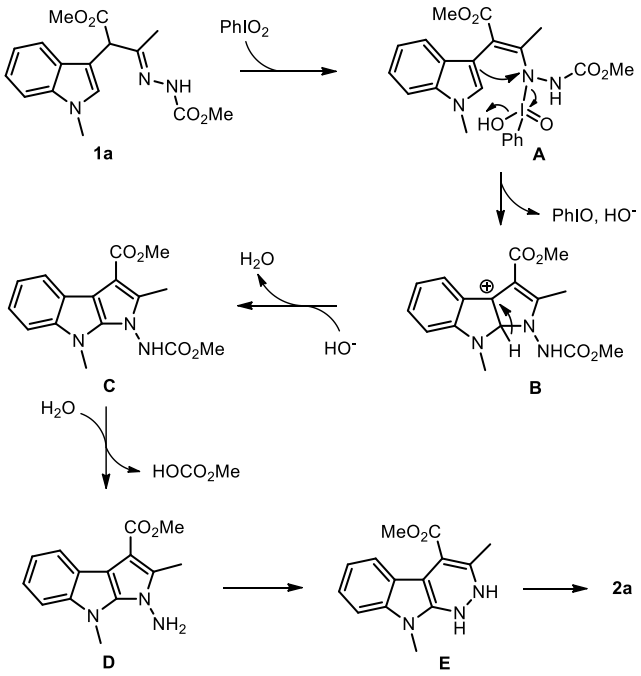
The synthesis of **2a** was successfully scaled up on a 3 mmol scale, and the product was isolated in 79% yield. Control experiments were performed to gather informations useful to define a plausible reaction mechanism. A radical pathway was ruled out by conducting the optimized reaction of **1a** with the addition of *N*-tert-butyl-α-phenylnitrone (PBN)[138] and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).[125] These radical traps did not inhibit the formation of **2a**, which was isolated in 51% and 48% yield, respectively (scheme **1a**).

In addition to this, the five-membered cyclization byproduct **C**, which was isolated in several conditions, underwent transformation to **2a** under the optimized conditions, suggesting that this might be a reaction intermediate (scheme **1b**). In fact, TLC checks showed that compound **C** initially forms during the reaction, and gradually disappears while **2a** is forming. Thus, a ring expansion step may be involved in the mechanism. It is important to note that conversion of **C** in the absence of TFA does not happen, suggesting that trifluoroacetic acid is involved, at least, in the ring expansion stage (scheme **1c**). Another possible intermediate might be compound **D1**, which was transformed to product **2b** when treated with the optimized conditions (scheme **1d**). Moreover, it is possible to use an amide *N*-protective group as the substrate (**1z**) and observe a good yield of **2b** (scheme **1e**).



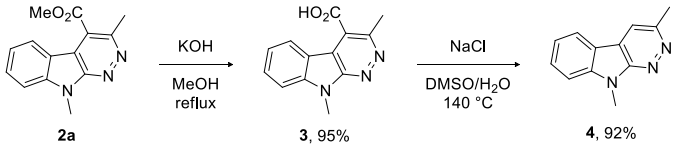
Scheme 1. Control experiments

Based on this data and on the literature findings, a plausible reaction mechanism for the $PhIO_2$-promoted oxidative amination of α-indolyl-hydrazones is depicted in scheme **2**. In the first stage, the ene-hydrazine form of **1a** reacts with iodosylbenzene, furnishing the *N*-iodo derivative intermediate **A**. Intermediate **A** bears an activated nitrogen, thanks to the highly electrophilic nature of the iodine center. At this stage, the cyclization on the indole C-2 occurs with the loss of PhIO and OH^-, forming the carbocationic intermediate **B** which gains aromaticity back after the loss of a proton, and furnishing pyrrolo[2,3-*b*]indole **C**. The hydrolysis of the carbamic residue forms intermediate **D**, which undergoes a ring expansion and an oxidative aromatization, finally yielding product **2a**.[139,140] The role of TFA is not completely understood, however control experiments (see scheme **1b–d**) suggest that it might be involved in the latter steps. Nonetheless, transformation of isolated intermediates **C** and **D** in the standard conditions furnishes product **2a** in lower yields with respect to the transformation of **1a**. This behavior may be explained by a competing mechanistic pathway, in which the cyclization step directly occurs at the other nitrogen.[141]



Scheme 2. Proposed mechanism

Compound **2a** was further transformed to highlight the broad synthetic usefulness of this protocol. The ester moiety can be rapidly hydrolyzed by treatment with KOH in refluxing methanol, giving carboxylic acid **3**.[142] Heating compound **3** at 140 °C in DMSO with NaCl as additive furnishes the decarboxylated product **4**.[143]



Scheme 3. Synthetic transformations

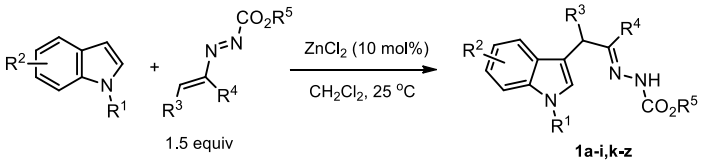
2.3 Conclusions

To conclude, we have disclosed a mild, sustainable, and metal-free procedure for the intramolecular oxidative cyclization of α-indolyl-hydrazones. This method allows to directly synthesize a variety of highly functionalized azacarbolines, by means of a C(sp^2)-N bond formation promoted by $PhIO_2$, an iodine (V) compound which, so far, had never been used in oxidative coupling reactions. With this work, we hope to spread encouragement for the further investigation of pentavalent iodine reagents in oxidative amination reactions, and to stimulate research on azacarbolines as compounds of potential interest in medicinal chemistry.

2.4 Experimental section

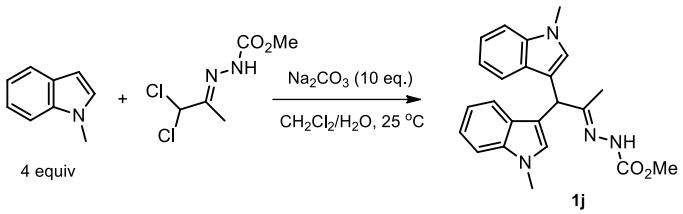
General remarks: All the commercially available reagents and solvents were used without further purification. The following compounds were synthesized according to literature procedures: HTIB,[144] PhIO,[145] $PhIO_2$,[146] IBX,[147] and DMP.[148] *CAUTION!* PhIO, $PhIO_2$, and IBX are explosive under impact or heating to >200 °C, and appropriate precautions should be taken while handling these products. However, we have not experienced any explosions while working with these compounds at room temperature. α-(Indol-3-yl)hydrazones **1a−i**,**k−z** were prepared according to our previously reported methods[81,82] with a slight modification. Bis(indolyl)methane hydrazone **1j** was prepared following literature procedure.[135] Chromatographic purification of compounds was carried out on silica gel (60−200 μm). TLC analysis was performed on preloaded (0.25 mm) glass-supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$ and 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using DMSO-d_6 or $CDCl_3$ as solvent on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA). Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, t = triplet, q = quartet, sex = sextet, sept = septet, m = multiplet, and br = broad signal. All coupling constants (*J* value) are given in Hertz [Hz]. High-resolution mass spectroscopy was performed on a Micromass Q-TOF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected.

General procedure for the preparation of α-(indol-3-yl)hydrazones 1a–i,k–z[81,82]:



To a stirred mixture of indole (1.0 mmol) and azoalkene (1.5 mmol, 1.5 equiv) in dichloromethane (4 mL), zinc dichloride (13.6 mg, 0.1 mmol, 10 mol%) was added. After the disappearance of indole (TLC check), the solvent was removed and the crude mixture was purified by column chromatography on silica gel to afford, after crystallization, the α-(indol-3-yl)hydrazones **1**.

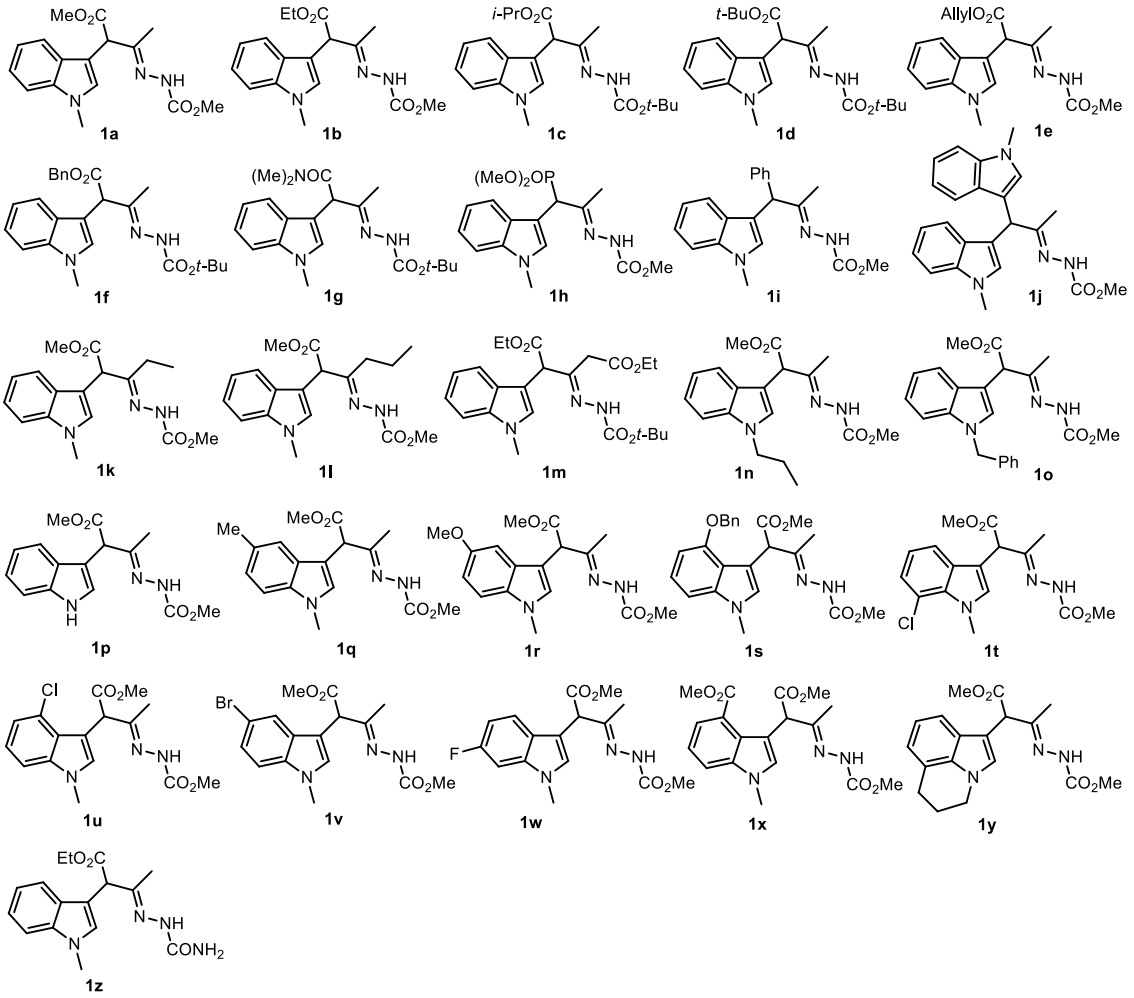
Procedure for the preparation of bis(indolyl)methane hydrazone 1j[135]:



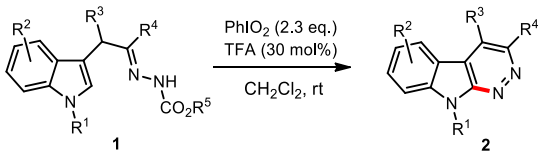
1-Methylindole (0.75 mL, 6 mmol, 4 equiv) was added to a previously stirred solution of Na_2CO_3 (1.59 g, 15 mmol, 10 equiv) in water (5 mL). The dichloroacetone hydrazone (298.5 mg, 1.5 mmol) in dichloromethane (5 mL) was added and the reaction mixture was stirred at room temperature. Upon completion of the reaction (1 h, TLC check), the mixture was diluted with water (10 mL), extracted with dichloromethane (3 x 20 mL), and the collected organic phases were dried over anhydrous Na_2SO_4. After filtration, the reaction was concentrated in vacuo, and the obtained crude was purified by flash chromatography to afford the bis(indolyl)methane hydrazone **1j**.

The NMR spectra in DMSO-d_6 showed that compounds **1** exist predominantly in the hydrazone structure; however, signals related to the hydrazine tautomeric form can be also observed.

List of substrates 1a–z prepared according to the general procedures.



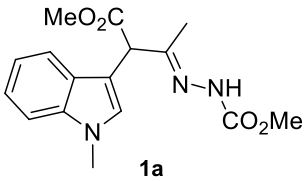
General procedure for the synthesis of azacarbolines 2 via $PhIO_2$-mediated intramolecular oxidative cyclization of α-indolylhydrazones 1:



To a stirred mixture of α-indolylhydrazone **1** (0.2 mmol) in dichloromethane (2 mL), $PhIO_2$ (108.6 mg, 0.46 mmol, 2.3 equiv) and TFA (5 μL, 0.06 mmol, 30 mol%) were added. After that, the solution was stirred overnight at room temperature. The crude product was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate) to give the corresponding product **2** (21–82% yields).

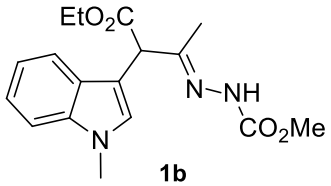
Hydrolysis of 2a: To a solution of **2a** (127.6 mg, 0.5 mmol) in MeOH (5 mL), KOH (280 mg, 5 mmol, 10 equiv) was added. The mixture was refluxed (heating mantle) until the disappearance of **2a** (1.5 h, TLC check). The reaction mixture was cooled to r.t. and the solvent evaporated in vacuo. The residue was dissolved in water (2 mL) and acidified to pH 2 via the addition of 4 N aq HCl under stirring at 0 °C. The precipitate was filtered off, then washed with diethyl ether and dried to afford the compound **3** (95% yield) as a yellow solid.

Decarboxylation of 3: To a solution of compound **3** (48.2 mg, 0.2 mmol) in DMSO/water (10:1, 2 mL), NaCl (81.8 mg, 1.4 mmol, 7 equiv) was added. The solution was stirred at 140 °C (oil-bath) until the disappearance of the starting material (24 h, TLC check). After cooling to room temperature, the mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 x 10 mL), washed with brine (10 mL) and dried over anhydrous sodium sulphate. The residue was purified by column chromatography on silica gel to give the product **4** (92% yield).



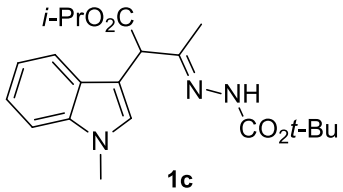
1a

Methyl 2-(4-methoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-lidene)hydrazinecarboxylate (1a): compound **1a** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 68% yield (216.8 mg), 1 h; white solid: mp: 122–124 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.47–7.43 (m, 1H), 7.43–7.39 (m, 1H), 7.32 (s, 1H), 7.19–7.13 (m, 1H), 7.04–7.00 (m, 1H), 4.87 (s, 1H), 3.80 (s, 3H), 3.68 (s, 6H), 1.79 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.1, 154.5, 151.0, 136.5, 128.5, 126.8, 121.3, 119.0, 118.7, 109.8, 107.5, 51.9, 51.7, 51.3, 32.4, 14.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}N_3O_4$ 318.1448; Found 318.1445.



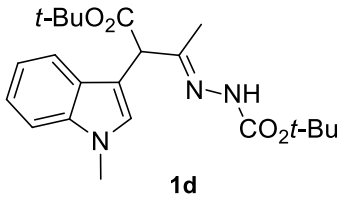
1b

Methyl 2-(4-ethoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1b): compound **1b** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 89% yield (294.0 mg), 0.5 h; white solid: mp: 119–121 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.47–7.45 (m, 1H), 7.42–7.40 (m, 1H), 7.32 (s, 1H), 7.18–7.14 (m, 1H), 7.04–7.00 (m, 1H), 4.84 (s, 1H), 4.20–4.12 (m, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H) 1.79 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.6, 154.6, 151.1, 136.5, 128.4, 126.8, 121.3, 119.0, 118.7, 109.8, 107.6, 60.6, 51.8, 51.4, 32.4, 14.4, 14.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1611.



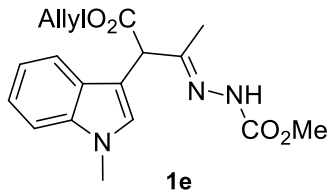
1c

***tert*-Butyl 2-(4-isopropoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1c):** compound **1c** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 84% yield (325.7 mg), 1 h; white solid: mp: 108–110 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.43–7.39 (m, 1H), 7.30 (s, 1H), 7.17–7.12 (m, 1H), 7.05–7.00 (m, 1H), 4.98 (sept, J = 6.4 Hz, 1H), 4.76 (d, J = 0.4 Hz, 1H), 3.77 (s, 3H), 1.76 (s, 3H), 1.45 (s, 9H), 1.21 (t, J = 6.4 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.1, 153.1, 150.3, 136.5, 128.3, 126.9, 121.3, 118.9, 118.8, 109.8, 107.8, 73.1, 68.0, 51.6, 32.4, 28.1, 21.5, 14.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{30}N_3O_4$ 388.2231; Found 388.2226.



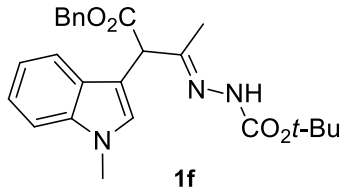
1d

***tert*-Butyl 2-(4-(*tert*-butoxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1d):** compound **1d** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 95% yield (380.1 mg), 7 h; orange solid: mp: 91–93 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.17–7.12 (m, 1H), 7.04–7.00 (m, 1H), 4.68 (s, 1H), 3.77 (s, 3H), 1.76 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.3, 153.6, 151.1, 137.0, 128.6, 127.4, 121.8, 119.4, 119.3, 110.2, 108.6, 81.2, 79.6, 52.9, 32.9, 28.6, 28.2, 14.8; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{32}N_3O_4$ 402.2387; Found 402.2400.



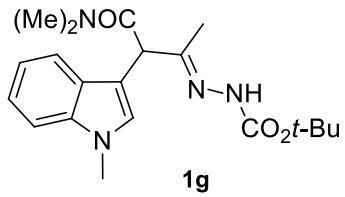
1e

Methyl 2-(4-(allyloxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1e): compound **1e** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 59 % yield (203.9 mg), 3 h; orange solid: mp: 178–180 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.46 (dt, J = 8.0, 0.8 Hz, 1H), 7.41 (dt, J = 8.0, 0.8 Hz, 1H), 7.33 (s, 1H), 7.16 (td, J = 8.0, 0.8 Hz, 1H), 7.02 (td, J = 8.0, 0.8 Hz, 1H), 5.99–5.89 (m, 1H), 5.32–5.27 (m, 1H), 5.21–5.18 (m, 1H), 4.90 (s, 1H), 4.65–4.62 (m, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.8, 155.1, 151.4, 137.0, 133.0, 129.0, 127.3, 121.8, 119.5, 119.3, 118.4, 110.3, 107.9, 65.5, 52.3, 51.8, 32.9, 15.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N_3O_4$ 344.1605; Found 344.1621.



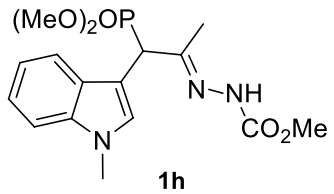
1f

***tert*-Butyl 2-(4-(benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1f):** compound **1f** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 75% yield (325.6 mg), 3 h; white solid: mp: 118–120 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.41–7.30 (m, 7H), 7.17–7.11 (m, 1H), 7.00 (t, J = 7.4 Hz, 1H), 5.21 (d, J = 12.4 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 4.91 (s, 1H), 3.75 (s, 3H), 1.78 (s, 3H), 1.47 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.6, 163.6, 153.0, 136.5, 136.0, 128.6, 128.3, 128.1, 128.0, 127.9, 126.9, 121.3, 118.9, 109.7, 107.6, 79.1, 66.0, 51.4, 32.4, 28.1, 14.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{30}N_3O_4$ 436.2231; Found 436.2234.



1g

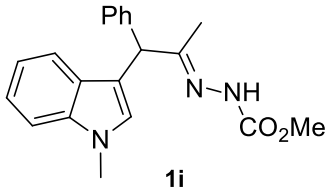
***tert*-Butyl 2-(4-(dimethylamino)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1g):** compound **1g** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 82% yield (303.8 mg), 24 h; white solid: mp: 108–110 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.17–7.13 (m, 1H), 7.03–7.00 (m, 1H), 5.02 (s, 1H), 3.76 (s, 3H), 2.88 (s, 3H), 2.87 (s, 3H), 1.73 (s, 3H), 1.45 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.4, 153.1, 136.6, 128.4, 126.8, 121.3, 118.9, 118.5, 109.8, 108.2, 79.0, 48.9, 37.0, 35.1, 32.4, 28.1, 14.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{29}N_4O_3$ 373.2234; Found 373.2238.



1h

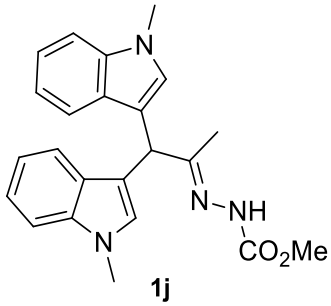
Methyl 2-(1-(dimethoxyphosphoryl)-1-(1-methyl-1*H*-indol-3-yl)propan-2-ylidene)hydrazinecarboxylate (1h): compound **1h** was isolated by column chromatography (ethyl acetate/methanol 95:5) in 69% yield (261.9 mg), 18 h; orange solid: mp: 159–161 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.92 (br, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.06–7.02 (m, 1H), 4.55 (d, $^2J_{HP}$ = 24.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.67 (d, $^3J_{HP}$ = 10.4 Hz, 3H), 3.60 (d, $^3J_{HP}$ = 10.4 Hz, 3H), 1.85 (d, $^4J_{HP}$ = 1.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 154.7, 150.0, 136.3, 129.0 (d, $^3J_{CP}$ = 5.6 Hz), 127.3 (d, $^2J_{CP}$ = 10.5 Hz), 121.5, 119.0, 118.7, 109.8, 105.0 (d, $^3J_{CP}$ =

6.5 Hz), 53.0 (d, $^2J_{CP}$ = 6.8 Hz), 52.9 (d, $^2J_{CP}$ = 6.8 Hz), 51.9, 43.7 (d, $^1J_{CP}$ = 138.0 Hz), 32.5, 15.0 (d, $^3J_{CP}$ = 3.0 Hz); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{23}N_3O_5P$ 368.1370; Found 368.1368.



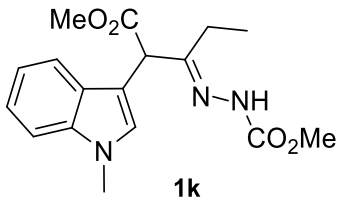
1i

Methyl 2-(1-(1-methyl-1*H*-indol-3-yl)-1-phenylpropan-2-ylidene)hydrazinecarboxylate (1i): compound **1i** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 73% yield (244.2 mg), 1 h; white solid: mp: 179–181 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.42–7.38 (m, 1H), 7.35–7.20 (m, 6H), 7.16–7.11 (m, 2H), 6.95 (t, J = 7.4 Hz, 1H), 5.19 (s, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 1.85 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 155.2, 141.5, 137.2, 128.9, 128.9, 128.7, 128.6, 127.5, 127.0, 121.7, 119.4, 119.1, 113.6, 110.1, 52.2, 51.4, 32.8, 15.8; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_3O_2$ 336.1707; Found 336.1717.



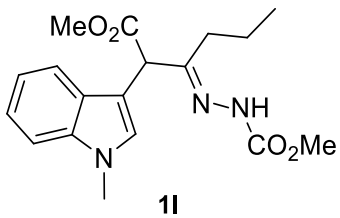
1j

Methyl 2-(1,1-bis(1-methyl-1*H*-indol-3-yl)propan-2-ylidene)hydrazinecarboxylate (1j): compound **1j** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 24% yield (142.0 mg), 1 h; white solid: mp: 188–190 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.16 (s, 2H), 7.16–7.12 (m, 2H), 7.00–6.96 (m, 2H), 5.40 (s, 1H), 3.74 (s, 6H), 3.67 (s, 3H), 1.83 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 155.6, 154.7, 136.7, 127.9, 127.1, 121.1, 119.0, 118.5, 113.1, 109.6, 51.7, 42.8, 32.3, 14.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_4O_2$ 389.1972; Found 389.1979.



1k

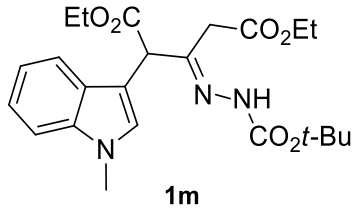
Methyl 2-(1-methoxy-2-(1-methyl-1*H*-indol-3-yl)-1-oxopentan-3-ylidene)hydrazinecarboxylate (1k): compound **1k** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 80% yield (264.1 mg), 1 h; white solid: mp: 124–126 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 7.51–7.49 (m, 1H), 7.41–7.39 (m, 1H), 7.33 (s, 1H), 7.17–7.13 (m, 1H), 7.03–7.00 (m, 1H), 4.88 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.45–2.35 (m, 1H), 2.21–2.12 (m, 1H), 0.74 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.2, 154.5, 154.5, 136.5, 128.8, 127.0, 121.3, 119.0, 119.0, 109.7, 107.6, 51.8, 51.8, 49.9, 32.4, 21.0, 9.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1598.



1l

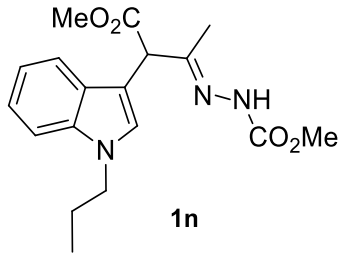
Methyl 2-(1-methoxy-2-(1-methyl-1*H*-indol-3-yl)-1-oxohexan-3-ylidene)hydrazinecarboxylate (1l): compound **1l** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 73% yield (251.8 mg), 2 h; white solid: mp: 124–126 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.51–7.49 (m, 1H), 7.41–7.39 (m, 1H), 7.33 (s, 1H), 7.16–7.12 (m, 1H), 7.03–6.99 (m, 1H), 4.86 (s, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.42–2.35 (m, 1H), 2.13–2.06 (m, 1H), 1.31–1.07 (m, 2H), 0.74 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.1, 154.4, 153.4,

136.5, 128.8, 127.0, 121.2, 119.0, 118.8, 109.6, 107.6, 51.7, 51.7, 50.0, 32.3, 29.7, 18.2, 13.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{24}N_3O_4$ 346.1761; Found 346.1752.



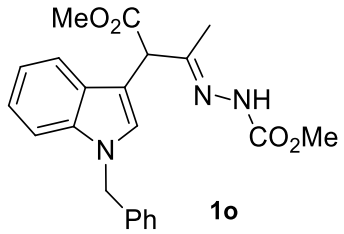
1m

Diethyl 3-(2-(*tert*-butoxycarbonyl)hydrazono)-2-(1-methyl-1*H*-indol-3-yl)pentanedioate (1m): compound **1m** was isolated as hydrazine tautomeric form by column chromatography (ethyl acetate/cyclohexane 40:60) in 75% yield (333.1 mg), 3 h; white solid: mp: 150–152 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.08 (br, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.03 (s, 1H), 6.98 (t, J = 7.2 Hz, 1H), 4.00–3.92 (m, 4H), 3.75 (s, 3H), 3.12 (s, 2H), 1.41 (s, 9H), 1.11 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.1, 168.7, 159.0, 156.9, 136.7, 130.1, 129.0, 121.3, 119.7, 119.0, 110.2, 110.0, 80.2, 60.8, 59.2, 35.9, 32.8, 28.5, 28.4, 14.8, 14.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{32}N_3O_6$ 446.2286; Found 446.2298.



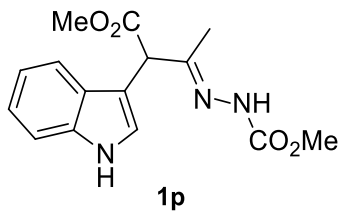
1n

Methyl 2-(4-methoxy-4-oxo-3-(1-propyl-1*H*-indol-3-yl)butan-2-ylidene)hydrazinecarboxylate (1n): compound **1n** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 70% yield (242.8 mg), 1 h; white solid: mp: 116–118 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.15–7.11 (m, 1H), 7.02–6.99 (m, 1H), 4.86 (s, 1H), 4.14–4.10 (m, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 1.76 (s, 3H), 1.75 (sex, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.1, 154.6, 151.0, 135.8, 127.6, 126.9, 121.3, 118.9, 118.8, 110.0, 107.5, 51.9, 51.8, 51.3, 47.0, 23.1, 14.3, 11.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{24}N_3O_4$ 346.1761; Found 346.1767.



1o

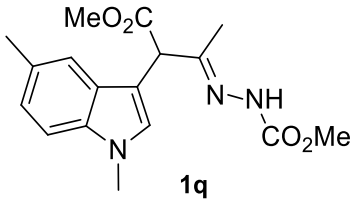
Methyl 2-(3-(1-benzyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1o): compound **1o** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 44% yield (147.1 mg), 3 h; white solid: mp: 128–130 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.53 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.32–7.28 (m, 2H), 7.25–7.23 (m, 1H), 7.21–7.17 (m, 2H), 7.12–7.08 (m, 1H), 7.03–6.99 (m, 1H), 5.42 (s, 2H), 4.91 (s, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.1, 154.6, 150.9, 138.1, 135.9, 128.5, 128.1, 127.3, 127.1, 126.9, 121.5, 119.2, 118.9, 110.3, 108.2, 52.0, 51.8, 51.3, 49.0, 14.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_3O_4$ 394.1761; Found 394.1768.



1p

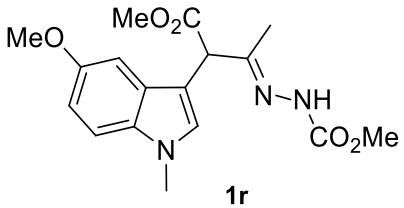
Methyl 2-(3-(1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1p): compound **1p** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 23% yield (69.0 mg), 6 h; whitish solid: mp: 112–114 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.90 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.10–7.06 (m, 1H), 7.00–6.96 (m, 1H), 4.86 (s, 1H), 3.67 (s, 6H), 1.77 (s, 3H); **^{13}C NMR** (100

MHz, DMSO-d_6) δ 171.3, 154.6, 151.2, 136.1, 126.5, 124.3, 121.3, 118.9, 118.5, 111.6, 108.3, 51.9, 51.8, 51.4, 14.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}N_3O_4$ 304.1292; Found 318.1297.



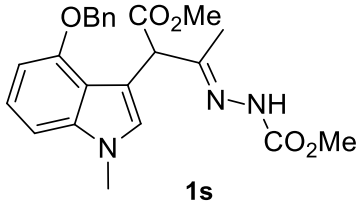
1q

Methyl 2-(3-(1,5-dimethyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1q): compound **1q** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (252.5 mg), 0.25 h; white solid: mp: 120–122 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 7.24–7.23 (m, 1H), 6.97 (dd, J = 8.4, 1.6 Hz, 1H), 4.82 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 2.36 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.2, 154.6, 151.2, 135.0, 128.5, 127.5, 127.0, 123.0, 118.2, 109.6, 106.9, 52.0, 51.8, 51.2, 32.4, 21.3, 14.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1593.



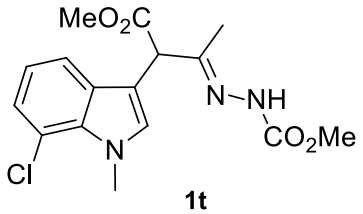
1r

Methyl 2-(4-methoxy-3-(5-methoxy-1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1r): compound **1r** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 62% yield (215.1 mg), 0.5 h; white solid: mp: 108–110 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.30 (d, J = 9.2 Hz, 1H), 7.28 (s, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 9.2, 2.4 Hz, 1H), 4.84 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 117.2, 154.6, 153.4, 151.1, 131.8, 128.9, 127.2, 111.3, 110.6, 106.9, 100.8, 55.2, 52.0, 51.8, 51.3, 32.6, 14.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_5$ 348.1554; Found 348.1543.



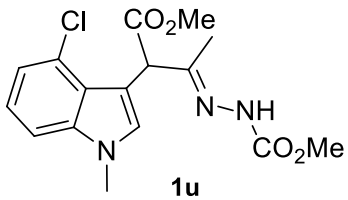
1s

Methyl 2-(3-(4-(benzyloxy)-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1s): compound **1s** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 32% yield (133.6 mg), 1 h; white solid: mp: 129–130 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.50–7.48 (m, 2H), 7.40–7.37 (m, 2H), 7.33–7.29 (m, 1H), 7.05–6.98 (m, 3H), 6.59 (d, J = 7.2 Hz, 1H), 5.22 (s, 1H), 5.19 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.48 (s, 3H), 1.88 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.4, 154.5, 152.7, 151.1, 138.0, 137.2, 128.3, 127.5, 127.4, 126.9, 122.2, 116.9, 108.2, 103.2, 100.8, 69.1, 51.9, 51.7, 51.6, 32.6, 15.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}N_3O_5$ 424.1867; Found 424.1872.



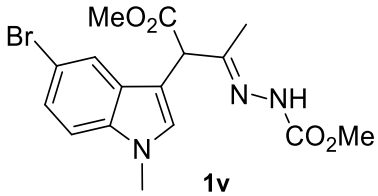
1t

Methyl 2-(3-(7-chloro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1t): compound **1t** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 50% yield (174.6 mg), 3 h; white solid: mp: 130–132 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.00–6.96 (m, 1H), 4.88 (s, 1H), 4.08 (s, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.9, 154.6, 150.6, 131.7, 131.4, 130.2, 122.8, 120.1, 118.2, 116.0, 108.0, 52.1, 51.8, 51.0, 36.2, 14.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}ClN_3O_4$ 352.1059; Found 352.1054.



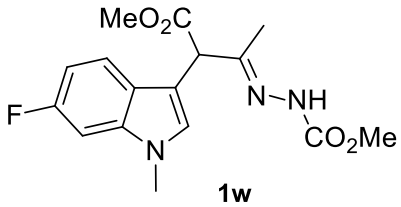
1u

Methyl 2-(3-(4-chloro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1u): compound **1u** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 32% yield (113.6 mg), 2 h; white solid: mp: 148–150 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.42 (dd, J = 8.0, 0.8 Hz, 1H), 7.22 (s, 1H), 7.16–7.12 (m, 1H), 7.05 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 5.31 (s, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 3.64 (s, 3H), 1.92 (s, 3H); interconversion to hydrazine tautomeric form occurred during the carbon spectrum acquisition; as a result, two distinct sets of signals of both hydrazone and hydrazine tautomers (ca. 50:50) were observed in DMSO-d_6 solution at 20°C; **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.3, 170.0, 162.2, 156.9, 154.5, 138.0, 137.7, 131.2, 130.1, 125.1, 124.7, 124.3, 123.4, 122.1, 121.6, 119.9, 119.4, 110.0, 109.4, 108.9, 108.1, 88.8, 52.2, 52.0, 51.8, 51.5, 50.4, 32.8, 32.6, 15.9, 15.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}ClN_3O_4$ 352.1059; Found 352.1051.



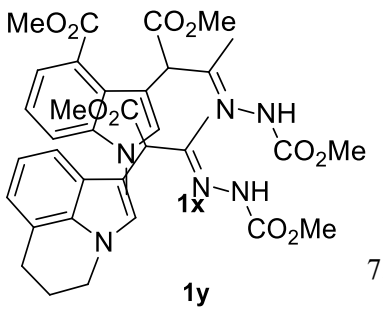
1v

Methyl 2-(3-(5-bromo-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1v): compound **1v** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 39% yield (156.3 mg), 1 h; white solid: mp: 155–157 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.42–7.40 (m, 2H), 7.26 (dd, J = 8.8, 2.0 Hz, 1H), 4.89 (s, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.9, 154.6, 150.8, 130.3, 130.2, 128.6, 123.8, 121.3, 112.0, 111.7, 107.3, 52.0, 51.8, 51.0, 32.6, 14.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}BrN_3O_4$ 396.0553; Found 396.0545.



1w

Methyl 2-(3-(6-fluoro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1w): compound **1w** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 56% yield (187.2 mg), 1 h; white solid: mp: 140–142 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.42 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.6 Hz, 1H), 7.33 (s, 1H), 7.29 (dd, $^3J_{HF}$ = 10.4 Hz, J = 2.4 Hz, 1H), 6.91–6.86 (m, 1H), 4.86 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.34 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.0, 159.0 (d, $^1J_{CF}$ = 233.6 Hz), 154.5, 150.9, 136.6 (d, $^3J_{CF}$ = 12.3 Hz), 129.1 (d, $^4J_{CF}$ = 3.3 Hz), 123.5, 120.0 (d, $^3J_{CF}$ = 10.2 Hz), 107.9, 107.4 (d, $^2J_{CF}$ = 24.4 Hz), 96.2 (d, $^2J_{CF}$ = 25.9 Hz), 52.0, 51.8, 51.2, 32.6, 14.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}FN_3O_4$ 336.1354; Found 336.1358.



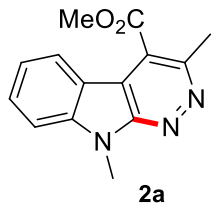
1y

Methyl 3-(1-methoxy-3-(2-(methoxycarbonyl)hydrazono)-1-oxobutan-2-yl)-1-methyl-1*H*-indole-4-carboxylate (1x): compound **1x** was isolated as hydrazine tautomeric form by column chromatography (ethyl acetate/cyclohexane 50:50) in 64% yield (200.3 mg), 1 h; white solid: mp: 162–164 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.45 (br, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 6.4 Hz, 1H), 7.21–7.17 (m, 2H), 3.80 (s,

3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.36 (s, 3H), 1.67 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.3, 169.2, 161.3, 157.4, 137.7, 133.0, 125.7, 124.8, 121.3, 120.3, 113.8, 110.8, 91.2, 52.6, 52.5, 50.6, 32.9, 16.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N_3O_6$ 376.1503; Found 376.1499.

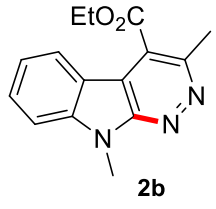
Methyl 2-(3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1y): compound **1y** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 44% yield (152.5 mg), 1 h; white solid: mp: 138–140 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.31 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 4.85 (s, 1H), 4.13 (t, J = 5.6 Hz, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 2.90 (t, J = 6.0 Hz, 2H), 2.14–2.08 (m, 2H), 1.80 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.3, 154.6, 151.3, 133.8, 125.8, 124.4, 121.9, 119.4, 118.3, 116.3, 107.5, 51.9, 51.8, 51.6, 43.4, 24.0, 22.3, 14.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N_3O_4$ 344.1605; Found 344.1604.

Ethyl 3-(2-carbamoylhydrazono)-2-(1-methyl-1*H*-indol-3-yl)butanoate: the chemical-physical data of compound **1z** are in agreement with those previously reported[16b]



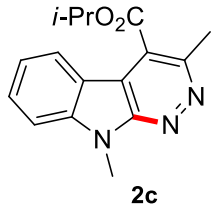
2a

Methyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2a): compound **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 82% yield (41.7 mg); yellow solid; mp: 112–114 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.0 Hz, 1H), 7.81–7.77 (m, 2H), 7.38–7.34 (m, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 2.82 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.6, 152.8, 146.8, 142.7, 131.2, 124.9, 121.7, 120.9, 115.9, 114.9, 110.5, 53.2, 28.1, 20.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3O_2$ 256.1081; Found 256.1078.



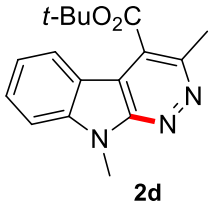
2b

Ethyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2b): compound **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 75% yield (40.2 mg); yellow solid; mp: 127–129 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.79–7.77 (m, 2H), 7.38–7.33 (m, 1H), 4.61 (q, J = 7.2 Hz, 2H), 4.04 (s, 3H), 2.82 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.1, 152.8, 146.7, 142.6, 131.1, 124.9, 122.1, 120.8, 115.9, 114.8, 110.5, 62.4, 28.1, 20.2, 13.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_2$: 270.1237; Found 270.1240.

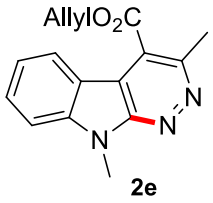


2c

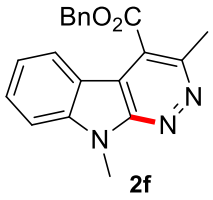
Isopropyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2c): compound **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 67% yield (38.1 mg); yellow solid; mp: 105–107 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.82–7.76 (m, 2H), 7.41–7.33 (m, 1H), 5.47 (sept, J = 6.4 Hz, 1 H), 4.04 (s, 3H), 2.82 (s, 3H), 1.44 (d, J = 6.4 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.6, 152.8, 146.4, 142.6, 131.1, 124.7, 122.5, 120.8, 115.9, 114.6, 110.6, 70.5, 28.1, 21.4, 20.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_2$ 284.1394; Found 284.1390.



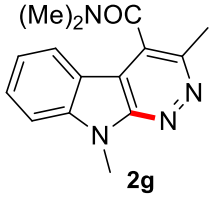
***tert*-Butyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2d):** compound **2d** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 56% yield (33.4 mg); yellow solid; mp: 160–162 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 1H), 7.80–7.76 (m, 2H), 7.41–7.35 (m, 1H), 4.04 (s, 3H), 2.81 (s, 3H), 1.69 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.4, 152.9, 146.2, 142.5, 131.0, 124.4, 123.4, 120.9, 115.9, 114.2, 110.6, 84.1, 28.1, 27.7, 19.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$Calcd for $C_{17}H_{20}N_3O_2$ 298.1550; Found 298.1561.



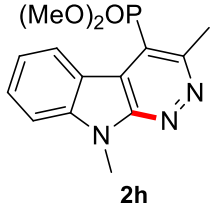
Allyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2e): compound **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 71% yield (39.8 mg); yellow solid; mp: 102–104 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.15 (dt, J = 8.0, 0.8 Hz, 1H), 7.80–7.78 (m, 2H), 7.37–7.33 (m, 1H), 6.20–6.10 (m, 1H), 5.53–5.48 (m, 1H), 5.40–5.36 (m, 1H), 5.10 (dt, J = 6.0, 1.2 Hz, 2H), 4.05 (s, 3H), 2.84 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.8, 152.8, 146.7, 142.7, 131.6, 131.1, 124.9, 121.7, 120.7, 119.7, 115.9, 114.8, 110.5, 66.6, 28.1, 20.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_2$ 282.1237; Found 282.1245.



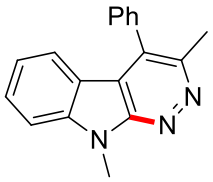
Benzyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2f): compound **2f** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 59% yield (39.0 mg); yellow solid; mp: 132–134 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.0 Hz, 1H), 7.78–7.41 (m, 2H), 7.47–7.38 (m, 3H), 7.58–7.54 (m, 2H), 7.24–7.19 (m, 1H), 5.64 (s, 2H), 4.03 (s, 3H), 2.79 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.9, 152.8, 146.6, 142.6, 134.9, 131.1, 129.1, 128.7, 128.6, 124.9, 121.9, 120.7, 115.8, 114.8, 110.5, 67.9, 28.1, 20.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$Calcd for $C_{20}H_{18}N_3O_2$ 332.1394; Found 332.1387.



***N,N*,3,9-Tetramethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxamide (2g):** compound **2g** was isolated by column chromatography (ethyl acetate/cyclohexane 100:0) in 46% yield (24.7 mg); yellow solid; mp: 154–156 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.82–7.72 (m, 3H), 7.38–7.32 (m, 1H), 4.04 (s, 3H), 3.24 (s, 3H), 2.77 (s, 3H), 2.67 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.6, 152.5, 145.9, 142.1, 130.6, 126.2, 123.3, 120.9, 116.3, 113.9, 110.4, 36.7, 33.9, 28.0, 18.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_4O$ 269.1397; Found 269.1404.

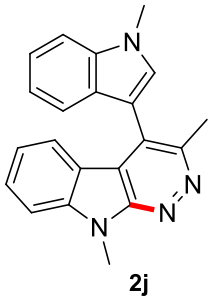


Dimethyl (3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indol-4-yl)phosphonate (2h): compound **2h** was isolated by column chromatography (ethyl acetate/cyclohexane 100:0) in 77% yield (46.8 mg); yellow solid; mp: 137–139 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.93 (d, J = 8.0 Hz, 1H), 7.82–7.75 (m, 2H), 7.39–7.33 (m, 1H), 4.05 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.03 (d, J = 1.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 152.2 (d, $^2J_{CP}$ = 11.0 Hz), 151.2 (d, $^2J_{CP}$ = 10.2 Hz), 143.1, 131.3, 127.9, 120.6, 120.1 (d, $^3J_{CP}$ = 8.8 Hz), 116.8, 116.7, 116.3 (d, $^1J_{CP}$ = 178.0 Hz), 110.1, 52.7 (d, $^2J_{CP}$ = 5.2 Hz), 28.1, 22.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}N_3O_3P$ 306.1002; Found 306.1006.



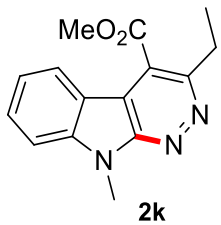
2i

3,9-Dimethyl-4-phenyl-9*H*-pyridazino[3,4-*b*]indole (2i): compound **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 46% yield (24.9 mg); yellow solid; mp: 166–168 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.73–7.59 (m, 5H), 7.56–7.49 (m, 2H), 7.11–7.03 (m, 2H), 4.03 (s, 3H), 2.56 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 152.9, 149.0, 142.1, 135.2, 132.7, 129.9, 129.2, 128.9, 128.3, 123.5, 120.1, 117.5, 116.6, 110.2, 28.0, 20.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3$ 274.1339; Found 274.1332.



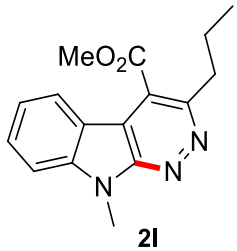
2j

3,9-dimethyl-4-(1-methyl-1*H*-indol-3-yl)-9*H*-pyridazino[3,4-*b*]indole (2j): compound **2j** was isolated by column chromatography (ethyl acetate/cyclohexane 90:10) in 67% yield (43.7 mg); orange solid; mp: 106–108 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60–7.56 (m, 1H), 7.30–7.26 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02–7.00 (m, 2H), 6.98–6.94 (m, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 2.66 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 152.8, 150.8, 142.0, 136.7, 129.6, 129.5, 126.6, 125.8, 124.2, 121.9, 119.8, 119.7, 119.4, 118.0, 117.6, 110.7, 109.8, 107.5, 32.9, 28.0, 20.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_4$ 327.1604; Found 327.1593.



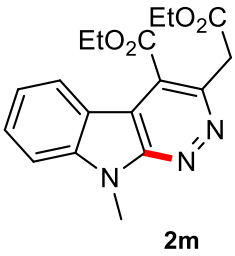
2k

Methyl 3-ethyl-9-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2k): compound **2k** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 80% yield (43.3 mg); yellow solid; mp: 148–150 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.05 (d, J = 8.0 Hz, 1H), 7.79–7.75 (m, 2H), 7.38–7.32 (m, 1H), 4.14 (s, 3H), 4.05 (s, 3H), 3.14 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.6, 152.6, 151.2, 142.6, 131.0, 124.5, 121.5, 120.9, 115.9, 114.7, 110.5, 53.2, 28.1, 26.8, 14.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_2$ 270.1237; Found 270.1254.



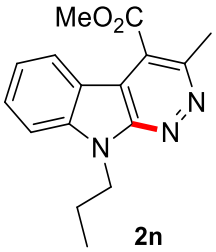
2l

Methyl 9-methyl-3-propyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2l): compound **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (43.1 mg); yellow oil; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.0 Hz, 1 H), 7.81–7.74 (m, 2 H), 7.38–7.32 (m, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 1.76 (sex, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.7, 152.6, 150.1, 142.5, 131.1, 124.5, 121.9, 120.9, 115.9, 114.7, 110.6, 53.3, 35.2, 28.1, 23.2, 13.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_2$ 284.1394; Found 284.1408.



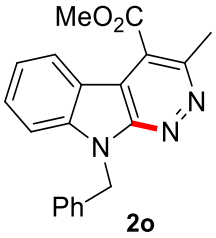
2m

Ethyl 3-(2-ethoxy-2-oxoethyl)-9-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2m): compound **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 60% yield (41.3 mg); yellow solid; mp: 102–104 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.31 (dt, J = 8.0, 0.8 Hz, 1H), 7.81–7.77 (m, 2H), 7.39–7.33 (m, 1H), 4.54 (q, J = 7.2 Hz, 2H), 4.38 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 4.05 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.3, 165.5, 153.3, 145.1, 142.9, 131.4, 126.0, 122.2, 120.9, 116.2, 115.7, 110.5, 62.4, 60.7, 28.2, 14.0, 13.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}N_3O_4$ 342.1448; Found 342.1439.



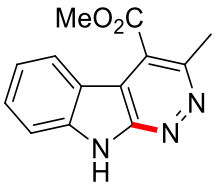
2n

Methyl 3-methyl-9-propyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2n): compound **2n** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 78% yield (44.2 mg); yellow solid; mp: 144–146 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.76 (dt, J = 7.2, 1.2 Hz, 1H), 7.35 (dt, J = 7.2, 1.2 Hz, 1H), 4.58 (t, J = 7.6 Hz, 2H), 4.13 (s, 3H), 2.82 (s, 3H), 1.86 (sex, J = 7.6 Hz, 2H), 0.88 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.5, 152.6, 146.7, 142.1, 131.1, 124.9, 121.8, 120.8, 115.9, 114.7, 110.7, 53.1, 43.0, 21.4, 20.1, 11.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_2$ 284.1394; Found 284.1399.



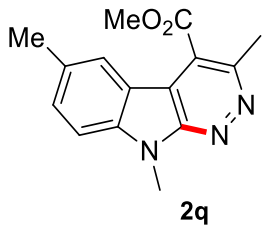
2o

Methyl 9-benzyl-3-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2o): compound **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (50.5 mg); yellow solid; mp: 132–134 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.73 (dt, J = 8.0, 1.2 Hz, 1H), 7.35 (dt, J = 8.0, 1.2 Hz, 1H), 7.31–7.21 (m, 5H), 5.87 (s, 2H), 4.13 (s, 3H), 2.83 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.4, 152.7, 147.4, 141.9, 136.9, 131.3, 128.6, 127.5, 127.1, 125.1, 121.9, 121.2, 116.2, 115.1, 110.9, 53.3, 44.7, 20.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}N_3O_2$ 332.1394; Found 332.1387.



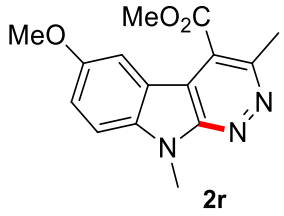
2p

Methyl 3-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2p): compound **2p** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 21% yield (10.0 mg); yellow solid; mp: 200–202 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.53 (br, 1H), 8.09 (dt, J = 8.4, 0.8 Hz, 1H), 7.72–7.68 (m, 1H), 7.62–7.60 (m, 1H), 7.33–7.29 (m, 1H), 4.13 (s, 3H), 2.81 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.7, 154.0, 146.6, 142.0, 131.1, 124.9, 121.7, 120.6, 116.4, 114.9, 112.2, 53.1, 20.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}N_3O_2$ 242.0924; Found 242.0932.



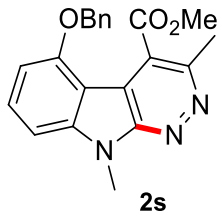
2q

Methyl 3,6,9-trimethyl-9H-pyridazino[3,4-*b*]indole-4-carboxylate (2q): compound **2q** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 79% yield (42.7 mg); yellow solid; mp: 118–120 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.84 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 8.4, 1.2 Hz, 1H), 4.13 (s, 3H), 4.01 (s, 3H), 2.80 (s, 3H), 2.47 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.7, 152.9, 146.6, 141.0, 132.6, 129.9, 124.4, 121.7, 115.9, 114.7, 110.4, 53.3, 28.2, 21.0, 20.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_2$ 270.1237; Found 270.1255.



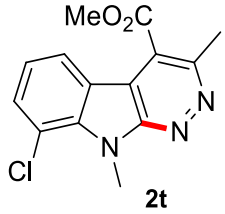
2r

Methyl 6-methoxy-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2r): compound **2r** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 81% yield (46.1 mg); yellow solid; mp: 117–119 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.71 (d, J = 9.2 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 9.2, 2.4 Hz, 1H), 4.13 (s, 3H), 4.00 (s, 3H), 3.85 (s, 3H), 2.82 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.5, 153.9, 153.0, 146.5, 137.7, 121.4, 120.8, 116.1, 114.6, 111.5, 106.7, 55.5, 53.1, 28.2, 20.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_3$ 286.1186; Found 286.1183.



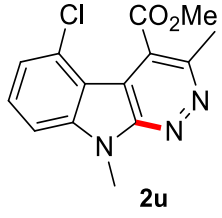
2s

Methyl 5-(benzyloxy)-9-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2s): compound **2s** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 80% yield (57.9 mg); yellow solid: mp: 176–178 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.60 (t, J = 8.4 Hz, 1H), 7.48–7.44 (m, 2H), 7.37–7.33 (m, 2H), 7.30–7.26 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.46 (s, 2H), 3.99 (s, 3H), 3.79 (s, 3H), 2.69 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.8, 155.9, 152.0, 145.8, 143.9, 136.5, 132.4, 128.5, 127.8, 127.4, 124.0, 112.6, 106.0, 103.7, 102.7, 69.5, 52.4, 28.3, 19.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}N_3O_3$ 362.1499; Found 362.1505.



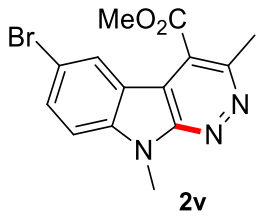
2t

Methyl 8-chloro-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2t): compound **2t** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 79% yield (45.8 mg); orange solid; mp: 140–142 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.00 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 4.35 (s, 3H), 4.12 (s, 3H), 2.80 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.2, 153.2, 147.5, 137.8, 132.5, 123.9, 122.0, 121.8, 119.1, 116.3, 114.2, 53.4, 31.2, 20.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}ClN_3O_2$ 290.0691; Found 290.0697.

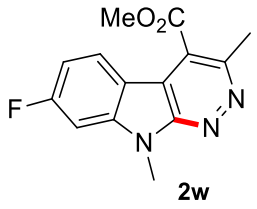


2u

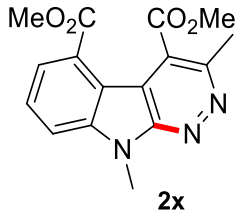
Methyl 5-chloro-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2u): compound **2u** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 65% yield (37.4 mg); orange solid; mp: 144–146 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.77–7.72 (m, 2H), 7.39 (dd, J = 7.2, 1.6 Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 2.72 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.1, 151.7, 146.2, 143.9, 131.7, 129.8, 124.3, 121.9, 114.1, 111.7, 109.6, 52.9, 28.6, 19.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}ClN_3O_2$ 290.0691; Found 290.0705.



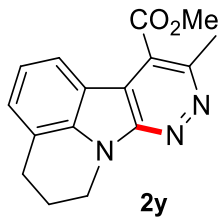
Methyl 6-bromo-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2v): compound **2v** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 80% yield (53.7 mg); yellow solid; mp: 131–133 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.28 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.8, 2.0 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 4.13 (s, 3H), 4.04 (s, 3H), 2.86 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.3, 152.9, 147.7, 141.6, 133.7, 127.5, 121.8, 117.7, 114.2, 112.8, 112.5, 53.3, 28.3, 20.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}BrN_3O_2$ 334.0186; Found 334.0182.



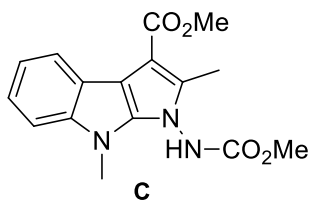
Methyl 7-fluoro-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (2w): compound **2w** was isolated by column chromatograpy (ethyl acetate/cyclohexane 30:70) in 80% yield (43.5 mg); yellow solid; mp: 188–190 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.12 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.2 Hz, 1H), 7.66 (dd, $^3J_{HF}$ = 10.4 Hz, J = 2.4 Hz, 1H), 7.17–7.12 (m, 1H), 4.11 (s, 3H), 3.98 (s, 3H), 2.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 164.9 (d, $^1J_{CF}$ = 249.4 Hz), 154.1, 148.7, 144.7 (d, $^3J_{CF}$ = 12.5 Hz), 128.0 (d, $^3J_{CF}$ = 10.9 Hz), 121.8, 116.5, 113.6, 109.6 (d, $^2J_{CF}$ = 24.1 Hz), 96.6 (d, $^2J_{CF}$ = 26.8 Hz), 53.0, 28.5, 21.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}FN_3O_2$ 274.0986; Found 274.0993.



Dimethyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4,5-dicarboxylate (2x): compound **2x** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 73% yield (45.8 mg); brown solid; mp: 136–138 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.07 (dd, J = 8.4, 0.8 Hz, 1H), 7.87 (dd, J = 8.4, 7.6 Hz, 1H), 7.79 (dd, J = 7.6, 0.8 Hz, 1H), 4.12 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.85 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.6, 166.4, 152.5, 147.3, 143.1, 130.4, 129.6, 123.4, 122.4, 114.6, 113.7, 113.5, 52.5, 52.5, 28.4, 20.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_4$ 314.1135; Found 314.1146.

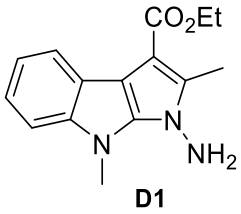


Methyl 10-methyl-5,6-dihydro-4*H*-pyridazino[4',3':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate (2y): compound **2y** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 67% yield (37.5 mg); yellow solid; mp: 130–132 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.92 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 7.2, 0.8 Hz, 1H), 7.23 (dd, J = 8.0, 7.2 Hz, 1H), 4.46 (t, J = 6.0 Hz, 2H), 4.12 (s, 3H), 3.08 (t, J = 6.0 Hz, 2H), 2.83 (s, 3H), 2.24 (quint, J = 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.6, 152.0, 146.8, 139.5, 128.6, 122.6, 122.6, 121.8, 120.7, 115.5, 114.1, 53.1, 40.2, 24.2, 21.2, 20.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_2$ 282.1237; Found 282.1239.



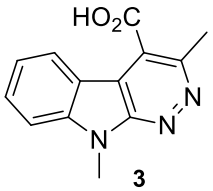
Methyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (C): intermediate **C** (entries 22, 25, and 27, Table 1) was isolated as a by-product by column chromatography (ethyl acetate/cyclohexane 40:60); mp: 164–166 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.99 (br, 1H), 7.93 (dd, J = 8.0, 0.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.19–7.14 (m, 1H), 7.12–7.08 (m, 1H), 3.89 (s, 3H), 3.79 (s, 6H), 2.48 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.1, 156.2, 139.7, 136.5,

136.3, 120.6, 120.1, 119.7, 119.2, 109.5, 102.7, 102.1, 53.3, 50.9, 29.1, 10.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_4$ 316.1292; Found 316.1288.



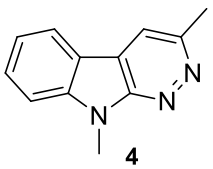
D1

Ethyl 1-amino-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (D1): compound **D1** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 30% yield (22.5 mg); red solid; mp: 168–170 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.93–7.91 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.12–7.08 (m, 1H), 7.06–7.02 (m, 1H), 6.02 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 2.62 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.0, 139.9, 137.5, 137.4, 120.4, 119.8, 119.5, 118.6, 109.1, 102.1, 100.2, 58.9, 29.7, 14.7, 10.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}N_3O_2$ 272.1394; Found 272.1388.



3

3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylic acid (3): compound **3** was isolated in 95% yield (114.2 mg); yellow solid; mp: 248–250 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.57 (br, 1H), 8.22 (dt, J = 8.0, 0.8 Hz, 1H), 7.80–7.77 (m, 2H), 7.39–7.35 (m, 1H), 4.04 (s, 3H), 2.84 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.2, 152.8, 146.4, 143.2, 131.6, 125.1, 124.5, 121.1, 116.1, 116.0, 110.7, 28.3, 19.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}N_3O_2$ 242.0924; Found 242.0916.



4

3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole (4): compound **4** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 92% yield (36.2 mg); light brown solid; mp: 142–144 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.31–8.30 (m, 1H), 8.28 (s, 1H), 7.74–7.69 (m, 2H), 7.36–7.32 (m, 1H), 3.98 (s, 3H), 2.78 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 152.4, 150.7, 142.2, 130.4, 123.7, 120.4, 119.5, 118.0, 117.6, 110.2, 28.0, 21.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}N_3$ 198.1026; Found 198. 1031.

CHAPTER 3

Practical and Sustainable Preparation of Pyrrolo[2,3-b]indoles by Cu/Fe Catalyzed Intramolecular C(sp^2)–H Amination

Corrieri, M., Crescentini, L. De, Mantellini, F., Mari, G., Santeusanio, S., Favi, G. *Green Chem.* **2022**, *24*, 7340–7345.

3.1 Introduction

Given the prevalence of *N*-heterocycles in natural products, pharmaceuticals, agrochemicals and innovative materials, carbon-nitrogen bond formation reactions are widely explored. In this field, since the seminal work of Buchwald-Hartwig, Ullmann and Chan-Evans-Lam, metal catalysts are vastly exploited thanks to their great versatility and efficiency in cross-coupling reactions between (hetero)aryl-(pseudo)halides and nitrogen compounds (mainly amines).[77,89,149–155] In particular, catalysts based on noble transition metals such as palladium[95,97], rhodium[98,99], gold[105,106] or ruthenium[103,104] have received great attention, since they often permit unprecedented reactivities. On the other hand, because of rising concerns regarding the health status of the environment, it is legit to question the sustainability of TM-based catalysis. In fact, TMs often require pre-activated substrates (for example, halides or pseudohalides) and high temperatures to operate. Moreover, also because of that, polar and high boiling solvents are used. In addition to this, working with transition metal catalysis can be tedious since TMs complex, as well as the reaction intermediates they form, often easily react with air and/or moisture. Precautions (use of gloveboxes, inert gases, expensive glassware, etc.) have therefore to be taken, so to assure reproducibility of the reactions. Another drawback is the fact that noble TMs, and especially their active complexes, are rare on Earth: this results in high prices and in their constant depletion from natural sources, with a high environmental impact derived from their mining.

For these reasons, developing greener and milder protocols for the construction of heterocycles from non-preactivated substrates is of utmost importance in modern synthesis (figure **1a**).[156] While recent contributions in the fields of electro-,[116–118,157] photo-,[107–110] flow chemistry[111–114] and their combinations[158–161] allowed for a rapid progress in green chemistry, lots of efforts have still to be made for a widespread use of non-toxic reagents and solvents. In particular, water, which is the greenest solvent, is rarely employed. A complementary achievement is to rely on abundant metals (iron, copper, zinc, nickel, etc.) rather than noble ones.[162–164]

Although a variety of intramolecular C–N bond formation reactions on hydrazones have been reported,[127,165–168] very little is known regarding indole-bearing hydrazones, which could be exploited for the preparation of interesting indole-fused compounds. In a previous work, we disclosed the synthesis of azacarbolines *via* an oxidative intramolecular amination of α-indolyl-hydrazones promoted by $PhIO_2$, an inexpensive and safe hypervalent iodine reagent (figure **1b**, *previous work*).[169] We envisioned that the hydrazone moiety of this class of substances could be also amenable to a five-membered oxidative cyclization (pyrrolo[2,3-*b*]indoles) instead of the six-membered one (azacarbolines) by varying the reaction conditions (figure **1b**, *this work*). Thus, we hypothesized that a metal catalyst could lead to a C–H activation on the substrate C-2, allowing for a subsequent intramolecular amination. The hydrazone part of the substrate would act as a directing and chelating group[170–172], promoting this transformation.

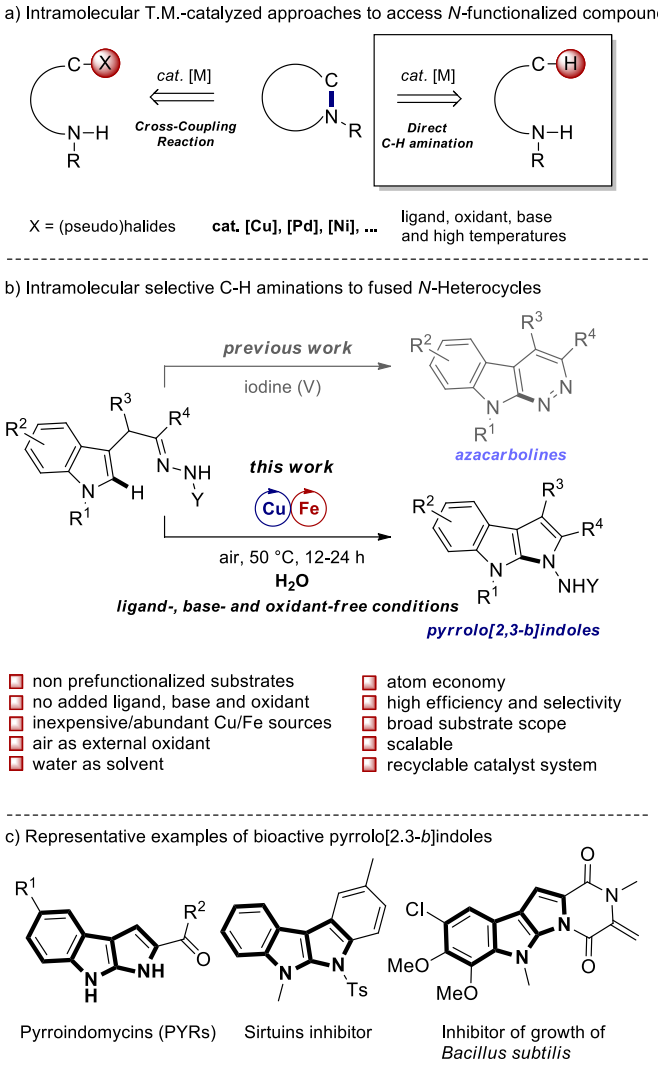


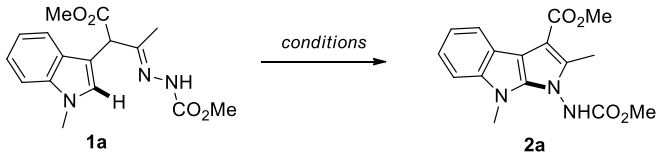
Figure 1

We herein disclose a synthetic approach to pyrrolo[2,3-*b*]indoles that involves the use of a Cu[173–176] and Fe[177–179] salts combination,[180,181] and that can be smoothly conducted in water[182–185] at 50 °C without the addition of an external stoichiometric oxidant. This method opens the synthetic access to a scaffold that showed to be of great interest in pharmaceutical chemistry. In figure **1c**, representative examples of bioactive compounds that include this tricyclic core are listed.

2.2 Results and discussion

To test our hypothesis of a metal-catalyzed intramolecular annulation for the construction of a new five-membered ring *N*-heterocycle on α-indolyl-hydrazones, we started our investigation using palladium, one of the most versatile TMs in C–H activation/C–X coupling protocols. $Pd(OAc)_2$ (10 mol%) was used in combination with AgOAc (2.0 equiv.) as the terminal oxidant and CH_2Cl_2 (0.1 M) as the solvent. In these conditions, **1a** smoothly reacted at room temperature, and the desired product **2a** was isolated in 90% yield (table **1**, entry 1). Once verified the feasibility of this reaction, and with the desired product in hands, we quickly moved to other catalysts. $FeCl_3 \cdot 6H_2O$ and $Cu(OAc)_2 \cdot H_2O$ were employed both in 10 mol% loading.

Interestingly, product **2a** was obtained in 28% and 33% yields, respectively, showing that either Fe and Cu possess a certain catalytic activity (entries 2 and 3). Next, the two salts were combined, and to our delight the desired product was obtained in 82% yield (entry 4). Heating the system at 50 °C in 1,2-dichloroethane allowed for a much more rapid consumption of the starting material, although the final product was isolated in a lower yield of 76% (entry 5). The addition of either a weak acid (pivalic acid, entry 6)[186] or a weak base (potassium carbonate, entry 7) showed to be detrimental in terms of product yield (60% and 47%, respectively). A slight improvement was achieved by increasing the $FeCl_3 \cdot 6H_2O$ loading from 5 mol% to 10 mol% (entry 8), while lowering the amount of the copper salt resulted in a lower yield (entry 9). A screening of several copper salts (bot Cu^I and Cu^{II}) did not show large variations in terms of product yield, and all copper species tested performed well (entries 10–14). On the other hand, the choice of the solvent showed to be of fundamental importance. In fact, when the reaction was carried out in toluene, only traces of the products were seen after 24 hours, and the starting material remained unreacted (entry 15). The use of acetonitrile, methanol, and acetone as solvents led to moderate yields (entries 16–18). Switching to an aqueous medium (water/acetone 9:1) allowed for a remarkable rise of the product yield (95 %, entry 19). When only water was used, a further increase of the yield was observed, and product **2a** was quantitatively obtained in 24 hours (entry 20). Having found the optimal medium, the catalytic system was re-optimized in water. While Fe_2O_3 and $Fe(acac)_3$ performed well (entries 21 and 25), further experiments with other Fe^{III} salts showed that the counter-ion plays a crucial role. In fact, the use of $Fe(NO_3)_3 \cdot 9H_2O$ led to a much lower yield (32%, entry 22); $Fe(ClO_4)_3$ worked better (73%, entry 23), while $Fe_2(SO_4)_3$ is basically inactive as catalyst for this transformation (entry 24). The screening thus confirmed that the best system is constituted of a combination of $Cu(OAc)_2 \cdot H_2O$ (10 mol%) and $FeCl_3 \cdot 6H_2O$ (5 mol%). The employment of a lower catalysts loading resulted in quantitative yield as well, albeit a longer reaction time was required (entry 26), while a mild heating at 50 °C allowed for a much faster conversion of the starting material (3 hours instead of 24, entry 27). Furthermore, control experiments showed that the combination of the two salts is required, since neither copper acetate nor iron chloride alone led to the formation of the product in water (entries 28 and 29).



1a **2a**

Entry[a]	Catalyst (mol%)	Co-catalyst (mol%)	Additive (eq.)	Solvent	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	–	AgOAc (2.0)	DCM	3	90
2	$FeCl_3 \cdot 6H_2O$ (10)	–	–	DCM	12	28[c, d]
3	$Cu(OAc)_2 \cdot H_2O$ (10)	–	–	DCM	12	33
4	$Cu(OAc)_2 \cdot H_2O$ (10)	$FeCl_3 \cdot 6H_2O$ (5)	–	DCM	5	82
5	$Cu(OAc)_2 \cdot H_2O$ (10)	$FeCl_3 \cdot 6H_2O$ (5)	–	DCE[e]	0.8	76
6	$Cu(OAc)_2 \cdot H_2O$ (10)	$FeCl_3 \cdot 6H_2O$ (5)	PivOH (5.0)	DCM	18	60

Entry[a]	Catalyst (mol%)	Co-catalyst (mol%)	Additive (eq.)	Solvent	Time (h)	Yield (%)[b]
7	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	K_2CO_3 (2.0)	DCM	6	47
8	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (10)	–	DCM	4	83
9	$Cu(OAc)_2·H_2O$ (5)	$FeCl_3·6H_2O$ (10)	–	DCM	5	76
10	CuO (10)	$FeCl_3·6H_2O$ (5)	–	DCM	4	83
11	$Cu(OTf)_2$ (10)	$FeCl_3·6H_2O$ (5)	–	DCM	8	76
12	$CuCl_2$ (10)	$FeCl_3·6H_2O$ (5)	–	DCM	12	82
13	CuI (10)	$FeCl_3·6H_2O$ (5)	–	DCM	24	79
14	CuCl (10)	$FeCl_3·6H_2O$ (5)	–	DCM	24	68
15	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	–	toluene	24	traces[c]
16	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	–	MeCN	1	35
17	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	–	MeOH	1	54
18	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	–	Me_2CO	1	57
19	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	–	H_2O(9)/ Me_2CO(1)	3	95[f]
20	$Cu(OAc)_2·H_2O$ (10)	$FeCl_3·6H_2O$ (5)	–	H_2O	24	99[f]
21	$Cu(OAc)_2·H_2O$ (10)	Fe_2O_3 (5)	–	H_2O	20	98[d,f]
22	$Cu(OAc)_2·H_2O$ (10)	$Fe(NO_3)_3·9H_2O$ (5)	–	H_2O	10	32
23	$Cu(OAc)_2·H_2O$ (10)	$Fe(ClO_4)_3$ (5)	–	H_2O	48	73
24	$Cu(OAc)_2·H_2O$ (10)	$Fe_2(SO_4)_3·H_2O$ (5)	–	H_2O	48	traces[c]
25	$Cu(OAc)_2·H_2O$ (10)	$Fe(acac)_3$ (5)	–	H_2O	40	99
26	$Cu(OAc)_2·H_2O$ (5)	$FeCl_3·6H_2O$ (2.5)	–	H_2O	40	99[f]
27	**$Cu(OAc)_2·H_2O$ (10)**	**$FeCl_3·6H_2O$ (5)**	**–**	**H_2O**	**3**	**99[e,f]**
28	$Cu(OAc)_2·H_2O$ (10)	–	–	H_2O	48	traces[c]
29	–	$FeCl_3·6H_2O$ (5)	–	H_2O	48	traces[c]

Table 1. Optimization studies - [a] All reactions were performed on 0.2 mmol scale of **1a** in 2 mL of solvent (0.1 M) under air atmosphere for the indicated time. [b] All yields refer to the isolated product after column chromatography, unless otherwise noted. [c] The unreacted starting material was recovered. [d] 38% Yield of **2a** with complete consumption of **1a** was observed with 1.0 equiv. of $FeCl_3·6H_2O$. [e] Performed at 50 °C. [f] Without column chromatography. DCM = dichloromethane; DCE = 1,2-dichloroethane; PivOH = pivalic acid.

To summarize, the optimized conditions for the synthesis of pyrrolo[2,3-*b*]indoles via intramolecular C–H amination involve the treatment of the α-indolylhydrazone substrates with $Cu(OAc)_2·H_2O$ (10 mol%) and $FeCl_3·6H_2O$ (5 mol%) in water (1 mL/0.1 mmol) at 50 °C. In these conditions, the reaction proceeds in such a smooth and clean way that the purification of **2a** can be achieved without column chromatography. In fact, in a typical procedure, an extraction with ethyl acetate is sufficient for the obtainment of a pure product, which can then be recrystallized from an appropriate solvent.

Next, the substrate scope for this reaction was investigated, and a series of variously substituted pyrrolo[2,3-*b*]indoles was synthesized (table 2). To start with, ester groups with different -OR chains were installed as R^3/R^5substituents (products **2a–f**). Only the use of an allyl substituent showed a substantial decrease in the final yield (64%, **2e**), while methyl, ethyl, Boc, isopropyl, and benzyl groups were all well tolerated, leading to high or excellent yields for the final products. In addition to this, the ester function could be replaced with a phosphonate moiety ($PO(OMe)_2$), and the product **2g** was formed in quantitative yield. As R^5, a

semicarbazone instead of a carbamate group was also used, and cyclization product **2h** was successfully obtained in 85% yield. Alkyl chains longer than methyl could be inserted as R^4 substituents (**2i,j**), as well as *N*-substituents (**2k**), and were all tolerated. On the other hand, the reaction on a *N*-unsubstituted α-indolylhydrazone led to a decreased yield (52%, **2l**) for the final product, which showed to be somehow unstable and spontaneously converts to azacarboline derivative **5a**.[187] Finally, a diverse range of substituents on the carbocycle could be inserted. The electronic nature of groups in this portion of the substrate does not affect the yield, and products were obtained in excellent or quantitative yields regardless of the electrondonating (**2m,n**) or the electronwithdrawing (**2o–s**) nature of the substitution. A three-carbon chain, which tethers the indole nitrogen to the indole C-7, was also well tolerated and the tetracyclic product **2t** was formed in 97% yield.

In most cases, the chromatographic purification was not needed, and products were isolated by extraction with ethyl acetate and subsequent recrystallization. The scalability of the procedure was evaluated, and a gram-scale (3.15 mmol) reaction was conducted, which led to an excellent 94% yield for the product **2a**.

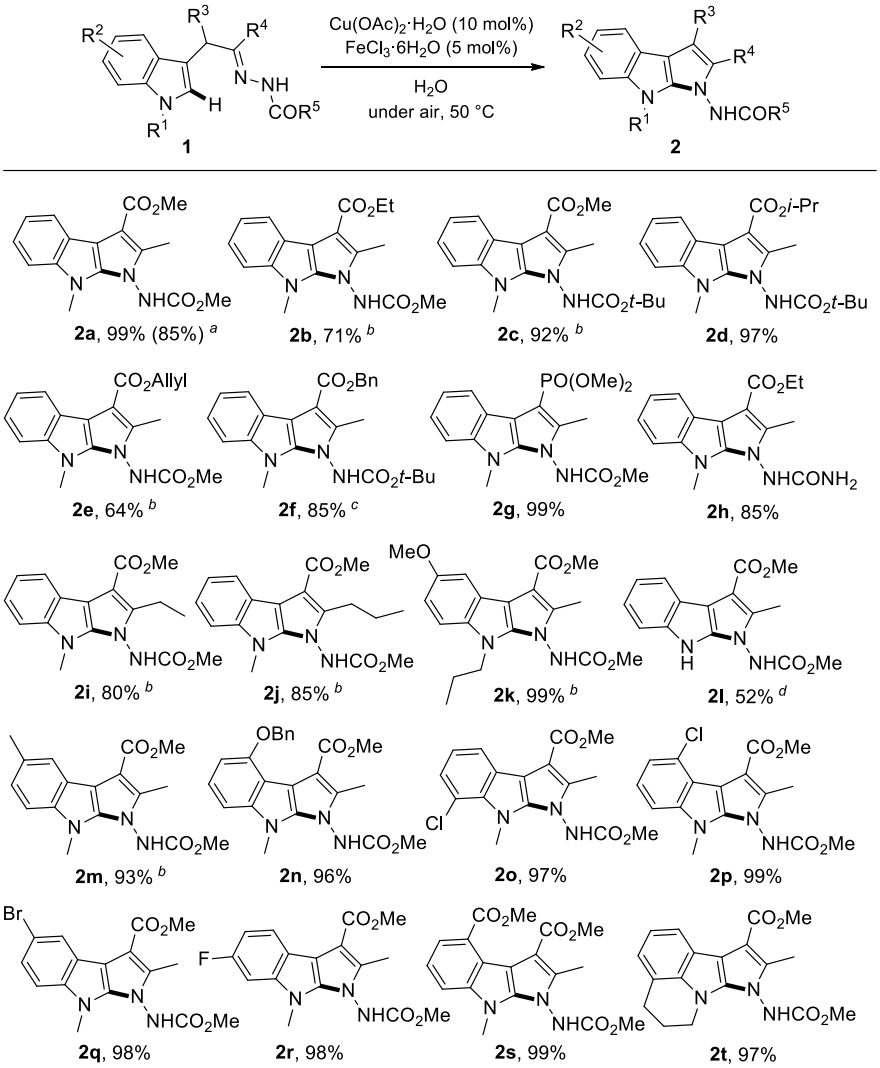


Table 2. Substrate scope – Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol%) and $FeCl_3 \cdot 6H_2O$ (5 mol%) in H_2O (2.0 mL) at 50 °C, 3–48 h. [a] 3.15 mmol scale reaction (0.933 g), yield in brackets. [b] Isolated yields after column chromatography. [c] 50 °C for 36 h, then 70 °C for 24 h. [d] A spontaneous conversion to azacarboline **5a**[187] was observed.

Next, having assessed the generality of the copper/iron co-catalyzed intramolecular amination of α-indolylhydrazones, it was evaluated whether it is possible to recover and reuse the aqueous catalytic system. The model substrate **2a** was thus synthesized with the optimized conditions on a 0.4 mmol scale. As soon as the reaction was completed, the usual extraction with ethyl acetate was carried out in order to isolate the product. The aqueous phase was then collected in a round bottom flask and used for a second run with the same substrate **1a**, without the addition of fresh catalysts. As summarized in **figure 2**, these cycles were reiterated up to five times and yields above 70% were obtained for the first four experiments. After that, a pronounced drop in the yield was observed, and reaction times got dilated as well.

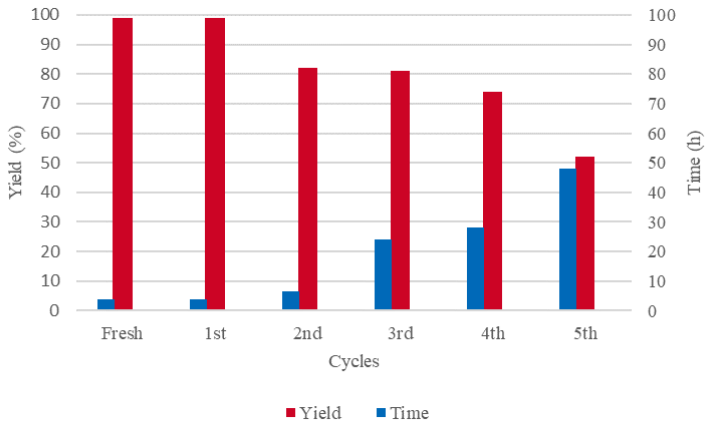
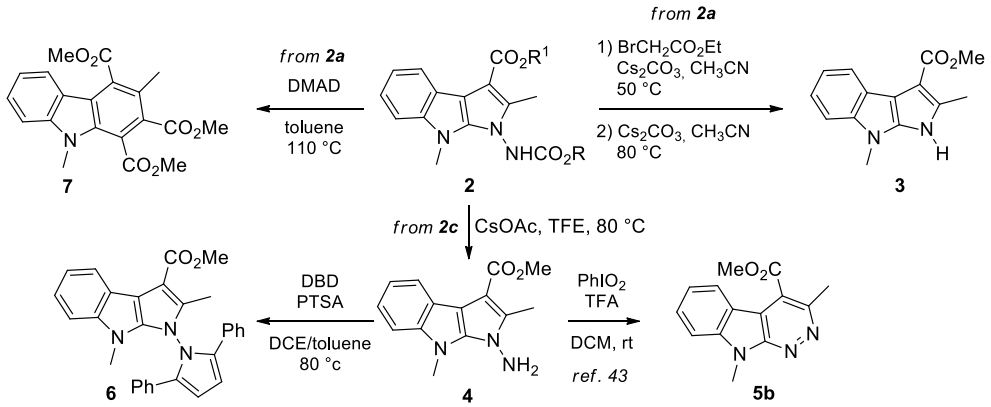


Figure 2. Recycling of the aqueous system

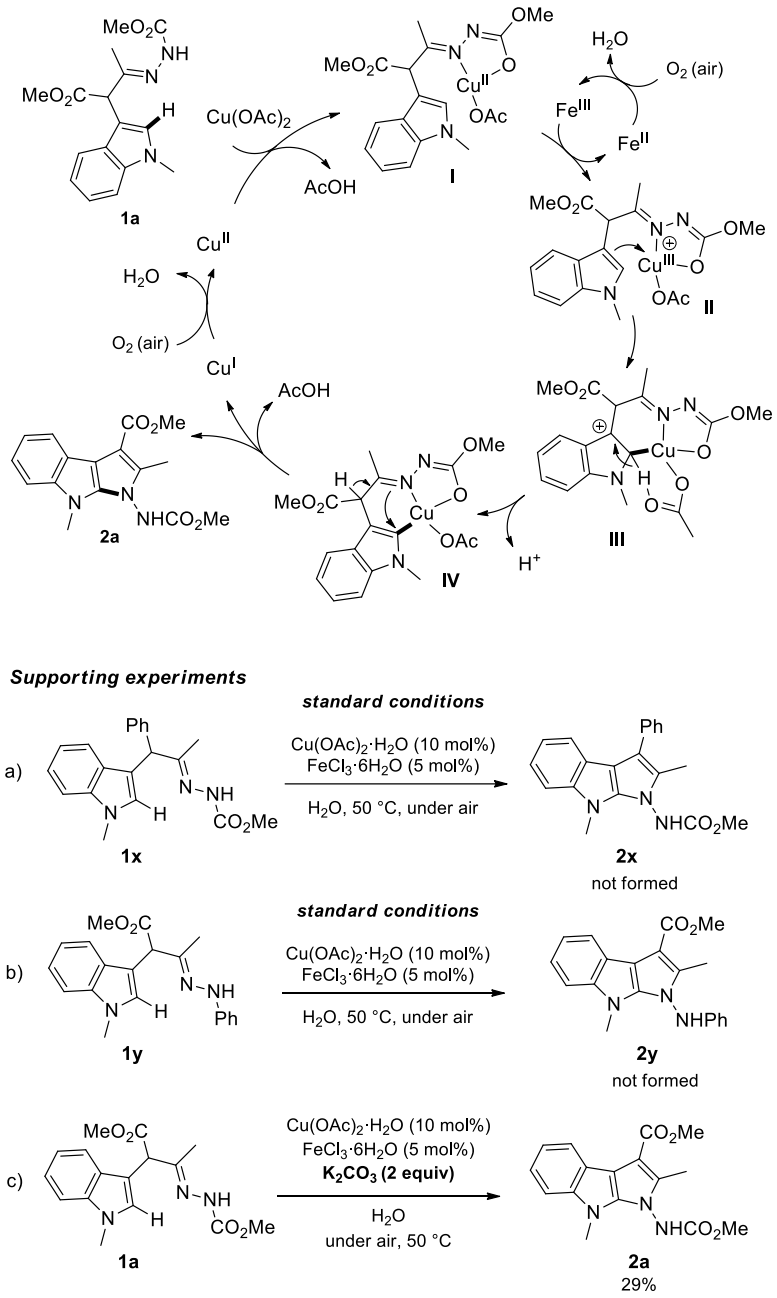
A series of transformations was conducted on some pyrrolo[2,3-*b*]indoles, in order to demonstrate the synthetic potential of the intramolecular C–H amination (scheme **1**). To begin with, pyrrolo[2,3-*b*]indole **3** was obtained by a reductive N–N bond cleavage, exploiting an E_{1cb} approach promoted by 2-bromoethyl acetate and cesium carbonate as the base.[188] The Boc protecting group was removed from derivative **2c**,[189] and unsubstituted *N*-aminopyrroloindole **4** was obtained. This compound was further manipulated: following our previously reported paper,[169] azacarboline **5b** was synthesized. Moreover, compound **4** underwent a Paal-Knorr pyrrolization when heated in toluene with 1,4-diphenyl-1,4-butanedione, in the presence of *p*-TsOH.[190] Finally, an aza-Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) in refluxing toluene, followed by the elimination of an *N*-aminonitrene portion, afforded product **7**.[191]



Scheme 1. Synthetic transformations – DMAD = dimethyl acetylenedicarboxylate; TFE = 2,2,2-trifluoroethanol; TFA = trifluoroacetic acid; DBD = 1,4-diphenyl-1,4-butanedione; PTSA = *p*-toluenesulfonic acid; DCE = 1,2-dichloroethane.

In scheme **2**, a possible mechanism, based on literature[186,192] and on data from our experiments, is illustrated. Initially, the hydrazone moiety acts as a directing group, and coordinates the copper species as a bidentate *N,O*-ligand. The Cu^{II} center of the complex **I** is then oxidized by Fe^{III} to Cu^{III}, forming the complex **II** and an iron (II) species. Thanks to the higher electrophilicity of the intermediate **II**, the insertion of the copper species into the C2-H bond of the indole portion is facilitated, and transition state **III** is formed. The loss of a proton leads to the formation of intermediate **IV**,[192] which then undergoes reductive elimination assisted by a C–H/N–

H tautomerization. The redox cycle is completed after the reoxidization of both Cu^{I} and Fe^{II} by air, which allows the regeneration of the two active catalysts species.



Scheme 2. Proposed mechanism and supporting experiments

To support the proposal of this mechanism, several experiments were conducted. As shown in scheme 2a, the presence of a phenyl group in the α-position inhibits the reaction. This result suggests that an electronwithdrawing group as R^3 substituent, which facilitates the C–H/N–H tautomerization, is needed. Secondly, the reaction does not occur if a *N*-phenyl ring, instead of a -CO_2R or -$CONH_2$ group, is present on the hydrazone portion, suggesting that the need of a bidentate coordination is plausible. Furthermore, given

that the use of K_2CO_3 as an additive results in a low yield of 29% for **2a**, an initial tautomerization instead of the loss of the acidic α proton at a later stage (from intermediate **IV**) can be excluded.

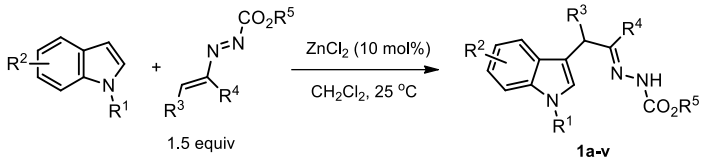
3.2 Conclusions

To summarize, an environmentally friendly protocol for the copper/iron co-catalyzed intramolecular C–H amination of α-indolyl-hydrazones has been developed. A redox catalytic cycle, in which the two metals act in synergy, and which does not require the use of an external oxidant is involved. This method allows for the synthesis in mild conditions of variously functionalized pyrrolo[2,3-*b*]indoles, which comprise an interesting scaffold, especially as pharmacophore in medicinal chemistry. An array of products has been prepared with high to excellent/quantitative yields, often with no need for a chromatographic purification. The use of a recoverable aqueous medium, as well as the scalability of the process, further highlight the potential of this synthetic procedure.

3.3 Experimental section

General remarks: All the commercially available reagents and solvents were used without further purification. α-(Indol-3-yl)hydrazones **1a–v** were prepared according to our previously reported method with a slight modification.[81,82] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using DMSO-d_6 or $CDCl_3$ as solvent on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA). Chemical shift (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, sex = sextet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. High-resolution mass spectroscopy was performed on a Micromass Q-TOF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected.

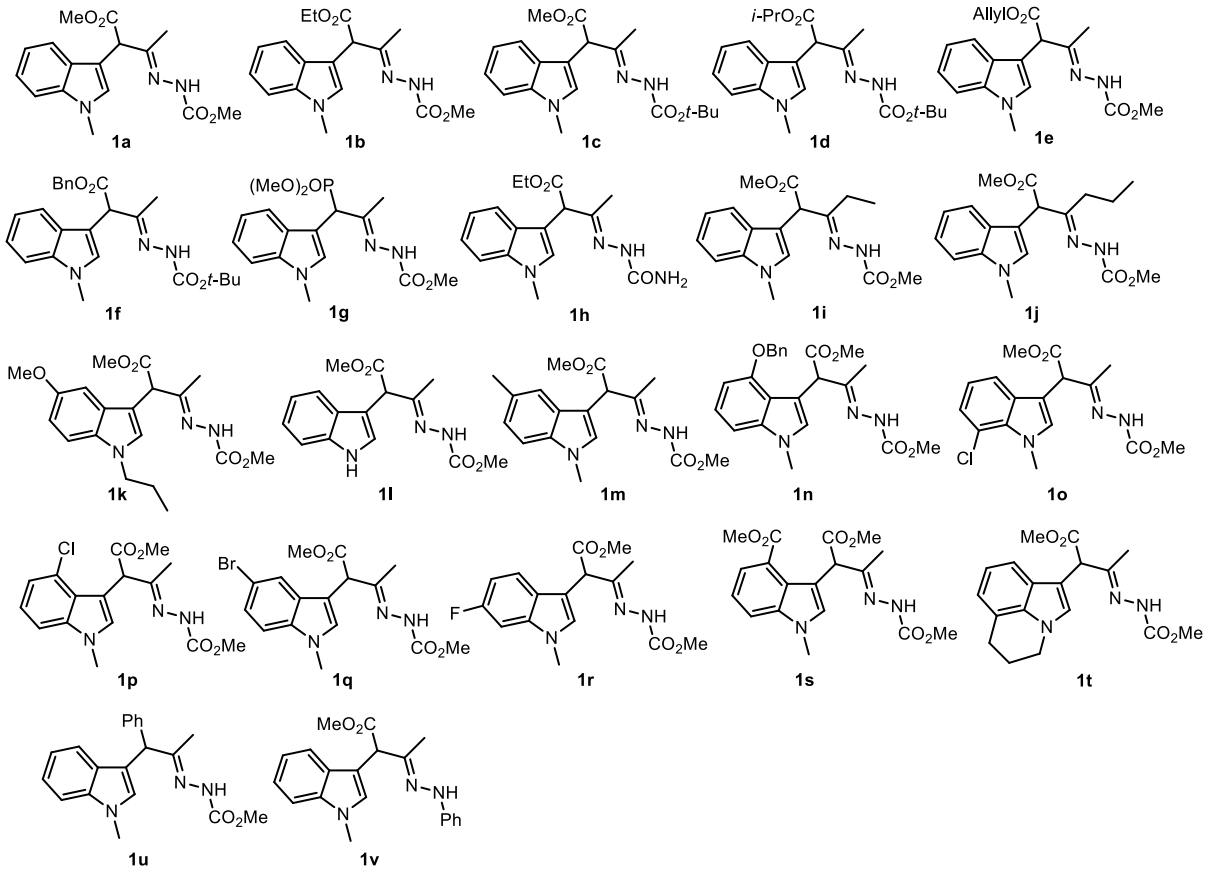
General procedure for the preparation of α-(indol-3-yl)hydrazones 1a–v[81,82]:

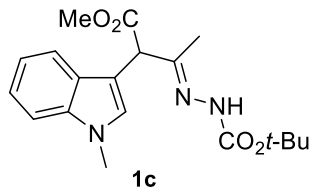


To a stirred mixture of indole (1.0 mmol) and azoalkene (1.5 mmol, 1.5 equiv) in dichloromethane (4 mL), zinc dichloride (13.6 mg, 0.1 mmol, 10 mol%) was added. After the disappearance of indole (TLC check), the solvent was removed and the crude mixture was purified by column chromatography on silica gel to afford, after crystallization, the α-(indol-3-yl)hydrazones **1**.

The characterization data of substrates **1a,b,d–u** was previously reported in chapter 2.4.

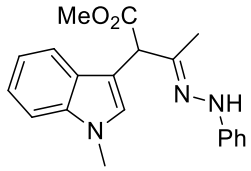
List of substrates 1a–v prepared according to the general procedures.





1c

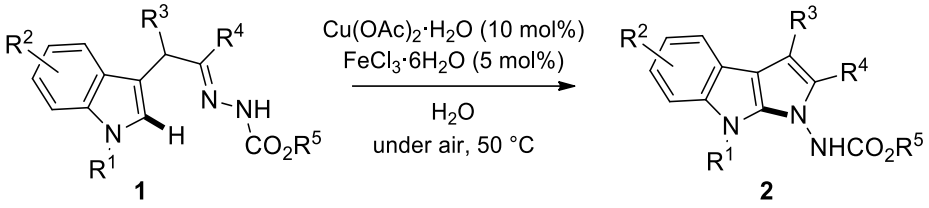
***tert*-Butyl 2-(4-methoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1c):** Compound **1c** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 60% yield (216.6 mg) as a white solid; 1h; mp: 138−140 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.57 (br, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.17−7.13 (m, 1H), 7.04−7.00 (m, 1H), 4.83 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 1.76 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.2, 153.0, 150.2, 136.5, 128.5, 126.8, 121.3, 118.9, 118.7, 109.8, 107.6, 79.1, 51.9, 51.3, 32.4, 28.1, 14.5. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{19}H_{25}N_3O_4$ 360.1918, found 360.1923.



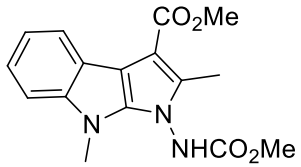
1v

Methyl 2-(1-methyl-1*H*-indol-3-yl)-3-(2-phenylhydrazono)butanoate (1v): Compound **1v** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 64% yield (215.0 mg) as a pale yellow solid; 4 h; mp: 121−122 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.50 (td, J = 0.8, 8.0 Hz, 1H), 7.41 (td, J = 0.8, 8.0 Hz, 1H), 7.32 (s, 1H), 7.20–7.12 (m, 3H), 7.10–7.07 (m, 2H), 7.02–6.98 (m, 1H), 6.74–6.69 (m, 1H), 4.91 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 1.83 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.6, 146.3, 142.7, 136.6, 128.8, 128.4, 127.0, 121.2, 118.9, 118.8, 118.4, 112.4, 109.7, 108.3, 51.8, 51.3, 32.4, 14.1. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{21}N_3O_2$ 336.1707, found 336.1701.

General procedure for the Cu/Fe Catalyzed C(sp^2)–H Amination

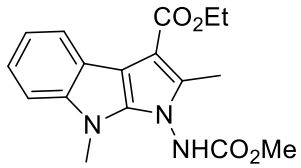


In a round-bottom flask, α-indolylhydrazone **1** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.02 mmol, 4.0 mg), $FeCl_3 \cdot 6H_2O$ (0.01 mmol, 2.7 mg) and water (2 mL) were added. The mixture was stirred at 50 °C (oil bath) until consumption of the starting material (TLC check). Then, the reaction mixture was diluted with brine and extracted with ethyl acetate (3 x 10 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent was removed under vacuum. The crude product was purified by recrystallization or by flash chromatography on silica gel (cyclohexane/ethyl acetate) to give the corresponding product **2** (52–99% yields).



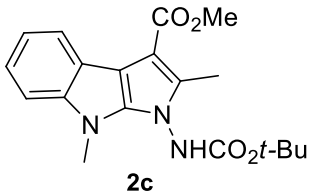
2a

Methyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2a): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether to afford compound **2a** as a pale brown solid in 99% yield; 3 h; the chemical-physical data of compound **2a** are in agreement with those reported.[169] mp: 164–166 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.99 (br, 1H), 7.93 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.19–7.14 (m, 1H), 7.12–7.08 (m, 1H), 3.89 (s, 3H), 3.79 (s, 6H), 2.48 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.1, 156.2, 139.7, 136.5, 136.3, 120.6, 120.1, 119.7, 119.2, 109.5, 102.7, 102.1, 53.3, 50.9, 29.1, 10.2; HRMS (ESI-Orbitrap, *m/z*): [M+H]+ Calcd for C16H18N3O4 316.1292; Found 316.1288.



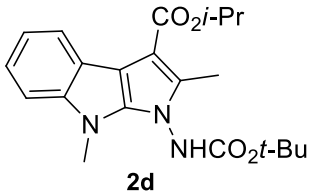
2b

Ethyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2b): compound **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 71% yield (46.6 mg) as a whitish solid; 4 h; mp: 149−151 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.04 (br, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.12–7.08 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.49 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.6, 156.2, 139.7, 136.5, 136.6, 120.5, 120.1, 119.7, 119.1, 109.5, 102.6, 102.4, 59.3, 53.2, 29.1, 14.6, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4$ 330.1448, found 330.1452.



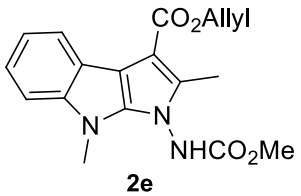
2c

Methyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2c): compound **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 92% yield (66.0 mg) as a whitish solid; 4 h; mp: 179–180 ; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.73 (br, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.11–7.07 (m, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.47 (s, 3H), 1.51 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.1, 154.7, 139.7, 136.5, 136.4, 120.5, 120.1, 119.6, 119.1, 109.4, 102.5, 101.8, 81.5, 50.8, 29.0, 27.8, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{19}H_{23}N_3O_4$ 358.1761, found 358.1752.



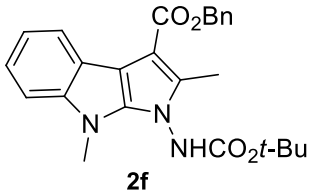
2d

Isopropyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2d): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether/petroleum ether to afford compound **2d** in 97% yield (74.5 mg) as a pale grey solid; 12 h; mp: 152–154 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.73 (br, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.17–7.07 (m, 2H), 5.19 (sept, J = 6.4 Hz, 2H), 3.79 (s, 3H), 2.45 (s, 3H), 1.51 (s, 3H), 1.40 (d, J = 6.0 Hz, 6H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.2, 154.7, 139.7, 136.5, 136.4, 120.4, 120.2, 119.7, 119.1, 109.4, 102.7, 102.6, 81.5, 66.4, 29.0, 27.8, 22.2, 10.4. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{21}H_{27}N_3O_4$ 386.2074, found 386.2077.



2e

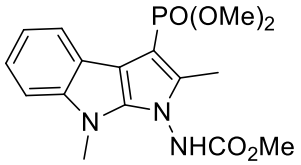
Allyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2e): compound **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 64% yield (49.2 mg) as a white solid; 20 h; mp: 134–136 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.06 (br, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.10–7.06 (m, 1H), 6.19–6.10 (m, 1H), 5.46–5.40 (m, 1H), 5.32–5.29 (m, 1H), 4.87–4.86 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.49 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.2, 156.2, 139.7, 136.7, 136.3, 133.4, 120.6, 120.0, 119.7, 119.1, 117.9, 109.5, 102.6, 102.0, 63.9, 53.3, 29.1, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{18}H_{19}N_3O_4$ 342.1448, found 342.1450.



2f

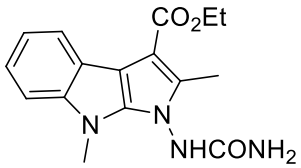
Benzyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2f): after the extraction of the reaction mixture, the residue was recrystallized from ethyl acetate/diethyl ether to afford compound **2f** in 85% yield (74.1 mg) as a brown solid; 20 h; mp: 188–190 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.76 (br, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.50 (m, 2H), 7.43–7.40 (m, 3H), 7.38–7.34 (m, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 5.41 (s, 2H), 3.78 (s, 3H), 2.47 (s, 3H), 1.50 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.4, 154.6, 139.6, 136.9, 136.8, 136.4, 128.5, 128.1,

127.9, 120.4, 120.0, 119.8, 119.0, 109.3, 102.6, 101.9, 81.5, 64.9, 29.0, 27.8, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{25}H_{27}N_3O_4$ 434.2074, found 434.2082.



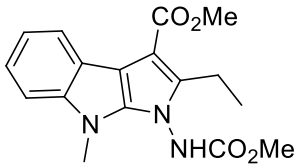
2g

Methyl (3-(dimethoxyphosphoryl)-2,8-dimethylpyrrolo[2,3-*b*]indol-1(8*H*)-yl)carbamate (2g): after the extraction of the reaction mixture, the residue was recrystallized from ethyl acetate/petroleum ether to afford compound **2g** in 99% yield (72.5 mg) as a brown solid; 12 h; mp: 184–186 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.98 (br, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.17–7.13 (m, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.65 (d, $^3J_{HP}$ = 8.4 Hz, 3H), 3.62 (d, $^3J_{HP}$ = 8.4 Hz, 3H), 2.40 (s,3 H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 156.3, 139.6, 137.8 (d, $^2J_{CP}$ = 26.2 Hz), 137.0 (d, $^2J_{CP}$ = 14.7 Hz), 120.5, 119.7, 119.3, 118.6, 109.6, 104.2 (d, $^2J_{CP}$ = 11.0 Hz), 93.4 (d, $^1J_{CP}$ = 215 Hz), 53.2, 51.8, 51.7, 29.1, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{20}N_3O_5P$ 366.1213, found 366.1216.



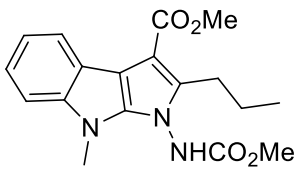
2h

Ethyl 2,8-dimethyl-1-ureido-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2h): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether to afford compound **2h** in 85% yield (53.2 mg) as a grey solid; 36 h; mp: 240–242 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.55 (br, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.55 (br, 2H), 4.35 (q, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 2.48 (s, 3H), 1.41 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.8, 157.6, 139.6, 137.3, 137.0, 120.3, 120.2, 119.6, 118.9, 109.3, 102.4, 101.9, 59.1, 29.0, 14.7, 10.4. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{18}N_4O_3$ 315.1452, found 315.1454.



2i

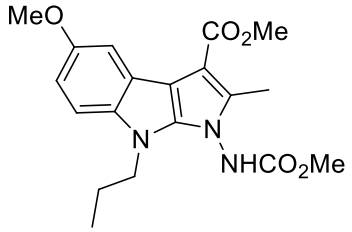
Methyl 2-ethyl-1-((methoxycarbonyl)amino)-8-methyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2i): compound **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 80% yield (52.6 mg) as a pale yellow solid; 4 h; mp: 188–190 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.10 (br, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.19–7.15 (m, 1H), 7.12–7.08 (m, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.06–2.97 (m, 1H), 2.87–2.78 (m, 1H), 1.14 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.8, 156.4, 142.3, 139.8, 136.2, 120.6, 120.1, 119.7, 119.1, 109.4, 102.7, 101.3, 53.2, 50.8, 29.0, 17.5, 14.0. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4$ 330.1448, found 330.1441.



2j

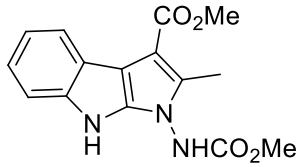
Methyl 1-((methoxycarbonyl)amino)-8-methyl-2-propyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2j): compound **2j** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 85% yield (58.7 mg) as a pale yellow solid; 12 h; mp: 122–124 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.07 (br, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.19–7.15 (m, 1H), 7.12–7.08 (m, 1H), 3.90

(s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.04–2.97 (m, 1H), 2.83–2.76 (m, 1H), 1.65–1.50 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.9, 156.3, 140.8, 139.8, 136.3, 120.6, 120.1, 119.7, 119.1, 109.4, 102.7, 101.9, 53.2, 50.8, 29.0, 25.9, 22.4, 13.7. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{18}H_{21}N_3O_4$ 344.1605, found 344.1609.



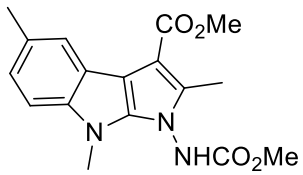
2k

Methyl 5-methoxy-1-((methoxycarbonyl)amino)-2-methyl-8-propyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate: (2l) compound **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 99% yield (73.9 mg) as a whitish solid; 6 h; mp: 186–188 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.02 (br, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.23–4.04 (m, 2H), 3.89 (s, 3H), 3.79 (s, 6H), 2.46 (s, 3H), 1.75–1.58 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.0, 156.1, 153.3, 136.6, 136.4, 134.3, 120.5, 110.3, 109.0, 103.1, 102.8, 102.1, 55.3, 53.1, 50.8, 44.3, 23.1, 11.1, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{19}H_{23}N_3O_5$ 374.1710, found 374.1715.



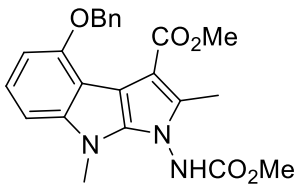
2l

Methyl 1-((methoxycarbonyl)amino)-2-methyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2h): compound **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 55:45) in 52% yield (31.1 mg) as a white solid; 12 h; for compound **2l**, a spontaneous ring enlargement reaction to azacarboline **5a** was observed, for which the chemical-physycal data are in agreement with those reported;[169] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.50 (br, 1H), 10.88 (br, 1H), 7.90–7.88 (m, 1H), 7.34–7.32 (m, 1H), 7.10–7.02 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.2, 155.7, 138.6, 137.3, 135.6, 120.9, 120.3, 119.5, 118.8, 111.7, 102.4, 102.0, 52.9, 50.7, 10.3. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{15}H_{15}N_3O_4$ 302.1135, found 302.1131.



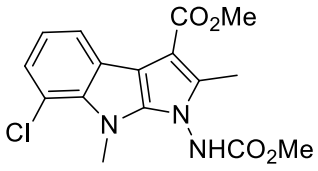
2m

Methyl 1-((methoxycarbonyl)amino)-2,5,8-trimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2o): compound **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 93% yield (61.4 mg) as a pale brown solid; 5 h; mp: 201–203 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.00 (br, 1H), 7.72 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 2.47 (s, 3H), 2.42 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.1, 156.2, 138.2, 136.5, 136.2, 127.6, 121.8, 120.2, 119.7, 109.1, 102.4, 102.1, 53.2, 50.8, 29.1, 21.3, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4$ 330.1448, found 330.1449.



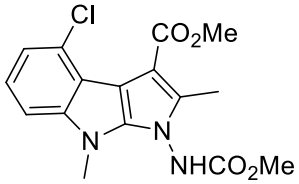
2n

Methyl 4-(benzyloxy)-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2p): after the extraction of the reaction mixture, the residue was recrystallized from ethyl acetate/diethyl ether to afford compound **2p** in 96% yield (80.7 mg) as a whitish solid; 48 h; mp: 150–152 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.98 (br, 1H), 7.49–7.47 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.27 (m, 1H), 7.05–7.02 (m, 2H), 6.67–6.65 (m, 1H), 5.25 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.38 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.8, 156.3, 151.6, 140.9, 138.0, 135.5, 134.3, 128.3, 127.6, 127.5, 121.3, 110.6, 103.9, 102.7, 100.6, 69.3, 53.2, 50.3, 29.3, 10.1. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{23}H_{23}N_3O_5$ 422.1710, found 422.1708.



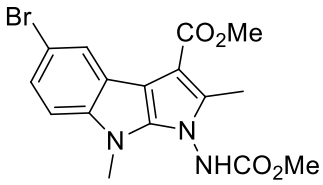
2o

Methyl 7-chloro-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2q): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether/petroleum ether to afford compound **2q** in 97% yield (67.6 mg) as a brownish solid; 24 h; mp: 189–191 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.10 (br, 1H), 7.95 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 4.12 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.8, 156.1, 137.9, 137.1, 134.4, 123.4, 122.5, 120.5, 119.0, 115.6, 102.9, 102.0, 53.3, 50.9, 32.2, 10.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{16}ClN_3O_4$, 350.0902, found 350.0909.



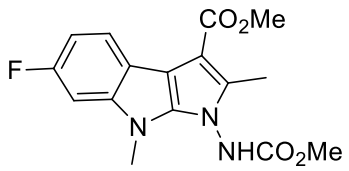
2p

Methyl 4-chloro-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2r): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether/petroleum ether to afford compound **2r** in 99% yield (69.1 mg) as a brownish solid; 2 h; mp: 170–172 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.02 (br, 1H), 7.48–7.43 (m, 1H), 7.16–7.11 (m, 2H), 3.81 (s, 6H), 3.78 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.6, 156.3, 140.5, 137.0, 134.7, 123.7, 121.1, 120.2, 118.4, 108.4, 104.1, 100.0, 53.3, 50.7, 29.4, 10.0. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{16}ClN_3O_4$, 350.0902, found 350.0911.



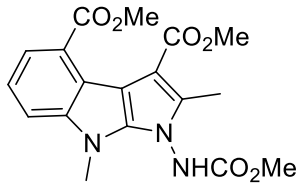
2q

Methyl 5-bromo-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2s): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether to afford compound **2s** in 98% yield (77.3 mg) as a brownish solid; 9 h; mp: 194–196 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.07 (br, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.8, 2.0 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 6H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.8, 156.2, 138.4, 137.3, 137.0, 122.8, 121.7, 121.5, 111.7, 111.5, 102.0, 53.4, 51.1, 29.3, 10.3. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{16}BrN_3O_4$, 394.0397, found 394.0404.



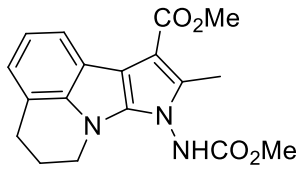
2r

Methyl 6-fluoro-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2t): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether to afford compound **2t** in 98% yield (65.4 mg) as a brownish solid; 8 h; mp: 200–202 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.07 (br, 1H), 7.88 (dd, J = 8.8 Hz, $^4J_{HF}$ = 6.0 Hz, 1H), 7.38 (dd, $^3J_{HF}$ = 10.8 Hz, J = 2.4 Hz, 1H), 6.96–6.91 (m, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.0, 158.3 (d, $^1J_{CF}$ = 232.4 Hz), 156.2, 139.8 (d, $^3J_{CF}$ = 12.2 Hz), 136.3, 120.3 (d, $^3J_{CF}$ = 9.9 Hz), 116.8, 106.7 (d, $^2J_{CF}$ = 23.4 Hz), 102.5, 101.9, 96.8 (d, $^2J_{CF}$ = 26.9 Hz), 59.7, 53.3, 50.9, 29.4, 10.1. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{16}FN_3O_4$, 334.1198, found 334.1201.



2s

Dimethyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3,4-dicarboxylate (2u): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether to afford compound **2u** in 99% yield (74.8 mg) as a whitish solid; 6 h; mp: 210–212 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.04 (br, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.8, 165.4, 156.3, 139.9, 137.8, 135.2, 123.0, 120.4, 119.5, 117.9, 113.0, 104.4, 101.9, 53.3, 51.4, 51.0, 29.2, 10.0. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{18}H_{19}N_3O_6$, 374.1347, found 374.1349.

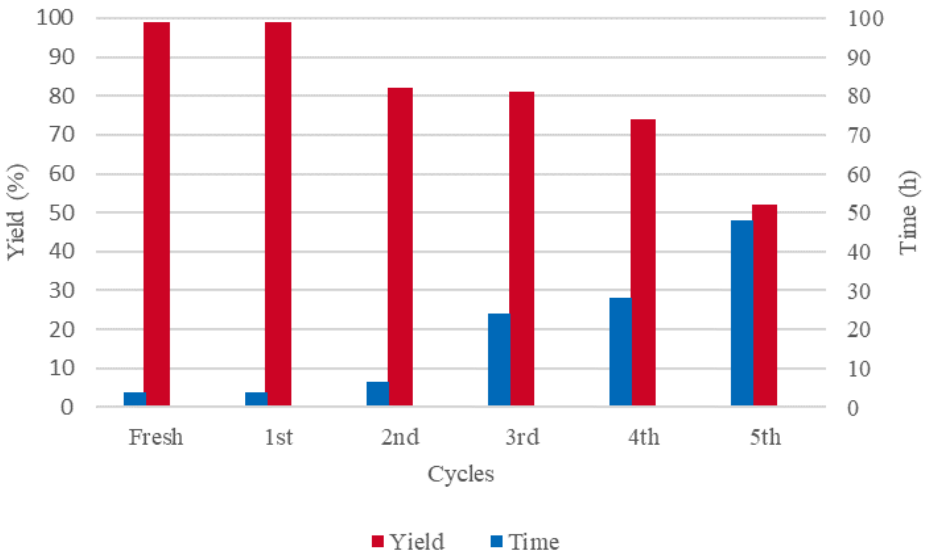


2t

Methyl 8-((methoxycarbonyl)amino)-9-methyl-4,5,6,8-tetrahydropyrrolo[3',2':4,5]pyrrolo[3,2,1-*ij*]quinoline-10-carboxylate (2v): after the extraction of the reaction mixture, the residue was recrystallized from diethyl ether to afford compound **2v** in 97% yield (65.9 mg) as a whitish solid; 4 h; mp: 169–171 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.00 (br, 1H), 7.66 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.32–4.27 (m, 1H), 4.09–4.02 (m, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.93 (t, J = 6.0 Hz, 2H), 2.48 (s, 3H), 2.18–2.13 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.1, 156.2, 135.9, 135.9, 135.6, 121.5, 119.0, 118.4, 118.1, 117.2, 102.6, 102.1, 53.2, 50.8, 41.2, 23.9, 21.9, 10.1. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{18}H_{19}N_3O_4$, 342.1448, found 342.1451.

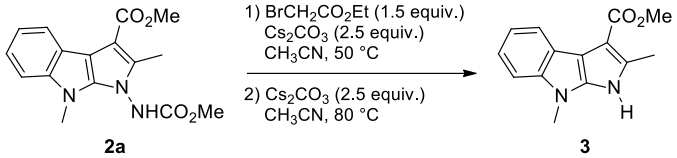
Recycling of the aqueous catalytic system: recycling of $Cu(OAc)_2 \cdot H_2O/FeCl_3 \cdot 6H_2O$, and water in the intramolecular oxidative cyclization of 1a.

In a round-bottom flask, α-indolylhydrazone **1a** (0.4 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.04 mmol, 8.0 mg), $FeCl_3 \cdot 6H_2O$ (0.02 mmol, 5.4 mg) and water (4 mL) were added. The aqueous suspension was stirred at 50 °C (oil bath) until consumption of the starting material (TLC check). At the end, the reaction mixture was extracted with ethyl acetate (3 x 3 mL). The aqueous phase containing the catalyst system was reused for the five runs with the catalyst activities indicated in the table below. On the other hand, the collected organic phase was dried over anhydrous sodium sulphate and the solvent was removed under vacuum. The crude was purified by crystallization (for the first 3 cycles) or by flash chromatography on silica gel (cyclohexane/ethyl acetate 60:40 for the last 2 cycles) to give the corresponding product **2a**.



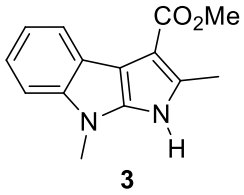
Cycle	Yield (%)	Time (h)
Fresh	99	4
1st	99	4
2nd	82	6.5
3rd	81	24
4th	74	28
5th	52	48

Access to compound 3



2a **3**

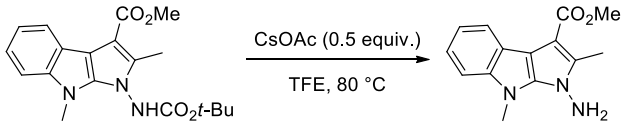
Compound **3** was prepared according to literature.[188] To a solution of **2a** (63.1 mg, 0.2 mmol) in acetonitrile (5 mL), ethyl bromoacetate (0.033 mL, 0.3 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) were added. The mixture was stirred at 50 °C (oil bath) until the disappearance of the starting material (0.5 h). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was dissolved in acetonitrile (5 mL) and Cs_2CO_3 (162.9 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C until TLC showed complete consumption of the intermediate (1 h). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 x 10 mL). The collected organic phase was washed with brine, dried over Na_2SO_4 and the solvent was removed under vacuum, the residue was purified by column chromatography (ethyl acetate) to afford compound **3** as a red solid (16.5 mg, 34% yield).



3

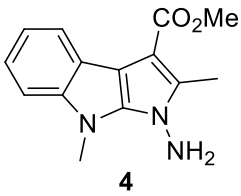
Methyl 2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (3): mp 88–90 °C (dec.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.95 (br, 1H), 7.82 (d, *J* = 6.8 Hz, 1H), 7.37–7.30 (m, 3H), 4.02 (s, 3H), 3.71 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.8, 169.5, 165.7, 144.8, 135.7, 124.2, 123.8, 123.8, 120.3, 110.4, 101.5, 53.0, 32.9, 24.4. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{14}H_{14}N_2O_2$, 243.1128, found 234.1121.

Access to compound 4



2c **4**

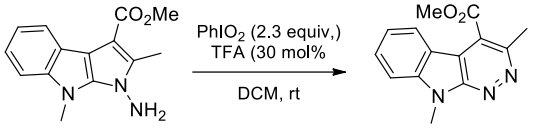
Compound **4** was prepared according to a literature procedure.[193] To a solution of **2c** (357.4 mg, 1.0 mmol) in trifluoroethanol (2 mL), CsOAc (96.0 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C (oil bath) for 24 hours. Upon the completion of the reaction (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane 30:70) to afford compound **4** as a red solid (120.2 mg, 47% yield b.r.s.m.).



4

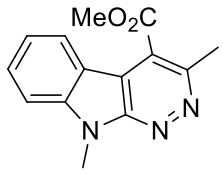
Methyl 1-amino-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (4): mp 228–230 °C; **^{1}H NMR** (400 MHz, **DMSO-*d*$_6$**) δ 7.91–7.88 (m, 1H), 7.40–7.37 (m, 1H), 7.13–7.03 (m, 2H), 6.04 (s, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 2.63 (s, 3H). **^{13}C NMR** (100 MHz, **DMSO-*d*$_6$**) δ 165.4, 139.9, 137.5, 137.3, 120.3, 119.9, 119.4, 118.6, 109.1, 102.2, 99.8, 50.5, 29.6, 10.6. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{14}H_{15}N_3O_2$, 258.1237, found 258.1243.

Access to compound 5b



4 **5b**

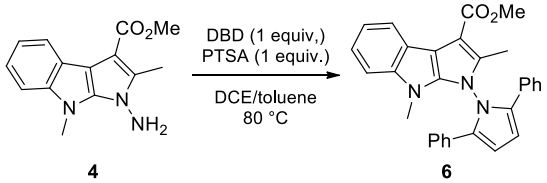
To a solution of compound **4** (48.6 mg, 0.2 mmol) in dichloromethane, $PhIO_2$ (108.6 mg, 0.46 mmol) and trifluoroacetic acid (0.05 mL, 0.06 mmol) were added. The solution was stirred at room temperature for 0.5 hours. After completion of the reaction (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane 50:50) to afford compound **5b** in as a yellow solid (27.6 mg, 54% yield).[169]



5b

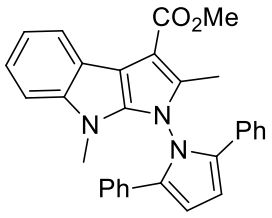
Methyl 3,9-dimethyl-9H-pyridazino[3,4-*b*]indole-4-carboxylate (5b): The chemical-physical data of compound **5b** are in agreement with those reported.[169]

Access to compound 6



4 **6**

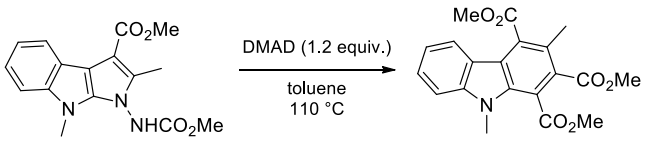
Compound **6** was prepared according to a literature procedure.[194] To a solution of compound **4** (48.6 mg, 0.2 mmol) in dichloroethane/toluene 1:1 (2 mL), 1,4-diphenylbutane-1,4-dione (47.7 mg, 0.2 mmol) and *p*-toluenesulfonic acid (34.4 mg, 0.2 mmol) were added. The solution was heated at 80 °C for 48 hours. After the disappearance of the starting material (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane/dichloromethane 20:80:10) to afford compound as a colorless oil (37.7 mg, 41%).



6

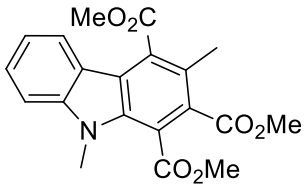
Methyl 1-(2,5-diphenyl-1H-pyrrol-1-yl)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-b]indole-3-carboxylate (6): **^{1}H NMR** (400 MHz, **DMSO-*d*$_6$**) δ 7.97–7.95 (m, 1H), 7.83–7.81 (m, 1H), 7.47–7.43 (m, 1H), 7.38–7.36 (m, 1H), 7.25–7.15 (m, 7H), 7.05–7.03 (m, 3H), 6.87 (s, 2H), 3.90 (s, 3H), 3.29 (s, 3H), 2.23 (s, 3H). **^{13}C NMR** (100 MHz, **DMSO-*d*$_6$**) δ 164.7, 152.6, 139.9, 135.2, 135.0, 130.1, 129.8, 129.0, 128.9, 127.7, 127.5, 126.1, 123.4, 121.1, 120.1, 119.9, 119.6, 109.9, 109.2, 108.2, 103.5, 102.9, 51.1, 28.5, 10.3. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{30}H_{25}N_3O_2$, 460.2020, found 460.2013.

Access to compound 7



2a 7

Compound **7** was prepared according to a literature procedure.[191] To a solution of **2a** (94.6 mg, 0.3 mmol) in toluene (1 mL), dimethyl acetylenedicarboxylate (DMAD) (0.049 mL, 0.36 mmol) was added and the reaction mixture was refluxed for 12 hours. After the disappearance of the starting material (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane 40:60) to afford compound **7** as a red oil (64.3 mg, 58% yield).



7

Trimethyl 3,9-dimethyl-9H-carbazole-1,2,4-tricarboxylate (7): **^{1}H NMR** (400 MHz, **DMSO-*d*$_6$**) δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.63–7.58 (m, 1H), 7.32–7.28 (m, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.75 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, **DMSO-*d*$_6$**) δ 168.5, 167.8, 166.8, 142.8, 134.7, 129.9, 129.0, 128.0, 121.7, 121.0, 120.8, 120.5, 118.6, 116.3, 110.3, 53.2 53.1, 52.8, 31.7, 16.2. **HRMS** (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{19}NO_6$, 370.1285, found 370.1279.

CHAPTER 4

A C–H Amination-Based Strategy for N-Amino Indole Synthesis

4.1 Introduction

The field of C–H activation is of pivotal interest in organic chemistry since it allows straightforward transformations of compounds. Direct functionalization of unsubstituted starting materials is an efficient and valuable strategy when compared to traditional methods, which usually rely on the use of preactivated substrates. Thus, thanks to this approach, the number of steps in synthetic pathways can be reduced, making them more attractive for both industrial and academic purposes. The C–H functionalization is particularly interesting within the field of heterocycles synthesis, in which substrates are coupled with heteroatom-containing molecules. A great variety of inter- and intramolecular methods for the formation of carbon-nitrogen bonds are known, and many *N*-heterocycles of pharmaceutical interest can be prepared. Among them, 1-aminoindoles represent a precious scaffold for biologically active compounds, including neuroprotective agents (e.g., antiparkinson, anticonvulsivant),[195,196] antioxidants,[197] compounds with cholinergic and adrenergic activities for the treatment of Alzheimer's disease,[198] anti-HIV,[199] and CB_1 receptor modulators.[200] Furthermore, 1-aminoindoles and 1-aminoindolines are useful building blocks, as they allow the access to more complex compounds.[190,201–206]

Several approaches for the synthesis of 1-aminoindoles are known. Traditional methods are represented by the direct *N*-amination of the indole core. For instance, a common strategy is the generation of NH_2^+ species which can react with indole anions, formed in the presence of a base. In this context, reagents such as monochloramine ($NHCl_2$) or hydroxylamine-*O*-sulfonic acid (HOSA) can be useful tools.[207] Alternatively, non-cyclic precursors bearing N–N portions can be exploited for the construction of the 1-aminoindole ring. Several procedures involve rhodium-catalyzed intermolecular annulation of hydrazines with alkynes,[51,208] maleimides[209] and diazo compounds.[210] Diazo compounds have been also coupled with hydrazones by Shi and colleagues, by means of Rh^{III} catalysis.[189] In addition to this, organocatalytic protocols that do not rely on expensive catalysts such as rhodium-based ones are also known. This includes a reaction developed by Li's group, in which a cheap, metal-free catalytic system promotes the [3 + 2] annulation between azonaphtalenes and aldehydes or ketones.[211] Along with the intermolecular strategy, access to 1-aminoindoles is also possible in intramolecular fashions. For example, $Pd(dba)_2$ catalyzes the intramolecular cyclization of hydrazines derived from *o*-chloro-arylacetaldehydes.[212] In another work, aryl ene-hydrazines, functionalized with a bromine in the ortho position, undergo cyclization under Cu^I catalysis.[213] Copper was also the catalyst employed by Hasegawa and colleagues. In their work, aryl iodides bearing a diazopropanoate portion are the starting materials for divergent synthesis of 1-aminoindolines and cinnolines.[214] Electrochemical intramolecular cyclization approaches are also known.[215]

The aforementioned methods, despite being highly efficient, are mainly developed on preactivated substrates (usually halides), and this represent their main limitation, along with the high costs of certain metal-based catalysts (Rh and Pd are the most common). To our knowledge, the literature reports only two examples of direct intramolecular C–H activation/C–N bond formation on α-arylhydrazones (figure 1). In Xiao's and Xu's work, copper was used as catalyst for a six-membered ring annulation to cinnolines.[216] In Zhang-Negrerie's and Du's work, a high excess of $FeBr_3$ (2.5 equiv.) was required for the formation of indole products.[165]

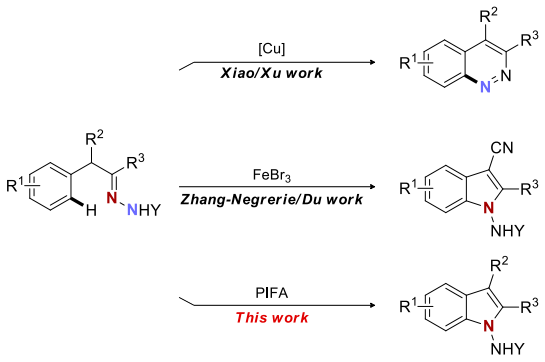


Figure 1

Following our interest in the synthesis of indole derivatives *via* green and sustainable direct C–H functionalization strategies (see chapters 2 and 3),[169,217] we envisioned the opportunity to employ easily available α-arylhydrazones as non-preactivated substrates for a metal-free direct intramolecular C–N bond formation.

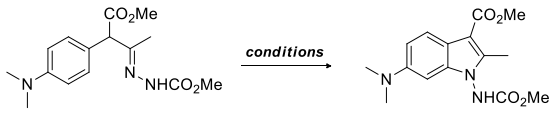
Here, we report a metal-free, bis(trifluoroacetoxy)iodobenzene (PIFA)-promoted method for a highly chemoselective, regioselective and atom economical C–H amination of hydrazones. The use of hypervalent iodine (III) reagents represents a valuable, safe, and sustainable alternative to metal-promoted transformations. The α-arylhydrazones substrates, bearing a *p*-*N*,*N*-dialkylamino substituent, can be readily synthesized by means of a Michael-type addition of anilines to azoalkenes, with $ZnCl_2$ as catalyst.[218] The presence of *N*,*N*-dialkylamino group is essential to ensure the success of these transformation. This behavior may be explained by a mechanism in which the electron pair on the *p*-amino group contributes to a dearomative step, followed by a subsequent migration that re-establish the aromaticity of the system. Moreover, consistent with a broad number of other hypervalent iodine chemistry works,[219–221] here the use of a fluorinated solvent was of benefit to the reaction efficiency.

4.2 Results and discussion

The α-anilinyl-hydrazone **1a** was selected as the model substrate for the intramolecular C–H amination. At first, a pre-optimization was conducted using transition metals as catalysts or promoters for this reaction. Palladium acetate was employed in combination with several oxidants such as silver acetate, PIDA, copper acetate and $PhIO_2$ (table **1**, entries 1–4), and the best result was obtained with the use of $PhIO_2$, which led to a 46% yield. Next, a combination of catalytic $Cu(OAc)_2{\cdot}H_2O$ and $FeCl_3{\cdot}6H_2O$ was tested,[217] and a low yield (15%) was observed as well (entry 5). $CuBr_2$ combined with $K_2S_2O_8$ as the terminal oxidant was then used, but also in this case the product was obtained in poor yield (entry 6). When superstoichiometric (2.5 equiv.) $FeCl_3$ was used,[165] a substantial improvement was observed, although the yield of **2a** still remained quite modest (45%, entry 7). Next, several hypervalent iodine reagents of different nature were examined. Considering the encouraging result reported in entry 4, we first conducted the reaction using the combination of $PhIO_2$ with TFA, that is, the same conditions reported in our previous work.[169] The cyclized product **2a** was recovered, albeit the yield remained low (entry 8). On the other hand, when the reaction was performed in the absence of TFA and heating at 60 °C in DCE, the desired product yield was significantly increased (63%, entry

9), despite the complete consumption of the starting material required 48 hours. In this case, a six-membered ring formation also occurred, affording a cinnoline byproduct in 7% yield.[222] Although an increase in temperature to 120 °C using DMF as the solvent revealed a complete consumption of **1a**, the desired product was isolated in only 34% yield (entry 10). Switching to other solvents, including CH_3NO_2 and HFIP, did not allow to achieve better results (entries 11, 12). The addition of a base (*t*-BuOK, entry 13) (K_2CO_3, entry 14), a Brønsted acid (pivalic acid, entry 15) or a Lewis acid (anhydrous $FeCl_3$, entry 16) were ineffective as well. Next, the focus of the screening switched to trivalent iodine species, rather than iodine (V). First, a reaction with PIDA (1.5 equiv.) in DCM was carried out, but a complex mixture of byproducts was detected on TLC (entry 17). A slight improvement was observed when, with PIDA, a catalytic amount of $CuBr_2$ was added (entry 18), albeit only 26% of product **2a** was isolated. The addition of 30 mol% of TFA was not of benefit (entry 19) as well. Using a DCM/TFE (1:1) co-solvent system for PIDA in the absence of any additive allowed for the best yield of this series, which however remained low (28%, entry 20). An attempt for the *in situ* generation of a hypervalent iodine species was conducted, using a catalytic amount of PhI and an excess of *m*-CPBA as the oxidant,[75] but the desired product was formed in traces (entry 21). Koser's reagent proved to be superior if compared to PIDA, but still unsatisfactory yields were obtained (entries 22–25). Better results were achieved using the hypervalent iodine reagent PIFA. With this compound, initial experiments led to encouraging results (entries 26–29), and the best yield was obtained when a mixture of DCM and TFE (1:1) was used as the solvent (76%, entry 30). Attempts to further improve the yield by adding $BF_3{\cdot}OEt_2$ (entry 33)[223] or lowering temperatures (entries 31, 32) were not successful.

Thus, the optimized reaction conditions were identified as follows: PIFA (1.3 equiv.), DCM/TFE 1:1 (0.1 M), room temperature. In a typical procedure, the substrate is dissolved in DCM. Then, under stirring, a solution of PIFA in TFE is slowly added dropwise with a syringe. It should be noted that a work-up with sat. $NaHCO_3$ is necessary, not only before the purification but also to monitor the reaction on TLC, probably because of the formation of a quaternary ammonium salt due to the generation of trifluoroacetic acid from PIFA.



1a **2a**

Entry[a]	Promoter/cat. (equiv.)	Additive/co-cat. (equiv.)	Solvent	T (°C)	Yield (%)[b]
1	$Pd(OAc)_2$ (0.1)	AgOAc (1.5)	DCM	rt	16
2	$Pd(OAc)_2$ (0.1)	$Cu(OAc)_2{\cdot}H_2O$ (2), PivOH (0.2)	DCE	50	28
3	$Pd(OAc)_2$ (0.1)	PIDA (1.5)	DCM	rt	traces
4	$Pd(OAc)_2$ (0.1)	$PhIO_2$ (1.5)	DCE	80	46
5	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	$FeCl_3{\cdot}6H_2O$ (0.1)	DCM	rt	15
6	$CuBr_2$ (0.1)	$K_2S_2O_8$ (5)	DCE	rt	10
7	$FeCl_3$ anhyd. (2.5)	—	DCM	rt	45
8	$PhIO_2$ (1.5)	TFA (1)	DCM	rt	18
9	$PhIO_2$ (2.3)	—	DCE	60	63[c]
10	$PhIO_2$ (2.3)	—	DMF	120	34
11	$PhIO_2$ (2.3)	—	CH_3NO_2	60	29

Entry[a]	Promoter/cat. (equiv.)	Additive/co-cat. (equiv.)	Solvent	T (°C)	Yield (%)[b]
12	$PhIO_2$ (2.3)	—	HFIP	rt, then 60	9
13	$PhIO_2$ (2)	*t*-BuOK	DCE	60	13
14	$PhIO_2$ (2.3)	K_2CO_3	DCE	60	traces
15	$PhIO_2$ (1.6)	PivOH (0.2)	DCE	rt	traces
16	$PhIO_2$ (1.5)	$FeCl_3$ anhyd. (0.1)	DCM	rt	traces
17	PIDA (1.5)	—	DCM	rt	traces
18	PIDA (1.5)	$CuBr_2$ (0.1)	DCM	rt	26
19	PIDA (1.5)	TFA (0.3)	DCM	rt	traces
20	PIDA (1.3)	—	DCM/TFE (1:1)	0	28
21	PhI (0.2)	*m*-CPBA (2.5)	MeOH	rt	traces
22	Koser (1 + 0.5)	—	DCM	rt	50
23	Koser (2)	—	DCM	rt	45
24	Koser (1.5 + 0.5)	K_2CO_3 (1 + 0.5)	DCM	rt	27
25	Koser (1.5 + 0.5)	DIPEA (1)	DCE	rt, then 60	14
26	PIFA (1.3)	—	DCM	rt	46
27	PIFA (1.3)	—	TFE	rt	57
28	PIFA (1.3)	—	HFIP	rt	67
29	PIFA (1.3)	—	DCM/HFIP (1:1)	0	56
30	**PIFA (1.3)**	**—**	**DCM/TFE (1:1)**	**rt**	**76**
31	PIFA (1.3)	—	DCM/TFE (1:1)	0	66
32	PIFA (1.3)	—	DCM/TFE (1:1)	-20	47
33	PIFA (1.3)	$BF_3{\cdot}OEt_2$ (1)	DCM/TFE (1:1)	rt	73

Table 1. Screening of the reaction conditions – [a] All reactions were performed on 0.2 mmol scale of **1a** in 2 mL of solvent (0.1 M). [b] All yields refer to the isolated product after column chromatography. [c] 7% of cinnoline product was formed.[222] DCM = dichloromethane; PIDA = (diacetoxyiodo)benzene; PivOH = pivalic acid; DCE = 1,2-dichloroethane; TFA = trifluoracetic acid; DMF = *N*,*N*-dimethylformamide; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFE = 2,2,2-trifluoroethanol; *m*-CPBA = 3-chloroperbenzoic acid; Koser (Koser's reagent) = hydroxy(tosyloxy)iodo benzene; DIPEA = N,N-diisopropylethylamine; PIFA = bis(trifluoroacetoxy)iodobenzene.

Next, the substrate scope for the synthesis of 1-aminoindoles *via* the PIFA-promoted intramolecular C–H amination of α-aryl-hydrazones was explored (table **2**). Different substituents were accommodated at the ester (R^4) and carbamate (R^5) portion. The synthesized products, including combinations of methyl, ethyl, isopropyl, allyl, *t*-butyl and benzyl groups (**2a-i**) were easily obtained in moderate to good yield (54–83%). Also, a scale-up reaction (953.2 mg, 2.728 mmol) was successfully carried out, with the Boc-derivative **2f** obtained in 74% yield. A considerable drop in terms of yield was observed for the product **2j**, which brings an ureido function (38%). At the indole C-2 position, an ethyl (**2k**, 46%) and a propyl (**2l**, 71%) were inserted. As regards the aniline portion, a *N*,*N*-diethyl group was well tolerated (**2m**, 79%), while a *N*-methyl-*N*-propargyl substituent led to diminished yield for product (**2n**, 40%). Tethering the aniline nitrogen to the aromatic ring allowed to synthesize two tricyclic indoles (**2o,q**) and a tetracyclic derivative (**2p**) in good yields. While the presence of an additional benzene ring lowered the yield to 45% (**2s**), a methyl ester group on the *o*-position gave product **2r** in 82% yield, suggesting that a poor electronic density on the aromatic system might be beneficial. Unfortunately, other attempts to confirm this hypothesis failed because of a lack of reactivity of electron-poor anilines in the Michael-type addition to azoalkenes. However, at the time this PhD thesis was written, this work was not submitted to any journal. Therefore, the final manuscript may include additional examples. It is

noteworthy that compounds **2o**, **2q** and **2r** were obtained with high regioselectivity, and no isomer was detected for each of these products.

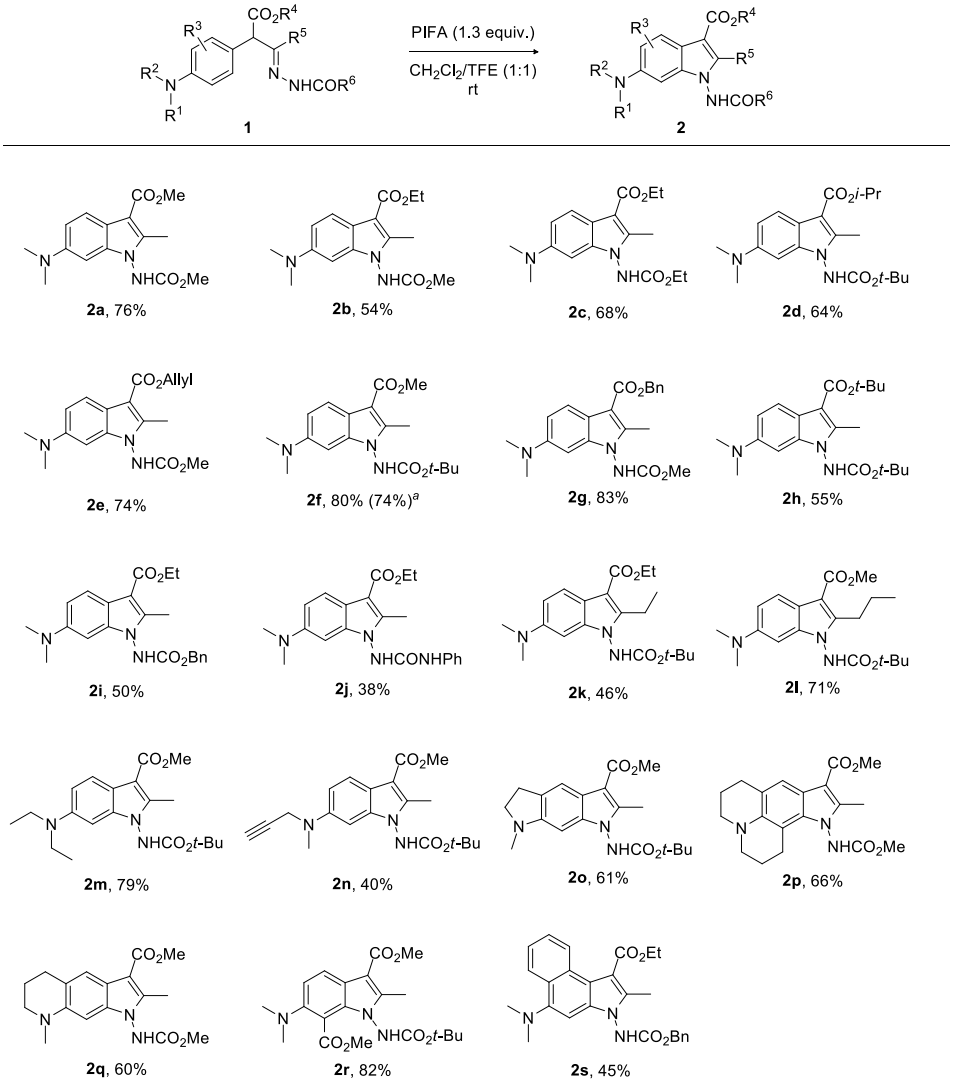
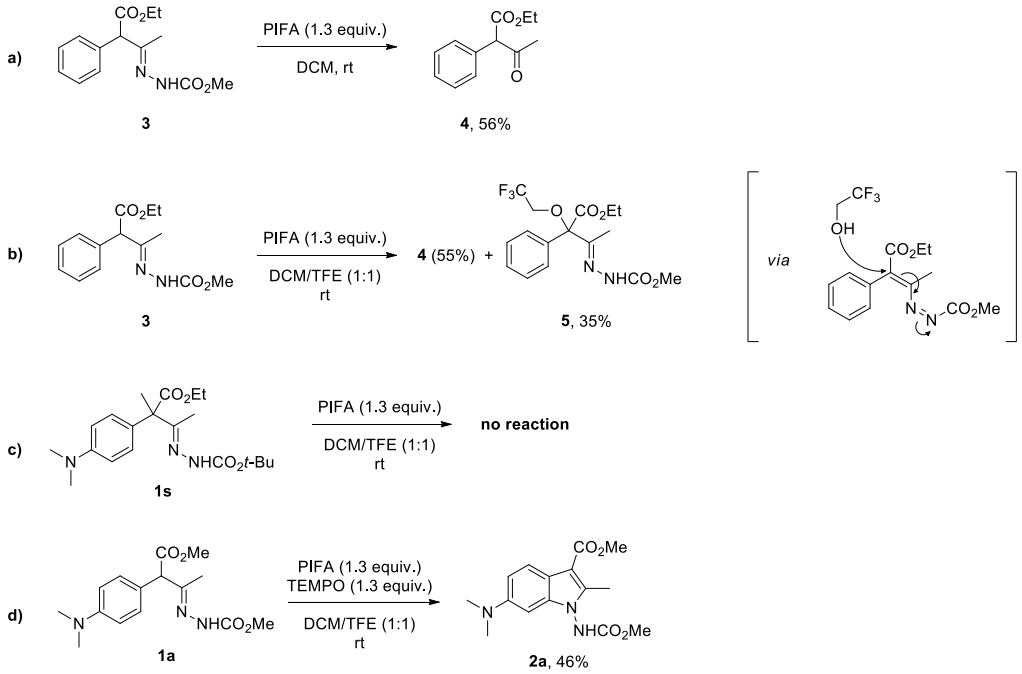


Table 2. Substrate scope for the PIFA-mediated intramolecular C–H amination – [a] Value in brackets denotes the yield for the scale-up process (953.2 mg, 2.728 mmol).

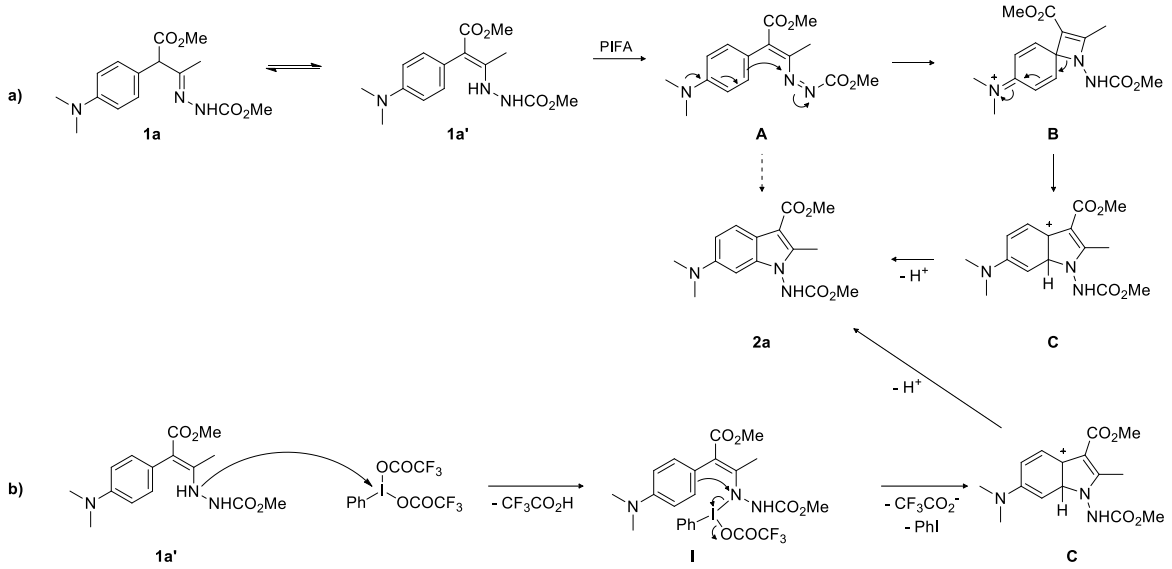
To gain mechanistical information on the intramolecular C–H amination promoted by PIFA, several experiments were conducted. First, compound **3**, in which the *N*,*N*-dialkyl group is absent, was treated with PIFA in DCM. The formation of hydrolyzed compound **4** as the main product (56% yield, scheme **1a**) was observed, along with traces of other unidentified byproducts and polar products that could not be isolated by flash chromatography. This result clearly indicates that the presence of the *N*,*N*-dialkyl moiety is fundamental for the reaction to proceed. The reaction was also carried out in DCM/TFE solvent mixture, according to the optimized conditions. In this case product **5**, in which the substrate underwent attack by 2,2,2,-trifluoroethanol on the α-position, was isolated along with product **4** (scheme **1b**). This behavior may be explained by the formation of an azoalkene intermediate, by means of a hypervalent iodine-promoted oxidation.[224,225] The

formation of such an intermediate is also supported by the fact that, usually, PIFA-mediated cyclizations reaction mixtures acquire an intensive red colouring (the typical colour of azoalkenes) during the addition of the iodine reagent. TLC analysis usually show a yellow/orange spot as well, however attempts to isolate and characterize it always failed, probably because of the instability of these intermediates. Thus, it is reasonable to suggest that the intramolecular C–H amination may proceed through oxidation of substrates **1** to conjugated azo compounds. Moreover, when the conditions were applied to compound **1s**, in which the acidic proton is substituted with a methyl, no reaction occurred (scheme **1c**). An additional control experiment was carried out on **1a** with the optimized conditions and the addition of TEMPO. The intramolecular amination was not inhibited, and product **2a** was isolated in 46% yield (scheme **1d**), indicating that a radical mechanism[226] can be excluded.



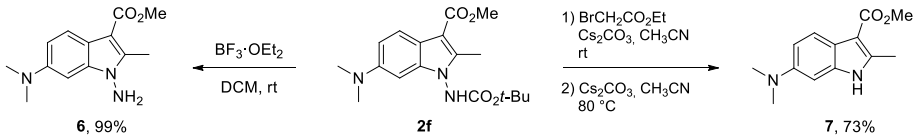
Scheme 1. Control experiments

Based on these observations, two possible mechanisms are depicted (scheme **2**). Initially, the starting material **1a** is subjected to CH-NH tautomerism. As shown in scheme **2a**, the ene-hydrazine form **1a′** is oxidized to azo compound **A**. This intermediate, thanks to the electronic contribution from the *N*,*N*-dialkyl moiety, leads to a dearomatizative spirocyclization forming intermediate **B**. The migration of the C–N bond brings to intermediate **C** which, after the loss of a proton, restores aromaticity affording the final product **2a**.[227–229] Considering the literature reports,[122,124,230] and taking into account the fact that non-hypervalent iodine based oxidants do not perform well for this C–H amination, an alternative/competing mechanism is also shown (scheme **2b**). The ene-hydrazine **1a′** attacks the electrophilic iodine center of PIFA, and trifluoroacetic acid is eliminated. The nitrogen in intermediate **I** is activated, and this allows the cyclization step through the new C–N bond formation, affording intermediate **C** with concomitant loss of a trifluroacetate anion and iodobenzene. Finally, the abstraction of a proton leads to product **2a**.



Scheme 2. Proposed reaction mechanisms

To demonstrate the synthetic utility of the reported method, compound **2f** was subjected to further transformations (scheme **3**). The Boc group can be easily removed with $BF_3 \cdot OEt_2$, and unprotected 1-aminoindole **6** is obtained in quantitative yield. A reductive N–N bond cleavage to furnish compound **7** can be successfully achieved using a protocol reported by Magnus et al., which consists in a E_{1cb} reaction promoted by ethyl 2-bromoacetate in the presence of cesium carbonate as the base.[188]



Scheme 3. Synthetic transformations of 2f

4.3 Conclusions

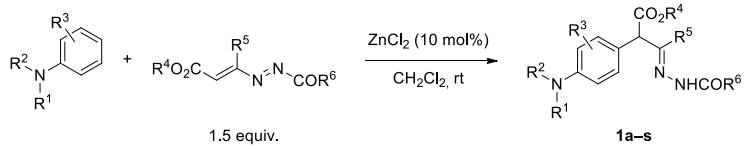
To conclude, we have developed a method for the synthesis of variously substituted 1-aminoindoles *via* an intramolecular C–H activation and oxidative C–N bond formation approach on α-aryl-hydrazones. A cheap and environmentally benign hypervalent iodine (III) reagent such as PIFA, and the presence of a *N*,*N*-dialkyl moiety on the *para* position of the aromatic ring are crucial for this transformation. This requirement may be rationalized by a dearomatizing spyrocyclization mechanism, followed by a ring expansion. The procedure allows the access to compounds that include a scaffold of high pharmaceutical value, with no need for the use of expensive transition-metal catalysts such as rhodium or palladium, which are commonly employed for the preparation of this class of substances.

4.4 Experimental Section

General remarks: All the commercially available reagents and solvents were used without further purification. α-arylhydrazones **1a–s** were prepared according to our previously reported method with slight

modifications.[218] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using DMSO-d_6 or $CDCl_3$ as solvent on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA). Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, qt = quintet, sex = sextet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. High-resolution mass spectroscopy was performed on a Micromass Q-TOF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected.

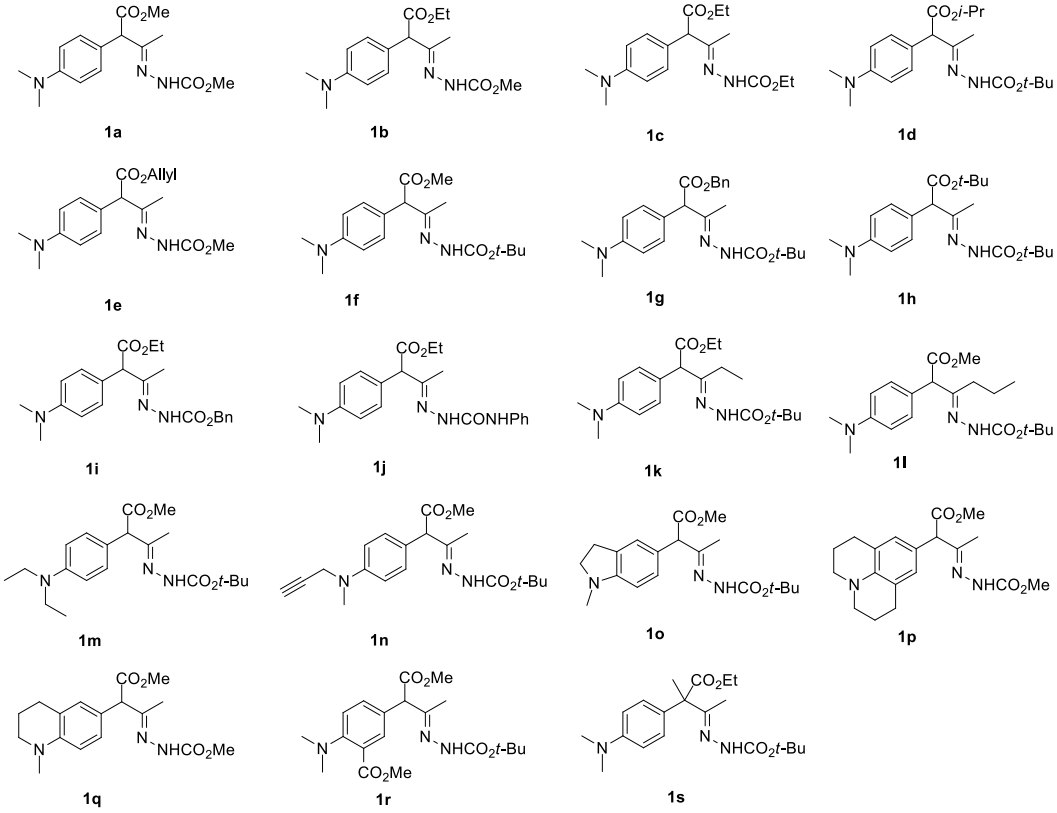
General procedure for the preparation of α-arylhydrazones 1a–s:[218]

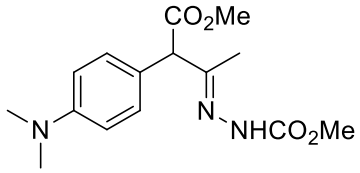


To a stirred mixture of aniline (1.0 mmol) and azoalkene (1.5 mmol, 1.5 equiv) in dichloromethane (4 mL), $ZnCl_2$ (13.6 mg, 0.1 mmol, 10 mol%) was added. After the disappearance of the aniline (TLC check), the solvent was removed and the crude mixture was purified by column chromatography on silica gel to afford, after crystallization, the α-arylhydrazones **1**.

The characterization data of substrates **1b–d,f,h–j,o,p,s** was previously reported.[218]

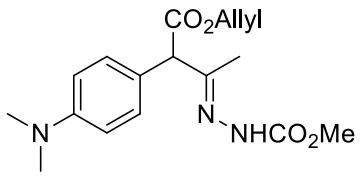
List of substrates 1a–s prepared according to the general procedure.





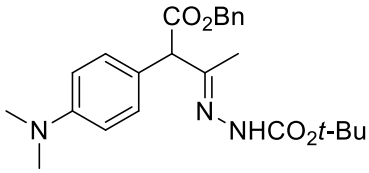
1a

Methyl 2-(3-(4-(dimethylamino)phenyl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1a): compound **1a** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 70% yield (214.7 mg) as a white solid; 2 h; mp: 153–155 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.68 (br, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 4.53 (s, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 2.87 (s, 6H), 1.73 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ 171.3, 154.6, 151.6, 149.7, 129.3, 122.5, 112.3, 58.2, 51.8, 51.8, 40.1, 14.9. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{15}H_{22}N_3O_4$ 308.1605, found 308.1611.



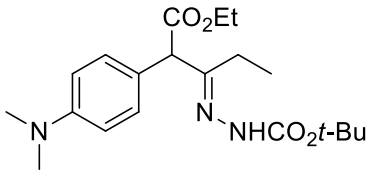
1e

Methyl 2-(4-(allyloxy)-3-(4-(dimethylamino)phenyl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1e): compound **1e** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) as a 70:30 mixture of hydrazone and hydrazine tautomeric forms in 31% yield (103.7 mg) as a white solid; 0.25 h; mp: 92–94 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) (hydrazone form) δ 9.87 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 5.96–5.87 (m, 1H), 5.30–5.25 (m, 1H), 5.20–5.17 (m, 1H), 4.60–4.58 (m, 2H), 4.56 (s, 1H), 3.65 (s, 3H), 2.87 (s, 6H), 1.74 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ 170.4, 154.6, 151.5, 149.7, 132.6, 129.4, 122.5, 117.8, 112.3, 64.9, 58.2, 51.8, 40.1, 15.0. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{17}H_{24}N_3O_4$ 334.1761, found 334.1763.



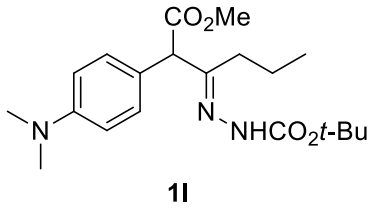
1g

***tert*-butyl 2-(4-(benzyloxy)-3-(4-(dimethylamino)phenyl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1g):** compound **1g** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 93% yield (397.1 mg) as a white solid; 4 h; mp: 123–125 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.55 (br, 1H), 7.38–7.30 (m, 5H), 7.06 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 5.19–5.08 (m, 2H), 4.56 (s, 1H), 2.87 (s, 6H), 1.71 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ 170.7, 153.0 150.8 149.7, 136.1, 129.5, 128.3, 127.9, 127.9, 122.6, 112.2, 79.2, 65.9, 58.4, 40.1, 28.1, 15.1. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{24}H_{32}N_3O_4$ 426.2387, found 426.2384.



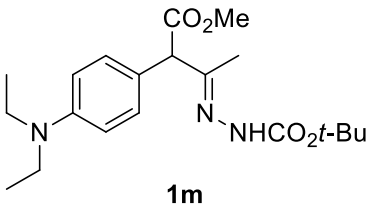
1k

***tert*-butyl 2-(2-(4-(dimethylamino)phenyl)-1-ethoxy-1-oxopentan-3-ylidene)hydrazinecarboxylate (1k):** compound **1k** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 70% yield (262.7 mg) as a white solid; 1.5 h; mp: 84–86 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.59 (br, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 4.48 (s, 1H), 4.12–4.04 (m, 2H), 2.87 (s, 6H), 2.42–2.33 (m, 1H), 2.09–2.00 (m, 1H), 1.44 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H), 0.74 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ 170.8, 154.4, 153.0, 149.7, 129.7, 122.7, 112.1, 79.1, 60.2, 56.8, 40.1, 28.1, 21.3, 14.0, 9.6. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{20}H_{32}N_3O_4$ 378.2387, found 378.2388.



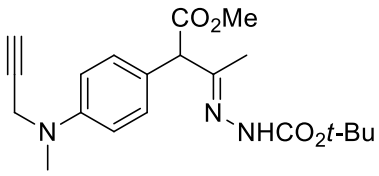
1l

***tert*-butyl 2-(2-(4-(dimethylamino)phenyl)-1-methoxy-1-oxohexan-3-ylidene)hydrazinecarboxylate (1l):** compound **1l** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 78% yield (293.7 mg) as a white solid; 8 h; mp: 64–66 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.67 (br, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 4.50 (s, 1H), 3.59 (s, 3H), 2.87 (s, 6H), 2.41–2.33 (m, 1H), 1.97–1.89 (m, 1H), 1.45 (s, 9H), 0.78 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.3, 153.3, 153.0, 149.7, 129.8, 122.8, 112.1, 79.1, 56.8, 51.7, 40.1, 30.1, 28.1, 18.1, 19.3. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{20}H_{32}N_3O_4$ 378.2387, found 378.2381.



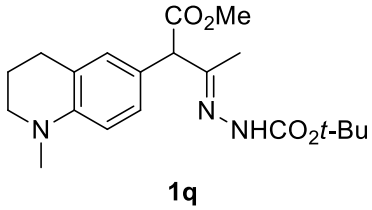
1m

***tert*-butyl 2-(3-(4-(diethylamino)phenyl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1m):** compound **1m** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 82% yield (308.1 mg) as a white solid; 4 h; mp: 94–96 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.52 (br, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 4.46 (s, 1H), 3.62 (s, 3H), 3.30 (q, J = 6.8 Hz, 4H), 1.72 (s, 3H), 1.44 (s, 9H), 1.07 (t, J = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.3, 153.0, 150.9, 146.7, 129.6, 121.3, 111.3, 79.1, 58.3, 51.7, 43.6, 28.1, 15.0, 12.4. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{20}H_{32}N_3O_4$ 378.2387, found 378.2389.



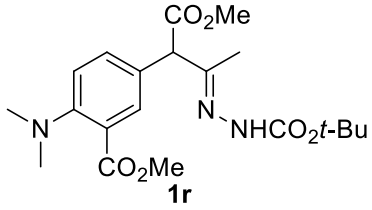
1n

***tert*-butyl 2-(4-methoxy-3-(4-(methyl(prop-2-yn-1-yl)amino)phenyl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1n):** compound **1n** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 31% yield (114.8 mg) as a white solid; 12 h; mp: 93–95 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.53 (br, 1H), 7.08 (d, J = 8.8 Hz, 2H), 6.80 (d J = 8.8 Hz, 2H), 4.53 (s, 1H), 4.11(d, J = 2.4 Hz, 2H), 3.63 (s, 3H), 3.06 (t, J = 2.4 Hz, 1H), 2.87 (s, 3H), 1.72 (s, 3H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.2, 153.0, 148.1, 129.4, 124.1, 113.7, 113.4, 80.0, 79.1, 74.4, 58.3, 51.8, 41.3, 38.0, 28.1, 15.1. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{20}H_{28}N_3O_4$ 374.2074, found 374.2071.



1q

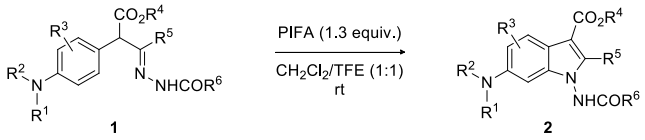
***tert*-butyl 2-(4-methoxy-3-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1q):** compound **1q** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 76% yield (283.1 mg) as a white solid; 0.75 h; mp: 119–121 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.50 (br, 1H), 6.84 (dd, J1 = 8.4 Hz, J2 = 2.0 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 4.42 (s, 1H), 3.61 (s, 3H), 3.16 (t, 5.6 Hz, 2H), 2.80 (s, 3H), 2.66 (t, J = 2.0 Hz, 2H), 1.89–1.83 (m, 2H), 1.71 (s, 3H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.3, 153.0, 150.9, 145.9, 128.9, 127.2, 122.3, 122.2, 110.7, 79.1, 58.4, 51.7, 50.5, 38.7, 28.1, 27.2, 21.8, 15.0. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_4$ 376.2231, found 376.2230.



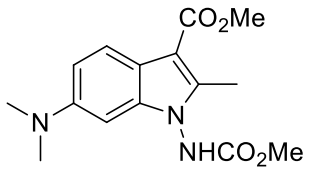
1r

***tert*-butyl 2-(3-(4-(dimethylamino)-3-(methoxycarbonyl)phenyl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate (1r):** compound **1r** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 25% yield (101.5 mg) as a white solid; 4 days; mp: 150–152 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.58 (br, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.26 (dd, J1 = 8.8 Hz, J2 = 2.0 Hz, 1H), 4.62 (s, 1H), 3.90 (s, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 2.76 (s, 6H), 1.73 (s, 3H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.8, 168.3, 152.9, 150.6, 132.6, 131.3. 124.7, 119.8, 116.4, 79.2, 64.9, 57.9, 51.9, 42.8, 28.1, 15.3. HRMS (ESI-Orbitrap, m/z) $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_6$ 408.2129, found 408.2125.

General procedure for the PIFA-promoted intramolecular C(sp^2)–H amination

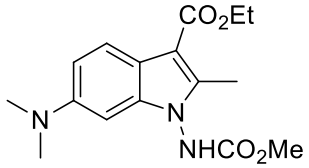


To a solution of α-arylhydrazone **1** (0.2 mmol) in CH_2Cl_2 (1 mL), a solution of PIFA (0.26 mmol, 111.8 mg) in TFE (1 mL) was added dropwise with a syringe. The mixture was stirred at room temperature until consumption of the starting material (TLC check). Then, saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (3 x 10 mL).



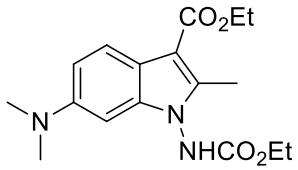
2a

Methyl 6-(dimethylamino)-1-((methoxycarbonyl)amino)-2-methyl-1*H*-indole-3-carboxylate (2a): compound **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (46.2 mg) as a white solid; 3 h; mp: 130–132 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.75 (br, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 6.79 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.91 (s, 6H), 2.51 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.3, 155.9, 147.9, 143.1, 137.1, 121.1, 114.9, 110.3, 101.6, 91.6, 52.9, 50.7, 40.9, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{15}H_{20}N_3O_4$ 306.1448, found 306.1454.



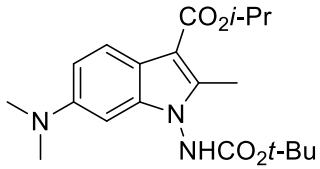
2b

Ethyl 6-(dimethylamino)-1-((methoxycarbonyl)amino)-2-methyl-1*H*-indole-3-carboxylate (2b): compound **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 54% yield (34.5 mg) as a whitish solid; 12 h; white solid; mp: 193–195 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.73 (br, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 2.91 (s, 6H), 2.51 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.8, 155.9, 147.9, 143.0, 137.1, 121.1, 115.0, 110.3, 101.7, 91.6, 59.0, 52.9, 40.9, 14.4, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{16}H_{22}N_3O_4$ 320.1605, found 320.1599.



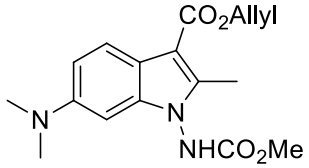
2c

Ethyl 6-(dimethylamino)-1-((ethoxycarbonyl)amino)-2-methyl-1*H*-indole-3-carboxylate (2c): compound **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 68% yield (45.5 mg) as a brown oil; 3 h; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.68 (br, 1H), 7.78 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 6.46 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 4.23–4.18 (m, 2H), 2.92 (s, 6H), 2.51 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.31–1.28 (m, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.8, 155.4, 147.8, 143.0, 137.1, 121.1, 115.0, 110.3, 101.7, 91.6, 61.7, 59.0, 40.9, 14.4, 14.4, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{17}H_{24}N_3O_4$ 334.1761, found 334.1763.



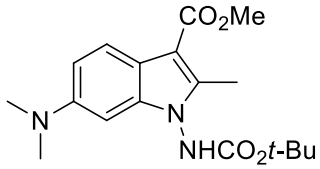
2d

Isopropyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (2d): compound **2d** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 64% yield (46.2 mg) as a whitish solid; 2 h; mp: 122–124 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.40 (br, 1H), 7.77 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 6.40 (s, 1H), 5.12 (sept, J = 6.0 Hz, 1H), 2.90 (s, 6H), 2.49 (s, 3H), 1.49 (s, 9H), 1.34 (d, J = 6.0 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.4, 154.4, 147.7, 142.9, 137.1, 121.1, 115.1, 110.2, 101.8, 91.5, 81.0, 66.0, 40.9, 27.8, 22.0, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_4$ 376.2231, found 376.2236.



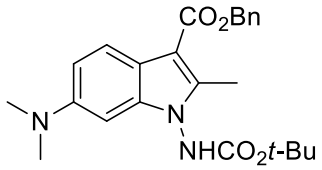
2e

Allyl 6-(dimethylamino)-1-((methoxycarbonyl)amino)-2-methyl-1*H*-indole-3-carboxylate (2e): compound **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 74% yield (48.9 mg) as a white solid; 1 h; mp: 100–102 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.69 (br, 1H), 7.77 (d, J = 8.8 Hz, 1H), 6.80 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.14–6.04 (m, 1H), 5.42–5.38 (m, 1H), 5.29–5.26 (m, 1H), 4.79 (d, J = 4.8 Hz, 2H), 3.76 (s, 3H), 2.91 (s, 6H), 2.51 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.4, 155.9, 147.9, 143.3, 137.1, 133.4, 121.0, 117.4, 114.9, 110.4, 101.4, 91.6, 63.7, 52.9, 40.9, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_4$ 332.1605, found 332.1609.



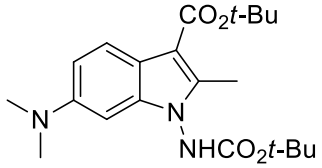
2f

Ethyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (2f): compound **2f** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 80% yield (55.7 mg) as a white solid; 3 h; mp: 125–128 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.40 (br, 1H), 7.75 (d, J = 8.8 Hz, 1H), 6.78 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.40 (s, 1H), 3.81 (s, 3H), 2.90 (s, 6H), 2.49 (s, 3H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.3, 154.4, 147.7, 143.2, 137.1, 121.1, 114.9, 110.2, 101.4, 91.6, 81.0, 50.6, 40.8, 27.8, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{18}H_{26}N_3O_4$ 348.1918, found 348.1916.



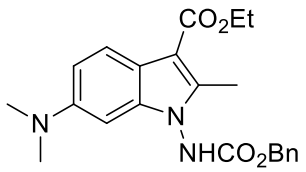
2g

Benzyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (2g): compound **2g** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 83% yield (70.6 mg) as a whitish solid; 2 h; mp: 161–163 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.41 (br, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.36–7.32 (m, 1H), 6.76 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.40 (s, 1H), 5.33 (s, 2H), 2.89 (s, 6H), 2.50 (s, 3H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.6, 154.4, 147.8, 143.5, 137.1, 136.9, 128.5, 127.9, 121.0, 114.9, 110.3, 101.2, 91.6, 81.0, 64.7, 40.8, 27.8, 10.7; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{24}H_{30}N_3O_4$ 424.2231, found 424.2230.



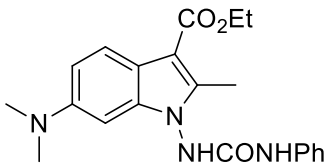
2h

***t*ert-butyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (2h):** compound **2h** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 55% yield (42.8 mg) as a yellowish solid; 12 h; mp: 143–145 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.42 (br, 1H), 7.79 (d, J = 8.4 Hz, 1H), 6.91–6.77 (m, 1H), 6.61–6.41 (m, 1H), 2.93, 2.47 (s, 3H), 1.57 (s, 9H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.2, 154.4, 142.9, 136.8, 129.4, 121.1, 112.1, 110.4, 102.9, 92.0, 81.0, 79.1, 41.3, 27.8, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{21}H_{32}N_3O_4$ 390.2387, found 390.2389.



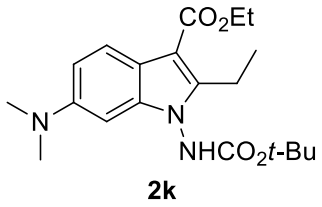
2i

Ethyl 1-(((benzyloxy)carbonyl)amino)-6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (2i): compound **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 50% yield (39.7 mg) as a whitish solid; 12 h; mp: 133-135 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.85 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.45–7.39 (m, 5H), 6.79 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.40 (s, 1H), 5.29–5.21 (m, 2H), 4.28 (J = 6.8 Hz, 2H), 2.89 (s, 6H), 2.50 (s, 3H), 1.35 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.8, 155.4, 147.8, 142.9, 137.0, 136.2, 128.5, 128.2, 127.8, 121.1, 115.0, 110.3, 101.8, 91.5, 66.9, 59.0, 40.8, 14.4, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{22}H_{26}N_3O_4$ 396.1918, found 396.1911.



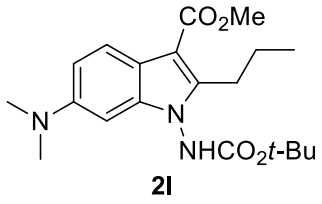
2j

Ethyl 6-(dimethylamino)-2-methyl-1-(3-phenylureido)-1*H*-indole-3-carboxylate (2j): compound **2j** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 38% yield (28.8 mg) as a white solid; 48 h; mp: 199–201 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 9.60 (br, 1H), 9.39 (br, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 6.99 (t, J = 7.2 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.53 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 2.89 (s, 6H), 2.54 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.0, 154.1, 147.7, 144.2, 139.3, 137.7, 128.7, 122.4, 121.0, 118.8, 115.3, 110.2, 101.5, 92.0, 58.9, 41.0, 14.5, 10.9; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{21}H_{25}N_4O_3$ 381.1921, found 381.1919.



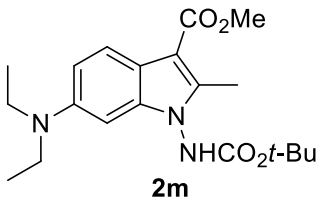
2k

Ethyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-ethyl-1*H*-indole-3-carboxylate (2k): compound **2k** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 46% yield (34.7 mg) as a white solid; 2 h; mp: 144–146 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.43 (br, 1H), 7.78 (d, J = 8.8 Hz, 1H), 6.79 (dd J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.04–2.90 (m, 8H, N(CH_3)$_2$ and CH_2CH_3), 1.50 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.6, 154.4, 148.5, 147.8, 137.0, 121.2, 115.1, 110.3, 100.7, 91.6, 80.9, 58.9, 40.8, 27.8, 26.3, 17.9, 14.4, 13.3; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_4$ 376.2231, found 376.2226.



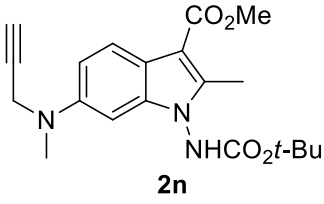
2l

Methyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-propyl-1*H*-indole-3-carboxylate (2l): compound **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 71% yield (53.1 mg) as a whitish solid; 1 h; mp: 44–46 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.41 (br, 1H), 7.76 (d, J = 8.8 Hz, 1H), 6.79 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.36 (s, 1H), 3.81 (s, 3H), 3.02–2.95 (m, 2H), 2.90 (s, 6H), 1.63–1.56 (m, 2H), 1.50 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.1, 154.4, 147.8, 147.2, 137.0 121.2, 115.0, 110.3, 101.2, 91.6, 80.9, 50.5, 40.8, 27.8, 26.3, 21.8, 13.9; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_4$ 376.2231, found 376.2236.



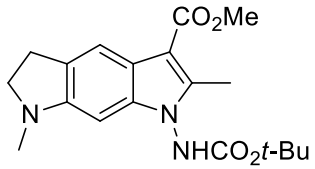
2m

Methyl 1-((*tert*-butoxycarbonyl)amino)-6-(diethylamino)-2-methyl-1*H*-indole-3-carboxylate (2m): compound **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 79% yield (59.1 mg) as a white solid; 1 h; mp: 120–122 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.37 (br, 1H), 7.71 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 6.33 (s, 1H), 3.80 (s, 3H), 6.68 (q, J = 7.2 Hz, 4H), 2.48 (s, 3H), 1.49 (s, 9H), 1.09 (t, J = 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.3, 154.4, 144.7, 142.8, 137.4, 121.3, 114.2, 109.7, 101.4, 91.0, 80.9, 50.5, 44.3, 27.8, 12.3, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_4$ 376.2231, found 376.2234.



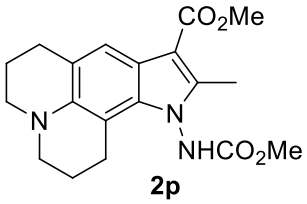
2n

Methyl 1-((*tert*-butoxycarbonyl)amino)-2-methyl-6-(methyl(prop-2-yn-1-yl)amino)-1*H*-indole-3-carboxylate (2n): compound **2n** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 40% yield (30.0 mg) as a yellow oil; 12 h; °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.43 (br, 1H), 7.78 (d, J = 8.8 Hz, 1H), 6.89 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.56 (s, 1H), 4.14 (d, J = 2.0 Hz, 2H), 3.82 (s, 3H), 3.04 (t, J = 2.0 Hz, 1H), 2.89 (s, 3H), 2.50 (s, 3H), 1.50 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.2, 154.4, 146.0, 143.6, 136.9, 121.0, 116.0, 115.5, 101.4, 93.6, 81.0, 79.9, 74.6, 50.6, 42.4, 38.6, 27.9, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{26}N_3O_4$ 372.1918, found 372.1912.



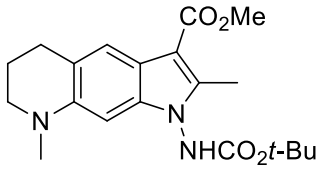
2o

Methyl 1-((*tert*-butoxycarbonyl)amino)-2,7-dimethyl-1,5,6,7-tetrahydropyrrolo[3,2-*f*]indole-3-carboxylate (2o): compound **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 61% yield (43.7 mg) as a whitish solid; 12 h; mp: 163–165 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.36 (br, 1H), 7.60 (s, 1H), 6.22 (s, 1H), 3.80 (s, 3H), 3.27 (td, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 2H), 2.94 (t, J = 8.0 Hz, 2H), 2.71 (s, 3H), 2.47 (s, 3H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.4, 154.4, 150.5, 141.8, 136.2, 126.5, 116.1, 115.6, 101.7, 87.1, 80.9, 56.1, 50.5, 36.0, 28.0, 27.9, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{19}H_{26}N_3O_4$ 360.1918, found 360.1918.



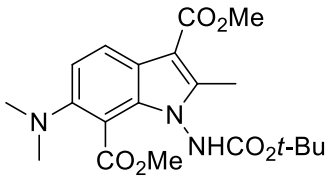
2p

Methyl 11-((methoxycarbonyl)amino)-10-methyl-2,3,5,6,7,11-hexahydro-1*H*-pyrido[3,2,1-*ij*]pyrrolo[2,3-*f*]quinoline-9-carboxylate (2p): compound **2p** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 66% yield (46.9 mg) as a brownish solid; 3 h; mp: 223–225 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.71 (br, 1H), 7.39 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.08–3.03 (m, 4H), 2.80–2.68 (m, 4H), 2.42 (s, 3H), 1.92–1.87 (m, 4H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.3, 156.0, 143.3, 140.2, 132.9, 118.6, 118.2, 115.2, 103.3, 101.3, 52.9, 50.5, 50.3, 49.2, 28.0, 22.1, 21.5, 21.2, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_4$ 358.1761, found 358.1761.



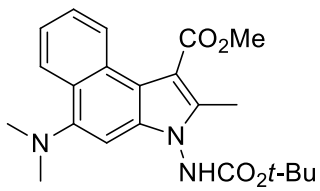
2q

Methyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*g*]quinoline-3-carboxylate (2q): compound **2q** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 60% yield (45.0 mg) as a white solid; 1.5 h; mp: 170–172 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10. 34 (br, 1H), 7.47 (s, 1H), 6.24 (s, 1H), 3.79 (s, 3H), 3.20 (t, J = 5.6 Hz, 2H), 2.83 (s, 3H), 2.80 (t, J = 6.4 Hz, 2H), 2.46 (s, 3H), 1.89 (qt, J = 6.4 Hz, 2H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.4, 154.4, 143.7, 142.3, 136.0, 120.1, 119.4, 114.2, 101.1, 89.7, 80.9, 50.7, 50.5, 39.0, 27.8, 22.5, 10.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{28}N_3O_4$ 374.2074, found 374.2070.



2r

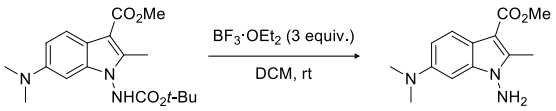
Dimethyl 1-((*tert*-butoxycarbonyl)amino)-6-(dimethylamino)-2-methyl-1*H*-indole-3,7-dicarboxylate (2r): compound **2r** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 82% yield (66.3 mg) as a white solid; 1 h; mp: 103–105 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.41 (br, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 3.84 (s, 6H), 2.66 (s, 6H), 2.46 (s, 3H), 1.47 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 167.4, 164.8, 154.0, 147.1, 146.1, 132.4, 122.0, 120.4, 114.9, 113.2, 102.1, 81.1, 52.3, 50.9, 45.5, 27.9, 10.5; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{20}H_{28}N_3O_6$ 406.1973, found 406.1980.



2s

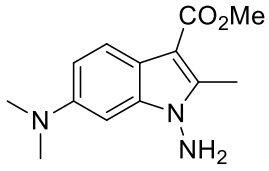
Methyl 3-((*tert*-butoxycarbonyl)amino)-5-(dimethylamino)-2-methyl-3*H*-benzo[*e*]indole-1-carboxylate (2s): compound **2s** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 45% yield (36.9 mg) as a whitish solid; 24 h; mp: 138–140 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.63 (br, 1H), 9.09 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.55–7.51 (m, 1H), 7.48–7.44 (m, 1H), 6.99 (s, 1H), 3.91 (s, 3H), 2.82 (s, 6H), 2.51 (s, 3H), 1.52 (s, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 166.1, 154.5, 147.7, 140.9, 132.9, 128.3, 126.1 125.8, 125.7, 124.6, 123.3, 113.5, 105.2, 98.5, 81.3, 51.2, 45.1, 27.8, 11.3 ; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{22}H_{28}N_3O_4$ 398.2074, found 398.2073.

Access to compound 6



2f **6**

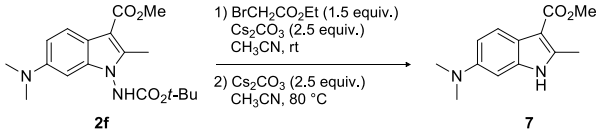
To a solution of **2f** (0.2 mmol) in CH_2Cl_2 (2 mL), $BF_3{\cdot}OEt_2$ (0.075 mL, 0.6 mmol) was added. The mixture was stirred at room temperature until the disappearance of the starting material (2.5 h). The solvent was removed under vacuum, ethyl acetate (5 mL) was added and the mixture was washed with saturated $NaHCO_3$ (3 x 5 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum to afford compound **6** as a pale grey solid, which was washed with diethyl ether (49.3 mg, 99%).



6

Methyl 1-amino-6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (6): mp: 154–156 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 7.71 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.74 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 5.73 (s, 2H), 3.77 (s, 3H), 2.91 (s, 6H), 2.64 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.5, 147.2, 144.2, 138.1, 120.6, 115.4, 109.9, 99.3, 93.3, 50.2, 41.1, 11.2; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{13}H_{18}N_3O_2$ 248.1394, found 248.1399.

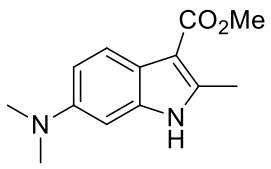
Access to compound 7



2f **7**

Compound 3 was prepared according to literature, with a slight modification.[188] To a solution of **2f** (69.5 mg, 0.2 mmol) in acetonitrile (2 mL), ethyl bromoacetate (0.033 mL, 0.3 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) were added. The mixture was stirred at room temperature until the disappearance of the starting material (3 h). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was dried over Na_2SO_4 and filtered. After the solvent was

removed under reduced pressure, the residue was dissolved in acetonitrile (2 mL) and Cs_2CO_3 (162.9 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C until TLC showed complete consumption of the intermediate (1 h). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 x 5 mL). The collected organic phase was washed with brine, dried over Na_2SO_4 and the solvent was removed under vacuum, the residue was purified by column chromatography (ethyl acetate) to afford compound **7** as a brownish solid (33.8 mg, 73% yield).



7

Methyl 6-(dimethylamino)-2-methyl-1*H*-indole-3-carboxylate (7): mp: 201–203 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 11.38 (br, 1H), 7.68 (d, J = 8.8 Hz, 1H), 6.71 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 3.77 (s, 3H), 2.87 (s, 6H), 2.58 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.6, 147.2, 142.4, 136.2, 120.6, 118.4, 109.7, 102.2, 94.4, 50.2, 13.6; HRMS (ESI-Orbitrap, *m/z*) $[M+H]^+$ calcd for $C_{13}H_{18}N_3O_2$ 233.1285, found 248.1282.

CHAPTER 5

$FeCl_3$-Catalyzed Formal [3 + 2] Cyclodimerization of 4-Carbonyl-1,2-diaza-1,3-dienes

Mari, G., Corrieri, M., De Crescentini, L., Favi, G., Santeusanio, S., Mantellini, F. *Eur. J. Org. Chem.* **2021**, 5202–5208.

4.5 Introduction

The pyrrole ring is undoubtedly among the most recurring heterocyclic scaffolds, and plays a key role in numerous branches of chemistry. To start with, the great biochemical relevance of the pyrrole system is witnessed by its presence as the core of chlorophylls, bacteriochlorophylls, hemes, vitamin B_{12} and bile pigments (bilirubin, biliverdin, etc.). Being ubiquitous in biological system, it is also a common structural motif in natural products as well: magnolamide,[231] pyrrolnitrin,[232] halitulin,[233] prodigiosin[234,235] and oroidin[236] are only few examples of the countless pyrrole-containing products derived from natural sources. Noteworthy, a large portion of them exhibit pharmacological activity, including anticancer,[237,238] antimicrobial,[239,240] antioxidant[241] and hepatoprotective[242] activities. Moreover, a great number of synthetic pyrroles also showed interesting profiles in medicinal chemistry,[243] and several common commercial drugs such as atorvastatine (antihyperlipidemic), ketorolac, tolmetin (both NSAIDs), sunitinib (anticancer) and pyrvinium (antihelmintic) contain this heterocyclic system. Pyrrole is also an important motif in dyes[244,245] and agrochemicals,[246–248] and has recently gained attention in materials chemistry.[249–251]

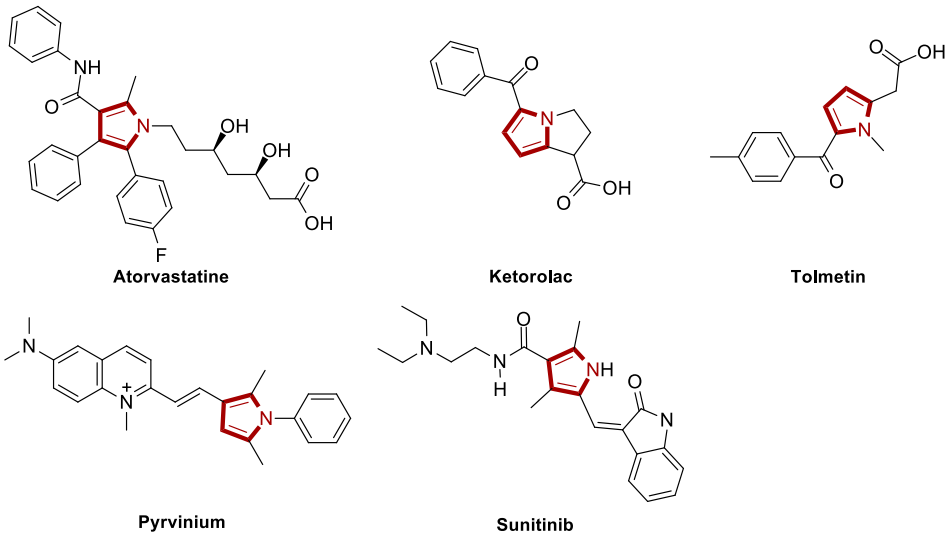


Figure 1. Selected examples of pyrrole-containing commercial drugs

Owing to the importance of this heterocycle, new methods for the construction of the pyrrole ring are constantly disclosed.[252,253] However, the synthesis of fully substituted symmetrical pyrroles, which represent an interesting subclass,[254–258] remains an underexplored field.

The development of straightforward and simple synthetic protocols is of high interest, since they allow to save time and financial resources. This constitutes an important advantage not only in academia but, especially, at the industrial level. In fact, step-economical procedures requiring easy and fast work-up are attractive because they can be easily scaled-up and automated. In this context, 1,2-diaza-1,3-butadienes (DDs, azoalkenes) have demonstrated to be highly versatile building blocks.[70,82,130,259–263] A plethora of heterocycles of very different nature can be synthesized when azoalkenes are reacted with nucleophilic partners.[264–270] DDs can also undergo dimerization reactions: for instance, Zhou[271] and Suryavanshi[272] reported two interesting [4 + 2] cycloadditions

of *in situ*-generated azoalkenes (figure **1a**). In their work, α-halohydrazones are employed as starting materials, as they form 4-unsubstituted azoalkenes when reacting with a base. These compounds must be generated *in situ* because of their high instability. On the other hand, when DDs are substituted on position 4 with EWG groups such as esters and amides, they are stabilized and thus they can be easily isolated and stored for long periods. With this consideration in mind and inspired by Zhou's and Suryavanshi's work, we envisioned a dimerization reaction employing stable 4-substituted azoalkenes. To our delight, we observed the selective formation of symmetrical, fully substituted pyrroles *via* a formal [3 + 2] cyclodimerization process (figure **1b**), differently from the aforementioned [4 + 2] reactions.

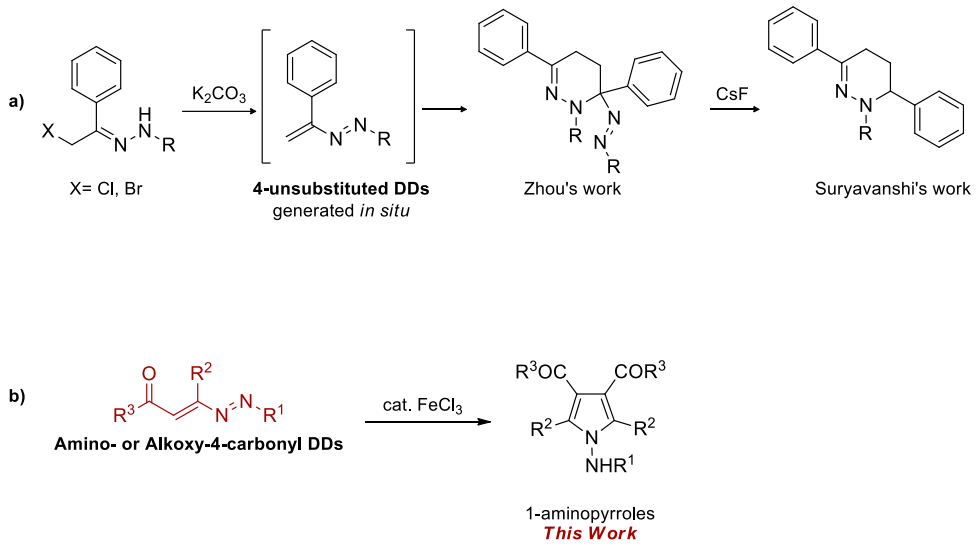
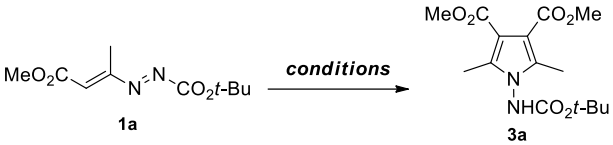


Figure 2

4.6 Results and discussion

We began our investigation on the cyclodimerization process of 4-substituted azoalkenes using compound **1a** as the model substrate. Initially, the conditions reported by Zhou and Suryavanshi were applied and the starting material was treated with K_2CO_3 in refluxing DCM (table **1**, entry 1). The formation of tetrahydropyridazine product **2** was not detected, and only traces of an α-oxo degradation product were isolated.[273] Heating **1a** in refluxing THF did not lead to the formation of the desired product as well (entry 2). Considering the fact that Lewis acids are widely recognized as useful catalysts in cycloadditions,[274] the next experiment involved the use of 10 mol% of $CuCl_2$ in DCM at room temperature (entry 3). To our surprise, 1-aminopyrrole **3a** was isolated in 32% yield, together with the α-oxohydrazone byproduct, while the [4 + 2] cyclodimerization expected product **2** was not detected. Encouraged by these results, we then focused our attention to other Lewis acids as catalysts for the formation of pyrrole **3a**. As shown in entries 4–12, the tested catalysts were $CuSO_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, $Yb(OTf)_3$, $ZnBr_2$, $TiCl_3$, $SmCl_3$, anhydrous $FeCl_3$ and $FeCl_3{\cdot}6H_2O$, each of them in 10 mol% loading, in DCM at room temperature. While the use of copper sulfate resulted in no formation of the desired product (entry 4), the other salts furnished product **3a** in 5–41% yield. The best result was obtained with anhydrous iron (III) chloride, which performed better than iron (III) chloride hexahydrate (entries 11, 12).

Refluxing the reaction mixture led to a slight improvement (entry 13), while $CHCl_3$ and CH_3CN, both used at room temperature or under reflux heating were less effective as solvents (entries 14–17). THF, instead, proved to be a better solvent for this reaction. In fact, as can be seen from entry 18, the reaction at room temperature furnished the desired product in 50%, although a complete conversion of the substrate was not observed after 72 hours. Refluxing in THF enabled for a further yield increase (71%, entry 19), and also in this case the starting material was recovered. When the catalyst loading was increased from 10 mol% to 20 mol%, the full conversion of **1a** was observed after 24 hours, although the yield for **3a** decreased to 63% (entry 20). While lowering the amount of $FeCl_3$ to 5 mol% resulted in a slight decreased yield (entry 21), a more pronounced drop was observed when the catalyst loading was further lowered to 2.5 mol% (entry 22), and in both cases the substrate was not fully converted after 72 hours. Finally, an experiment was carried out in which 5 mol% of iron (III) chloride were initially used, and the same amount was added after 6 hours to the reaction mixture. Satisfyingly, after 24 hours the pyrrole **3a** was isolated in 95% yield (entry 23).



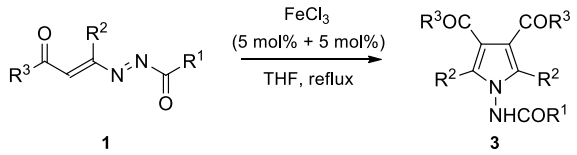
1a **3a**

Entry[a]	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1[c,d]	K_2CO_3	DCM	reflux	48	0
2	–	THF	reflux	48	0
3[e]	$CuCl_2$	DCM	rt	72	32
4[f]	$CuSO_4$	DCM	rt	72	0
5[e]	$Cu(OTf)_2$	DCM	rt	72	36
6[e]	$Bi(OTf)_3$	DCM	rt	72	18
7[e]	$Yb(OTf)_3$	DCM	rt	72	14
8[e]	$ZnBr_2$	DCM	rt	72	5
9[e]	$TiCl_3$	DCM	rt	72	14
10[e]	$SmCl_3$	DCM	rt	72	17
11[e]	$FeCl_3$	DCM	rt	72	41
12[e]	$FeCl_3 \cdot 6H_2O$	DCM	rt	72	24
13[e]	$FeCl_3$	DCM	reflux	72	43
14[e]	$FeCl_3$	$CHCl_3$	rt	72	7
15[e]	$FeCl_3$	$CHCl_3$	reflux	72	28
16[e,g]	$FeCl_3$	CH_3CN	rt	72	traces
17[e,g]	$FeCl_3$	CH_3CN	reflux	72	traces
18[e]	$FeCl_3$	THF	rt	72	50
19[e]	$FeCl_3$	THF	reflux	72	71
20	$FeCl_3$	THF	reflux	24	63
21[e]	$FeCl_3$	THF	reflux	72	69
22[e]	$FeCl_3$	THF	reflux	72	48
23[h]	**$FeCl_3$ (5 + 5)**	**THF**	**reflux**	**24**	**95**

Table 1. Optimization studies – [a] All reactions were conducted on 0.5 mmol of DD **1a** in 5.0 mL of solvent. [b] Isolated yields. [c] 0.46 mmol of **1a** were recovered. [d] 0.027 mmol of α-oxo-hydrazone were isolated.[273] [e] DD **1a** was not fully converted. [f] No reaction occurred, apart from the formation of a small amount of α-oxo-hydrazone.[273] [g] A complicated mixture was formed, with traces of **3a** detected on

TLC. [h] 5 mol% of $FeCl_3$ were initially added and the reaction refluxed; a second portion of 5 mol% of the catalyst was added after 6 hours, then the reaction was refluxed for additional 18 hours.

With the optimized conditions, a library of 1-aminopyrroles was constructed with different 1,2-diaza-1,3-dienes. Various *N*-protecting groups were utilized, and products bearing esters (**1a**–**m**, R^1 = Me, Et, *t*-Bu) or amides (**1n**–**q**, R^1 = NH_2, NHPh) in this position were obtained with good to excellent yields. Aside from methyl as the R^2 substituent, longer alkyl chains (ethyl and propyl) could also be included (**3f**,**g**,**j**), although they negatively affect the yield (41%, 29% and 55%, respectively) when compared to the other products, thus suggesting that increasing the steric hindrance within this portion is not desirable. As regards the substituent on the position 4, DD's with different ester groups such as ethyl (**3b**,**f**,**m**,**o**,**q**), isopropyl (**3c**), benzyl (**3d**) and 2-methoxyethyl (**3e**) were successfully used, and the presence of a *N*,*N*-dimethyl amide group was also well tolerated (**3h**,**k**). Notably, the reaction on substrate **1p** also led to tetrahydropyridazine **2a** as a minor product.



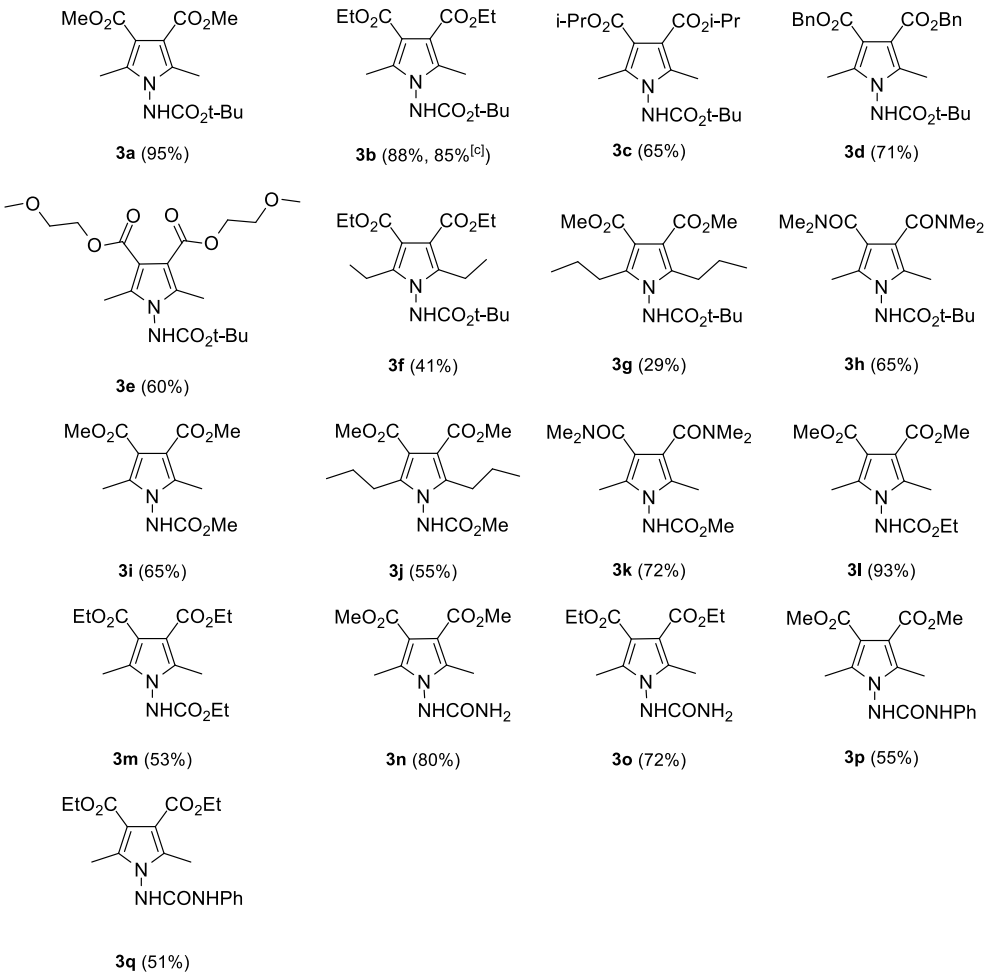
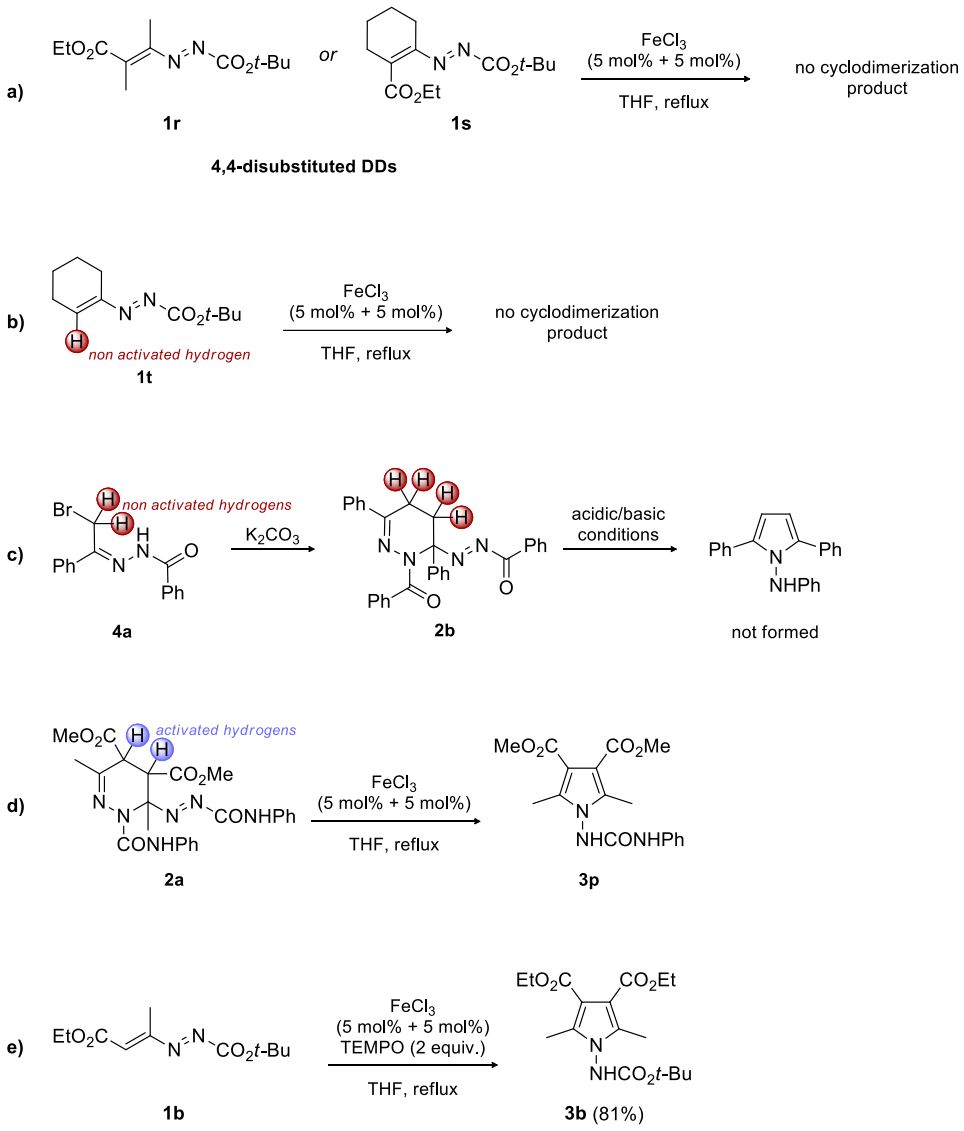


Table 2. Substrate scope for the formal [3 + 2] DDs 1a–q cyclodimerization catalyzed by $FeCl_3$ – Reaction conditions: **1** (1.0 mmol), $FeCl_3$ (0.05 mmol), THF (10 mL), reflux 6 h, then another 0.05 mmol of $FeCl_3$ are added and the mixture refluxed for 18-24 h. All yields reported refer to the isolated product. [a] Yield of the scale-up reaction (8.0 mmol of **1b**).

The synthesis of pyrrole **3b** was successfully scaled-up without a significant loss in terms of yield (85%, see table **2**).

Control experiments were conducted to gain mechanistic details. As expected, the hydrogen on the position 4 of the azoalkene substrate is required, and this is highlighted by the lack of reactivity of 4,4-disubstituted substrates **1r** and **1s** (scheme **1a**). The pyrrole product is not formed also in the opposite case, i.e. when the hydrogen is present in position 4 but the EWG is not (scheme **1b**). Moreover, an experiment was carried out on the 3,4-unsubstituted tetrahydropyridazine **2b**, obtained by reacting the halohydrazone **4a** according to Zhou's method. Neither the basic nor the acidic treatment of **2b** led to the formation of a pyrrole ring (scheme

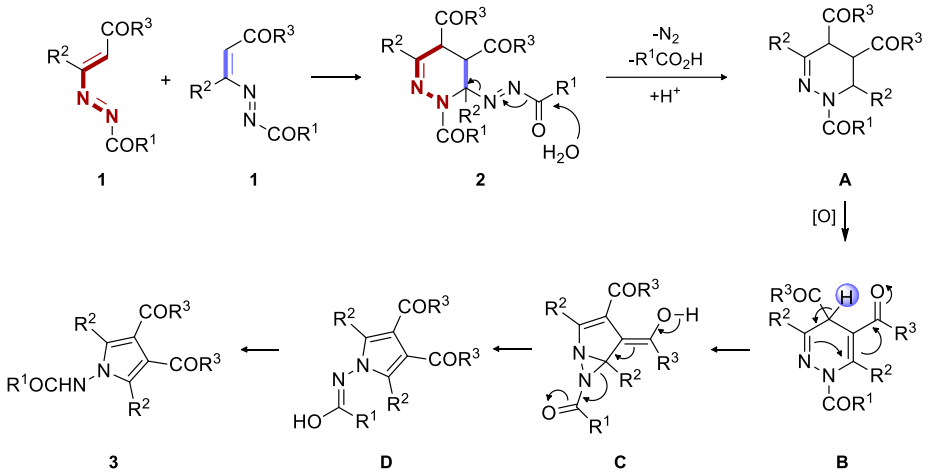
1c). When isolated tetrahydropyridazine product **2a**, which bears acidic protons, is treated under the optimized conditions, pyrrolization product is obtained in 87% yield (scheme **1d**).



Scheme 1. Control experiments

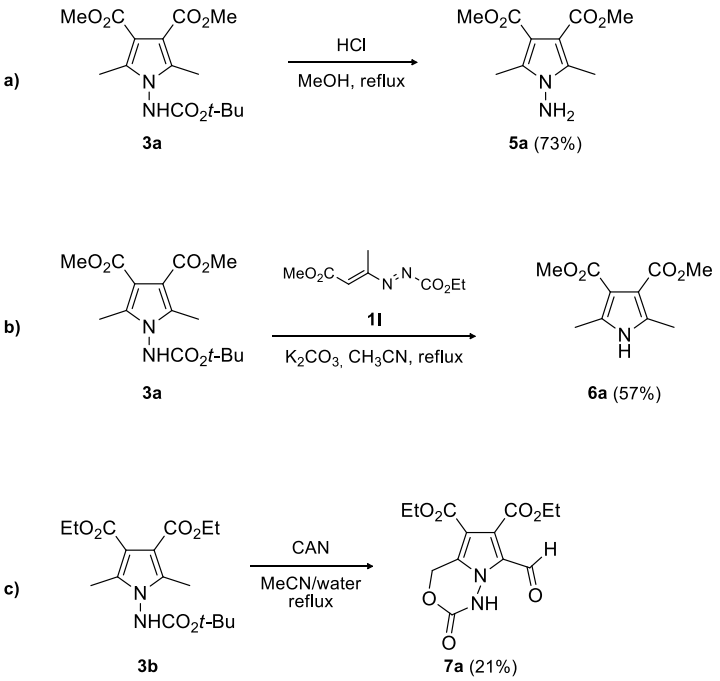
Having analyzed this data, it is reasonable to suggest that an intermediate bearing an activated, acidic proton has to be formed in order for the pyrrolization to occur. Furthermore, a radical mechanism[275] can be ruled out, given the fact that the addition of 2 equiv. of the radical trap TEMPO did not inhibit the formal [3 + 2] cyclodimerization on **1b**, which furnished pyrrole **3b** in 81% yield under these conditions (scheme **1e**). On the basis of these experimental observations, a mechanism is proposed (scheme **2**). The first step involves an inverse electron demand aza-Diels-Alder reaction (the presence of the azo and the ester or amide group makes the diene electron poor), that furnishes diazenyl-tetrahydropyridazine-3,4-dicarboxylate **2**. It is known that Lewis acids, including iron salts, can favor this kind of Diels-Alder reactions.[276–279] Next, the nucleophilic attack of water allows the loss of both the acyl and the aza group, leading to a carbanion which, after being protonated, affords intermediate **A**.[272] This intermediate undergoes spontaneous oxidation to 1,4-dihydropyridazine **B** in which, thanks to the acidic proton (highlighted in the scheme), an internal aza-Michael addition occurs, leading to a ring contraction that forms diaziridin-pyrrolinic intermediate **C**.[280] The keto-enolic

tautomerism brings to the opening of the three-membered ring, forming intermediate **D** which, after a final tautomerism, affords pyrrole **3**.



Scheme 2. Proposed reaction mechanism

Along with the spectroscopic data, further transformations of products **3** made possible to assure that those are indeed pyrrole products, rather than six-membered rings. In fact, as shown in scheme **3**, it is possible to conduct a Boc-group removal in the presence of HCl in methanol which furnishes 1-aminoindole **5**, as well as a N–N bond cleavage that leads to pyrrole **6**.[281] Another possible synthetic transformation is the access to pyrrolo[1,2-*d*][1,3,4]oxadiazine **7**, obtained by treating **3b** with ceric ammonium nitrate (CAN) in an acetonitrile/water solvent mixture.[282] This reaction proceeds *via* the oxidation of a methyl group to a hydroxymethyl group, which reacts with the Boc appendage by transesterification, while the other methyl is further oxidized to a formyl appendage.



Scheme 3. Synthetic transformations of pyrroles **3**

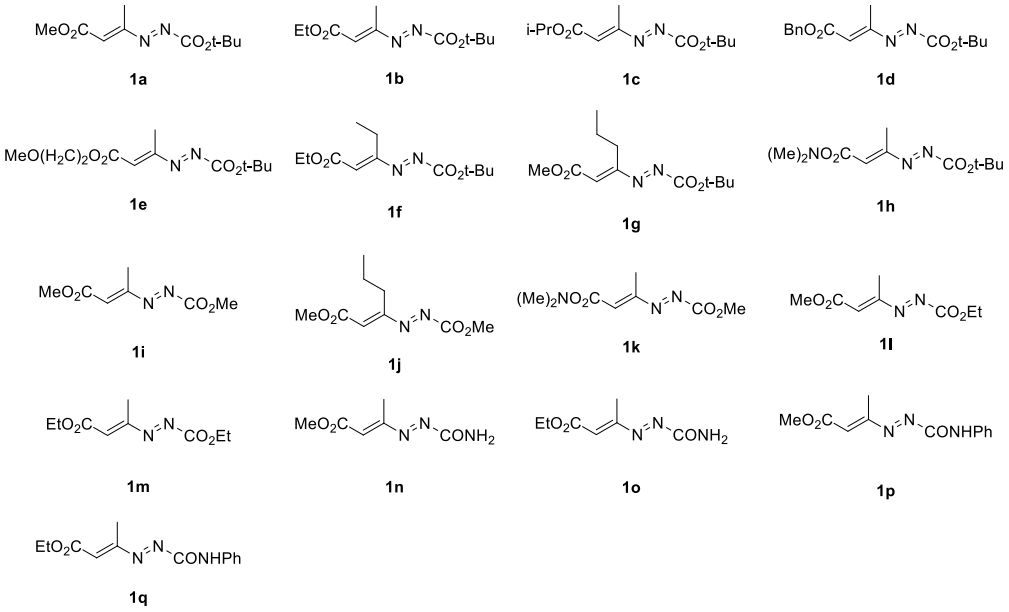
4.7 Conclusions

In conclusion, we have developed a formal [3 + 2] cyclodimerization of 4-substituted azoalkenes, catalyzed by $FeCl_3$ as a cheap, environmentally friendly and non-toxic Lewis acid. Under simple and mild reaction conditions, stable and isolable 1,2-diaza-1,3-dienes can be transformed into fully substituted symmetrical 1-aminopyrroles. The reaction involves an aza-Diels-Alder step, followed by a ring contraction enabled by the presence of activated hydrogens. This reactivity differs from *in situ* generated azoalkenes which instead, according to previously reported works, lead to six-membered rings.

4.8 Experimental section

General remarks: 1,2-Diaza-1,3-dienes **1a–q** were synthesized as a mixture of *E/Z* isomers as previously reported.[283] For the synthesis of 1-aminopyrroles **3a–q** commercial tetrahydrofuran RPE grade that contains 250 ppm BHT as inhibitor were employed without any other purification. Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. Structural assignments were made with additional information from gHSQC, and gHMBC experiments. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in ascending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. FT-IR spectra were obtained as Nujol mulls. High-and low-resolution mass spectroscopy was performed on a Micromass Q-ToF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were within ± 0.4 of the theoretical values (C, H, N).

List of 1,2-Diaza-1,3-dienes 1a–q employed.



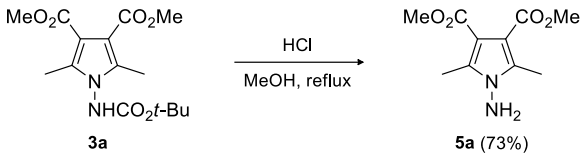
General procedure for the synthesis of 1,4,5,6-tetrahydropyridazine 2a and 1-aminopyrroles 3a–q

To a solution of 1,2-diaza-1,3-dienes **1a–q** (1.0 mmol) in tetrahydrofuran (10.0 mL) $FeCl_3$ (0.05 mmol) was added and the mixture was refluxed. After 6.0 h a second aliquot of $FeCl_3$ (0.05 mmol) was added to the solution that was refluxed for other 18.0–24.0 h until the complete disappearance of the starting 1,2-diaza-1,3-dienes **1a–q** (TLC monitoring). Then, the solvent was removed *in vacuo*; the so-formed 1-aminopyrroles **3a–q** were purified by silica gel column chromatography using cyclohexane/ethyl acetate mixtures as eluent and then were crystallized from ethyl acetate/petroleum ether. In the case of the reaction of 1,2-diaza-1,3-diene **1p** it was possible to isolate the corresponding diazenyl-1,4,5,6-tetrahydropyridazine **2a** by stopping the reflux after 2.0 h from the first addition of $FeCl_3$ (0.05 mmol). In this case, the solvent was evaporated under *vacuo* and the crude was chromatographed very quickly to obtain the pure compound **2a**.

Conversion of diazenyl 1,4,5,6-tetrahydropyridazine 2a to 1-aminopyrrole 3p

To a solution of diazenyl 1,4,5,6-tetrahydropyridazine **2a** (0.2 mmol), in tetrahydrofuran (3.0 mL) $FeCl_3$ (0.01 mmol) was added and the mixture was refluxed the complete disappearance of the starting 1,4,5,6-tetrahydropyridazine **2a** (2.5 h, TLC monitoring). Then, the solvent was removed *in vacuo*; the so-formed 1-aminopyrrole **3p** was purified by silica gel column chromatography using cyclohexane/ethyl acetate mixture as eluent.

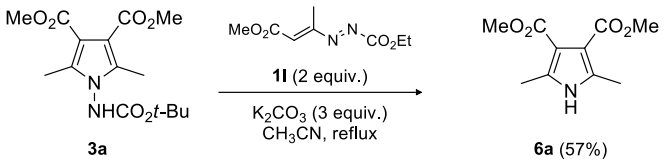
Synthesis of 1-amino-1*H*-pyrrole 5a



3a **5a** (73%)

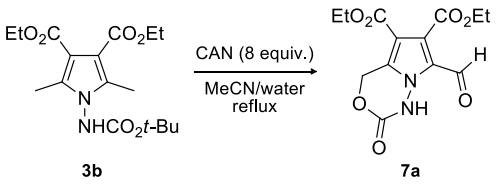
The dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **3a** (0.3 mmol) was dissolved in 15.0 mL of methanol and then 0.15 mL of HCl 37 % was added. The reaction was refluxed for 2 h (TLC monitoring). The reaction mixture was then neutralized by addition of Na_2CO_3, anhydrified with Na_2SO_4. Successively, the solution was filtered, and the crude was concentrated under reduced pressure. Products **5a** were isolated by chromatography on silica gel column with ethyl acetate-cyclohexane and purified by crystallization from ethyl acetate.

Synthesis of 1*H*-pyrrole 6a[281]

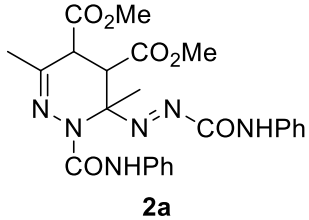


To a magnetically stirred solution of dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **3a** (0.5 mmol) in CH_3CN (10.0 mL), the DD **2l** (1.0 mmol) and K_2CO_3 (1.5 mmol) were added and the reaction mixture was refluxed for 1 hour, until the TLC analysis revealed the disappearance of the starting reagent **3** and the formation of 1*H*-pyrrole **6a**. After the filtration of K_2CO_3, the solvent was removed *in vacuo*; the so-formed product **6a** was purified by silica gel column chromatography using cyclohexane/ethyl acetate mixtures as eluent and then was crystallized from ethyl acetate/petroleum ether. In solution, the derivative **2a** degrades after a short period of time: also in dimethyl sulfoxide, after a few minutes, it is observed the formation of signals attributable to degradation products.

Synthesis of 7-formyl-2-oxo-2,4-dihydro-1*H*-pyrrolo[1,2-*d*][1,3,4]oxadiazine 7a



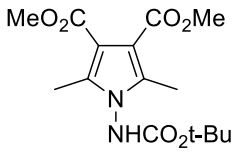
The dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **3a** (0.3 mmol) was dissolved in 9.0 mL of a mixture of acetonitrile/water (8:1) and then cerium(IV) ammonium nitrate was added (2.4 mmol). The reaction was refluxed for 5 h (TLC monitoring). The reaction mixture was cooled to room temperature, concentrated under vacuum, washed with H_2O (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 10 mL), brine (10 mL), and dried over $NaSO_4$. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a short silica column (ethyl acetate-cyclohexane).



2a

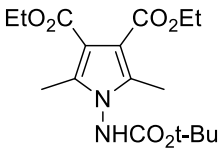
Dimethyl 3,6-dimethyl-1-(phenylcarbamoyl)-6-(phenylcarbamoyl)diazenyl)-1,4,5,6-tetrahydropyridazine-4,5-dicarboxylate (2a): The product **2a** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 22% yield (21.6 mg); colorless oil; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.90 (s, 1H), 9.39 (s, 1H), 7.74 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 3.99 (d, J = 7.2 Hz, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 3.51 (d, J = 7.2 Hz, 1H), 2.16 (s, 3H), 1.84 (s, 3H); **^{13}C NMR**

(100 MHz, DMSO-d_6, 25 °C): δ 169.5, 152.8, 142.0, 141.5, 139.2, 138.1, 129.5, 128.9, 125.2, 123.3, 120.4, 120.2, 83.3, 53.2, 53.0, 46.7, 42.9, 22.8, 19.8; IR (nujol): ν_{max} = 3357, 3311, 1754, 1733 cm^{-1}.



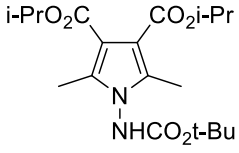
3a

Dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3a):[284,285] The product **3a** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 95% yield (309.9 mg); white solid; mp: 132–134 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ = 10.41 (br, 1H), 3.70 (s, 6H), 2.16 (s, 6H), 1.47 (br, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.6, 154.1, 134.0, 109.5, 81.2, 51.1, 27.7, 9.6; IR (nujol): ν_{max} = 3257, 1724, 1665 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{23}N_2O_6$ $[M + H]^+$: 327.1551; found: 327.1556.



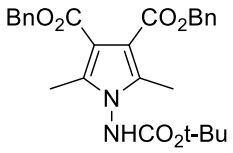
3b

Diethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3b): The product **3b** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 88% yield (310.9 mg) or 85% (1202.6 mg) starting from 8.0 mmol of **1b**; white solid; mp: 128–130 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.39 (br, 1H), 4.15 (q, J = 7.2 Hz, 4H), 2.15 (s, 6H), 1.46 (br, 9H), 1.22 (t, J = 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.2, 154.1, 133.6, 109.7, 81.2, 59.6, 27.7, 14.4, 9.5; IR (nujol): ν_{max} = 3317, 1743, 1685 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}N_2O_6$ $[M + H]^+$: 355.1864; found: 355.1869.



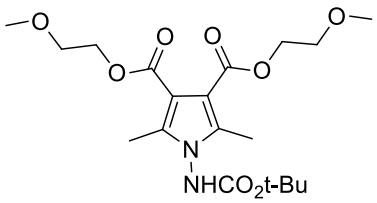
3c

Diisopropyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3c): The product **3c** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 65% yield (248.3 mg); white solid; mp: 141–143 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.39 (br, 1H), 4.98 (sept, J = 6.4 Hz, 2H), 2.14 (s, 6H), 1.46 (br, 9H), 1.24 (d, J = 6.4 Hz, 12H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 163.6, 154.2, 133.1, 110.2, 81.2, 66.9, 27.8, 21.6, 9.6; IR (nujol): ν_{max} = 3344, 1728, 1703 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{31}N_2O_6$ $[M + H]^+$: 383.2177; found: 383.2182.



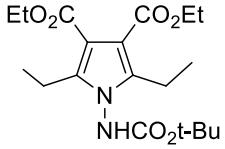
3d

Dibenzyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3d): The product **3d** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 71% yield (339.5 mg); white solid; mp: 123–125 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.44 (br, 1H), 7.32–7.39 (m, 10 H), 5.12 (s, 4H), 2.17 (s, 6H), 1.47 (br, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 163.9, 154.1, 136.2, 134.2, 128.3, 127.9, 126.4, 109.4, 81.3, 65.4, 27.7, 9.6; IR (nujol): ν_{max} = 3358, 1742, 1685 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{31}N_2O_6$ $[M + H]^+$: 479.2177; found: 479.2182.



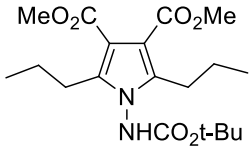
3e

Bis(2-methoxyethyl) 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3e): The product **3e** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 60% yield (249.1 mg); white solid; mp: 132–134 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.42 (br, 1H), 4.22 (t, J = 4.8 Hz, 4H), 3.56 (t, J = 4.8 Hz, 4H), 3.26 (s, 6H), 2.16 (s, 6H), 1.47 (br, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.0, 154.1, 134.0, 109.6, 81.2, 69.8, 62.8, 58.0, 27.8, 9.6; IR (nujol): ν_{max} = 3385, 1755, 1683 cm^{-1}; MS (ESI) *m/z*: 415 (M + H$^+$); anal. calcd. for $C_{19}H_{30}N_2O_8$ (414.45): C 55.06, H 7.30, N 6.76; found: C 55.22, H 7.21, N 6.81.



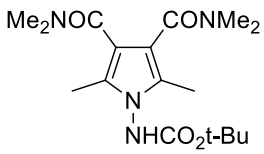
3f

Diethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-diethyl-1*H*-pyrrole-3,4-dicarboxylate (3f): The product **3f** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 41% yield (157.2 mg); white solid; mp: 116–118 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.48 (s, 1H), 4.16 (q, J = 7.2 Hz, 4H), 2.47–2.67 (m, 4H), 1.48 (br, 9H), 1.23 (t, J = 7.2 Hz, 6H), 1.05 (t, J = 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.1, 154.3, 138.9, 109.3, 81.1, 59.5, 27.7, 17.2, 14.0, 13.5; IR (nujol): ν_{max} = 3368, 1758, 1714 cm^{-1}; MS (ESI) *m/z*: 382 (M + H$^+$); anal. calcd. for $C_{19}H_{30}N_2O_6$ (382.45): C 59.67, H 7.91, N 7.32; found: C 59.52, H 7.99, N 7.37.



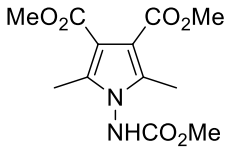
3g

Dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dipropyl-1*H*-pyrrole-3,4-dicarboxylate (3g): The product **3g** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 29% yield (112.2 mg); white solid; mp: 118–121 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.45 (br, 1H), 3.68 (s, 6H), 2.54–2.62 (m, 2H), 2.42–2.47 (m, 2H), 1.48 (br, 9H), 1.40–1.53 (m, 4H), 0.86 (t, J = 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.8, 154.3, 137.8, 109.7, 81.1, 51.2, 27.8, 25.7, 21.8, 13.6; IR (nujol): ν_{max} = 3364, 1726, 1688 cm^{-1}; MS (ESI) *m/z*: 383 (M + H$^+$); anal. calcd. for $C_{19}H_{30}N_2O_6$ (382.45): C 59.67, H 7.91, N 7.32; found: C 59.80, H 7.83, N 7.39.



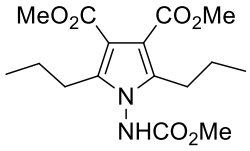
3h

***tert*-Butyl (3,4-bis(dimethylcarbamoyl)-2,5-dimethyl-1*H*-pyrrol-1-yl)carbamate (3h):** The product **3h** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 65% yield (227.9 mg); white solid; mp: 152–154 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 9.87 and 10.20 (2br, 1H), 2.85 (br, 12H), 1.98 (s, 6H), 1.46 (br, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 166.3, 154.4, 127.6, 112.4, 80.7, 37.5, 34.2, 27.8, 9.5; IR (nujol): ν_{max} = 3357, 1714, 1663 cm^{-1}; MS (ESI) *m/z*: 353 (M + H$^+$); anal. calcd. for $C_{17}H_{28}N_4O_4$ (352.43): C 57.94, H 8.01, N 15.90; found: C 58.07, H 7.94, N 15.83.



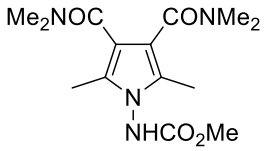
3i

Dimethyl 1-((metoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3i):[285,286] The product **3i** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 65% yield (183.6 mg); white solid; mp: 167–168 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.73 (br, 1H), 3.74 (br, 3H), 3.70 (s, 6H), 2.17 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.1, 156.1, 134.4, 110.1, 53.5, 51.7, 10.1; IR (nujol): ν_{max} = 3337, 1725, 1676 cm^{-1}; MS (ESI) *m/z*: 285 (M + H$^+$); anal. calcd. for $C_{12}H_{16}N_2O_6$ (284.27): C 50.70, H 5.67, N 9.85; found: C 50.54, H 5.54, N 9.94.



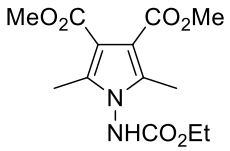
3j

Dimethyl 1-((methoxycarbonyl)amino)-2,5-dipropyl-1*H*-pyrrole-3,4-dicarboxylate (3j): The product **3j** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 55% yield (186.4 mg); white solid; mp: 153–155 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.78 (br, 1H), 3.73 (br, 3H), 3.69 (s, 6H), 2.58–2.65 (m, 2H), 2.40–2.50 (m, 2H), 1.44–1.53 (sex, *J*= 7.2 Hz, 4H), 0.84 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.7, 155.7, 137.6, 109.8, 52.9, 51.2, 25.6, 21.9, 13.6; IR (nujol): ν_{max} = 3348, 1712, 1673 cm^{-1}; MS (ESI) *m/z*: 341 (M + H$^+$); anal. calcd. for $C_{16}H_{24}N_2O_6$ (340.37): C 56.46, H 7.11, N 8.23; found: C 56.57, H 7.05, N 8.18.



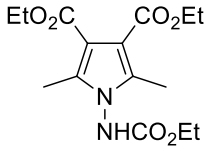
3k

Methyl (3,4-bis(dimethylcarbamoyl)-2,5-dimethyl-1*H*-pyrrol-1-yl)carbamate (3k): Product **3k** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 72% yield (225.0 mg); white solid; mp: 167–168 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.54 (br, 1H), 3.72 (br, 3H), 2.86 (s, 12H), 1.99 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 166.2, 155.8, 127.4, 112.6, 52.7, 9.5; IR (nujol): ν_{max} = 3385, 1773, 1704 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}N_4NaO_4$ [M + Na]$^+$: 333.1533; found: 333.1524.



3l

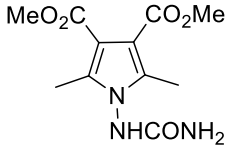
Dimethyl 1-((etoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3l):[284] The product **3l** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 93% yield (275.9 mg); white solid; mp: 88–91 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.68 (br, 1H), 4.12–4.21 (m, 2H), 3.70 (s, 6H), 2.17 (s, 6H), 1.24–1.28 (m, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.6, 155.1, 133.9, 109.6, 61.8, 51.2, 14.3, 9.6; IR (nujol): ν_{max} = 3337, 1722, 1668 cm^{-1}; MS (ESI) *m/z*: 299 (M + H$^+$); anal. calcd. for $C_{13}H_{18}N_2O_6$ (298.29): C 52.34, H 6.08, N 9.39; found: C 52.18, H 6.16, N 9.48.



3m

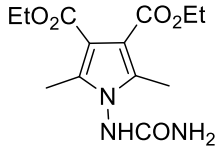
Diethyl 1-((etoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (3m): Product **3m** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 53% yield (171.7 mg); white solid; mp: 108–111 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 10.67 (br, 1H), 4.16 (q, *J*= 7.2 Hz, 6H), 2.17 (s,

6H), 1.23 (t, J = 7.2 Hz, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.1, 155.2, 133.6, 109.8, 61.8, 59.6, 14.3, 14.0, 9.5; IR (nujol): ν_{max} = 3328, 1747, 1707 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{23}N_2O_6$ $[M + H]^+$: 327.1551; found: 327.1557.



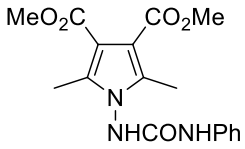
3n

Dimethyl 2,5-dimethyl-1-ureido-1*H*-pyrrole-3,4-dicarboxylate (3n):[285,286] Product **3n** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 80% yield (214.7 mg); white solid; mp: 236–238 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 9.22 (br, 1H), 6.35 (br, 2H), 3.69 (s, 6H), 2.16 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 165.0, 157.0, 134.9, 109.3, 51.2, 9.9; IR (nujol): ν_{max} = 3420, 3260, 1710, 1680 cm^{-1}; MS (ESI) *m/z*: 270 ($M + H^+$); anal. calcd. for $C_{11}H_{15}N_3O_5$ (269.25): C 49.07, H 5.62, N 15.61; found: C 48.93, H 5.67, N 15.68.



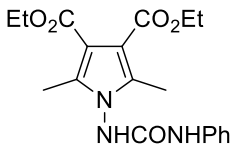
3o

Diethyl 2,5-dimethyl-1-ureido-1*H*-pyrrole-3,4-dicarboxylate (3o): The product **3o** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 72% yield (213.7 mg); white solid; mp: 201–203 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 1.22 (t, J = 6.8 Hz, 6H), 2.15 (s, 6H), 4.14 (q, J = 7.2 Hz, 4H), 6.36 (br, 2H), 9.23 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.4, 156.9, 134.5, 109.4, 59.5, 14.1, 9.8; IR (nujol): ν_{max} = 3420, 3260, 1705, 1680 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{20}N_3O_5$ $[M + H]^+$: 298.1397; found: 298.1397.



3p

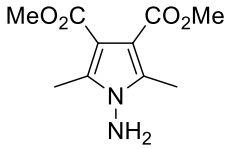
Dimethyl 2,5-dimethyl-1-(3-phenylureido)-1*H*-pyrrole-3,4-dicarboxylate (3p):[285,286] The product **3p** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 55% yield (191.2 mg) from **1p** and in 87% yield (60.1 mg) from **2a**; white solid; mp: 216–219 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 2.21 (s, 6H), 3.71 (s, 6H), 7.01 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 9.36 (br, 1H), 9.46 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.7, 153.6, 139.0, 134.7, 128.6, 122.4, 118.8, 109.3, 51.0, 9.8; IR (nujol): ν_{max} = 3340, 3240, 1710, 1690 cm^{-1}; MS (ESI) *m/z*: 346 ($M + H^+$); anal. calcd. for $C_{17}H_{19}N_3O_5$ (345.13): C 59.12, H 5.55, N 12.17; found: C 59.03, H 5.64, N 12.28.



3q

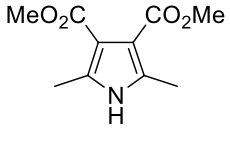
Diethyl 2,5-dimethyl-1-(3-phenylureido)-1H-pyrrole-3,4-dicarboxylate (3q): The product **3q** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 51% yield (188.9 mg); pale yellow solid; mp: 203–205 °C; **^{1}H NMR** (400 MHz, DMSO-d_6, 25 °C): δ 1.23 (t, J = 6.8 Hz, 6H), 2.21 (s, 6H), 4.17 (q, J = 7.2 Hz, 4H), 7.01 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 8.4 Hz, 2H), 7.46 (dd, J = 8.4 Hz, J = 1.2 Hz, 2H), 9.38 (br, 1H), 9.48 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6, 25 °C): δ 164.3, 153.7, 139.0, 134.5, 128.7, 122.5, 118.8, 109.6, 59.5, 14.1, 9.8; IR (nujol): ν_{max} = 3311, 1732, 1684 cm^{-1}; MS (ESI)

m/z: 374 ($M + H^+$); anal. calcd. for $C_{19}H_{23}N_3O_5$ (373.16): C 61.11, H 6.21, N 11.25; found: C 61.25, H 6.18, N 11.12.



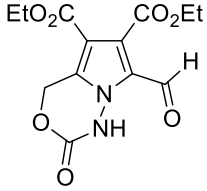
5a

Dimethyl 1-amino-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (5a): The product **5a** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 73% yield (49.3 mg); yellowish solid; mp: 114–116 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, 25 °C): δ 2.29 (s, 6H), 3.66 (s, 6H), 5.62 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-*d*$_6$, 25 °C): δ 165.1, 134.3, 108.3, 50.8, 10.2; IR (nujol): ν_{max} = 3328, 3440, 1755, 1762 cm^{-1}; MS (ESI) *m/z*: 227 ($M + H^+$); anal. calcd. for $C_{10}H_{14}N_2O_4$ (226.23): C 53.09, H 6.24, N 12.38; found: C 53.24, H 6.28, N 12.27.



6a

Dimethyl 2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate (6a):[281] The product **6a** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 52% yield (55.3 mg); pale yellow solid; mp: 112–113 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ 2.31 (s, 6H), 3.78 (s, 6H), 8.97 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, 25 °C): δ 166.0, 132.8, 112.0, 51.3, 12.3; IR (nujol): ν_{max} = 3262, 1736, 1715, 1675 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{14}NO_4$ $[M + H]^+$: 212.0917; found: 212.0923.



7a

Diethyl 7-formyl-2-oxo-2,4-dihydro-1*H*-pyrrolo[1,2-*d*][1,3,4]oxadiazine-5,6-dicarboxylate (7a): The product **7a** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 21% yield (19.8 mg); yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ 1.35 (t, *J* = 7.2 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.96 (s, 2H), 9.76 (s, 1H), 10.40 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, 25 °C): δ 180.0, 163.5, 163.4, 158.8, 143.6, 129.8, 126.2, 112.9, 61.8, 61.0, 57.8, 14.2; IR (nujol): ν_{max} = 3320, 1743, 1710, 1685, 1620 cm^{-1}; MS (ESI) *m/z*: 311 ($M + H^+$); anal. calcd. for $C_{13}H_{14}N_2O_7$ (310.26): C 50.33, H 4.55, N 9.03; found: C 50.16, H 4.64, N 8.98.

CHAPTER 6

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12. Maiti, S., Mal, P. *Org. Lett.* **2017**, *19*, 2454–2457.
13. For a complete list of the works published by this group, here are reported the ORCIDs of the members:
    Lucia De Crescentini: https://orcid.org/0000-0002-8239-3340
    Gianfranco Favi: https://orcid.org/0000-0003-3112-819X
    Fabio Mantellini: https://orcid.org/0000-0002-1140-5404
    Giacomo Mari: https://orcid.org/0000-0002-5076-942X
    Stefania Santeusanio: https://orcid.org/0000-0001-7987-5309
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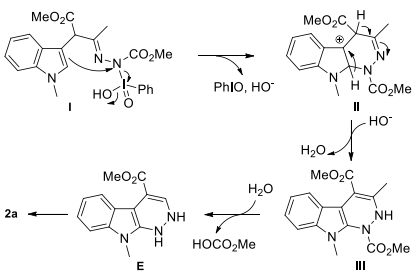

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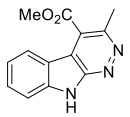
187. 

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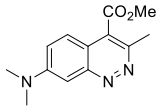
222. 

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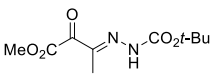
273. 

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