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Development of a comprehensive study on base-controlled regioselective functionalization and Iridium-catalysed borylation of indolizines

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Resumo

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Indolizina é um importante bioisótero do indol, sendo considerada uma estrutura privilegiada, com aplicações nas áreas farmacêutica, agroquímica e de ciências de materiais. Nesse contexto, o foco desta tese foi o desenvolvimento de novas metodologias para a preparação de derivados indolizínicos mais complexos, utilizando diferentes estratégias, como (a) metalação dirigida utilizando bases de lítio e bases mistas de Mg complexadas com LiCl e (b) borilações C-H usando $[Ir(OMe)(COD)]_2$ como catalisador. Este trabalho permitiu o isolamento de 39 novos derivados funcionalizados nas posições C-2, C-3 ou C-5 em rendimentos de 48 a 95%, através de uma abordagem regiosseletiva controlada por base, utilizando amidetos de lítio e TMPMgCl·LiCl. Nos últimos anos, a borilação direta de arenos e heteroarenos vem se destacando como uma abordagem eficiente para a preparação de derivados funcionalizados que dificilmente poderiam ser preparados empregando métodos tradicionais. No entanto, embora muitos compostos heterocíclicos como indol, azaindóis, piridinas, pirróis e quinolinas tenham sido investigados, essa é a primeira vez que um estudo foi realizado para o núcleo indolizínico. Sete indolizinas inéditas puderam ser sintetizadas através deste protocolo.

Keywords: *N*-heterocíclicos, indolizinas, metalação, ativação C-H, C-H borilação, acoplamento cruzado de Negishi, acoplamento cruzado de Suzuki.

Abstract

Bertallo, C. R. S. **Desenvolvimento de um estudo abrangente sobre a funcionalização regiosseletiva base-dependente e reações de borilações catalisadas pelo irídio em indolizinas. 2020, 228f.** PhD Thesis. Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2020.

Indolizines is an important bioisostere of indole being considered as privileged structure with application in pharmaceutical, agrochemical and material sciences field. In this context, the focus of this thesis was to develop new methodologies for the preparation of more complex indolizine scaffolds using different strategies such as (a) directed metalation using lithium bases and Mg bases complexed with LiCl and (b) C-H borylation using $[Ir(OMe)(COD)]_2$ as catalyst. This work allowed the isolation of 39 new indolizine derivatives functionalized at C-2, C-3 or C-5 position in 48-95% yields through a base-controlled regioselective approach using lithium amides and TMPMgCl·LiCl. Over the last years, the direct C-H borylation of arenes and heteroarenes has become an attractive method for the preparation of functionalized derivatives that could be hardly to prepare through the traditional methods. However, whilst many heterocycles such as indole, azaindoles, pyridines, pyrroles and quinolines have been investigated, to the best of our knowledge this is the first time that a study has been conducted for indolizine. Seven new modified indolizines could be synthetized using this protocol.

Keywords: *N*-heterocycles, indolizines, metalation, C-H activation, C-H borylation, Negishi cross-coupling, Suzuki cross-coupling.

1. Introduction

1.1 Thesis Overview

This thesis is divided in two chapters and discusses new approaches for the regioselective functionalization of indolizines using (a) directed metalation reactions and (b) C-H activation/borylation reactions.

Chapter 1 provides a brief introduction to indolizine ring (synthesis and regioselectivity) and directed metalation strategy using lithium and mixed lithium/magnesium amides. The work presented in this chapter is focused on the development of a base-controlled regioselective approach to prepare a library of functionalized indolizines derivatives with different groups such as halogens, esters, carboxylic acids, amides, aryl, heteroaryl and formyl groups. Some of these derivatives displayed an interesting fluorescence property and consequently the photochemical and photophysical properties of these compounds were evaluated (Figure 1).

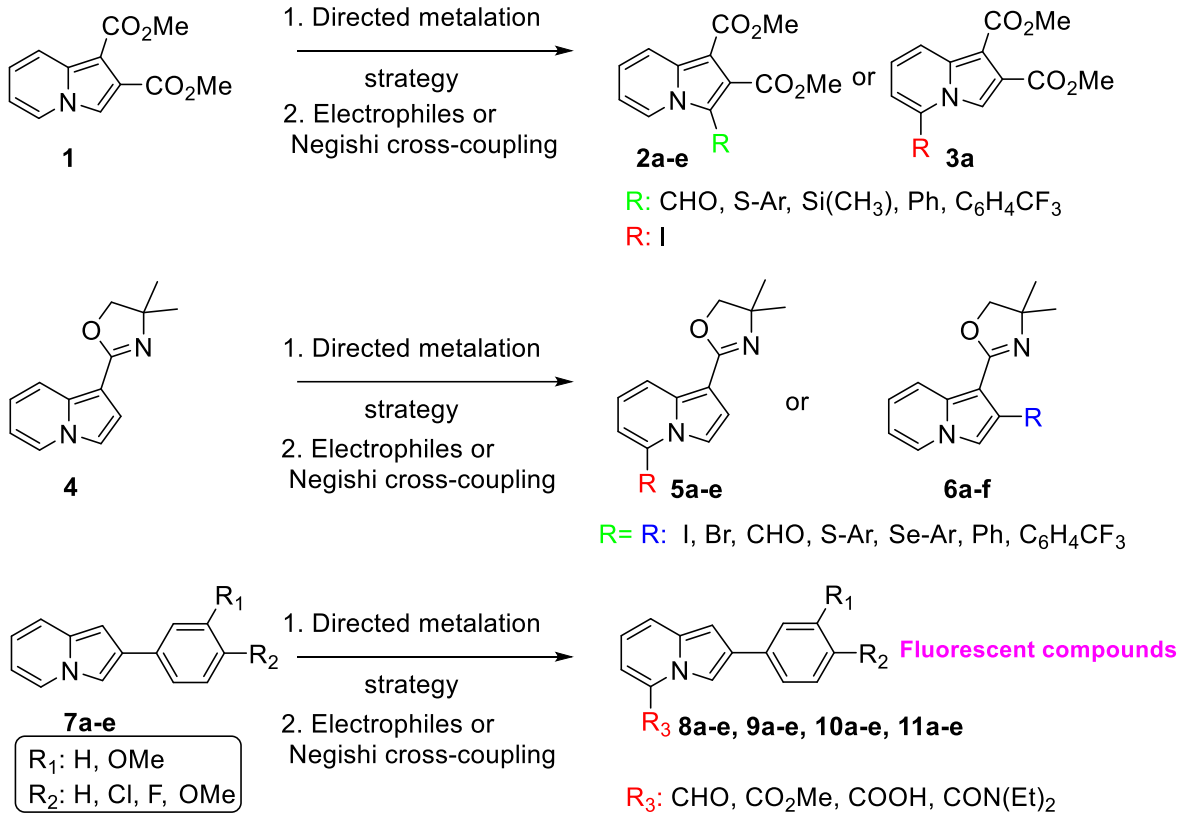


Figure 1. Directed metalation strategy to prepare functionalized indolizine derivatives.

Chapter 2 provides a brief introduction to C-H activation and C-H borylation of *N*-heterocycles. A comprehensive study was conducted focusing on the application of Ir-catalysed C-H activation/borylation of indolizines aiming the preparation of a small library of indolizines derivatives, which would be hardly to obtain by traditional methods (Figure 2).

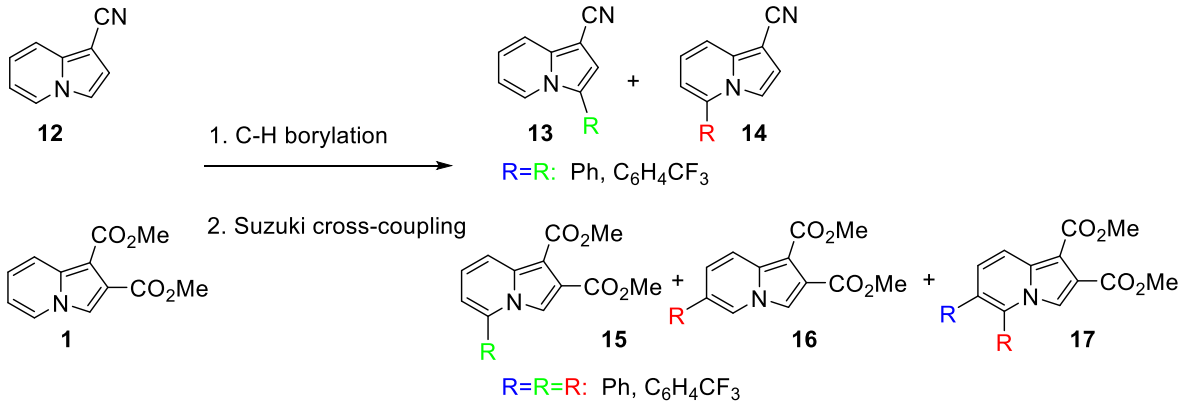


Figure 2. C-H borylation strategy to prepare functionalized indolizines derivatives.

1.2 *N*-heterocycles

N-heterocyclic compounds are the most abundant scaffolds found in nature and play an important role in the biochemical process that maintain life in different organisms. For example, they are important buildings blocks of vital vitamins, hormones, amino acids, DNA and RNA (Figure 3) (BALABAN; ONICIU; KATRITZKY, 2004; BARREIRO; FRAGA, 2001; VITAKU; SMITH; NJARDARSON, 2014).

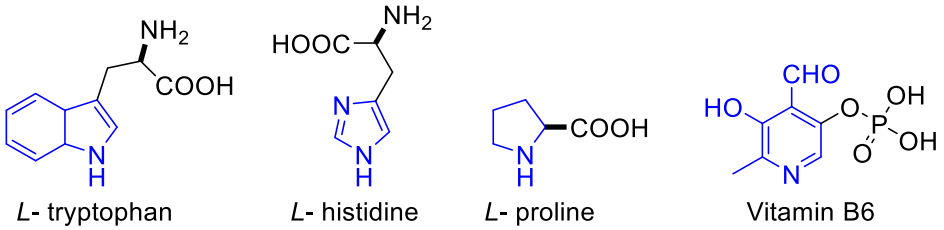


Figure 3. Examples of vital molecules that contain a *N*-heterocycle in their structures.

Their subunits can also be found in important pharmaceutical drugs such antibiotics, anticancer, antifungal, central nervous system depressant, antilipidemic, antihistaminic, proton pump inhibitor, antipsychotic and others (Figure 4) (SANDEEP et al., 2017).

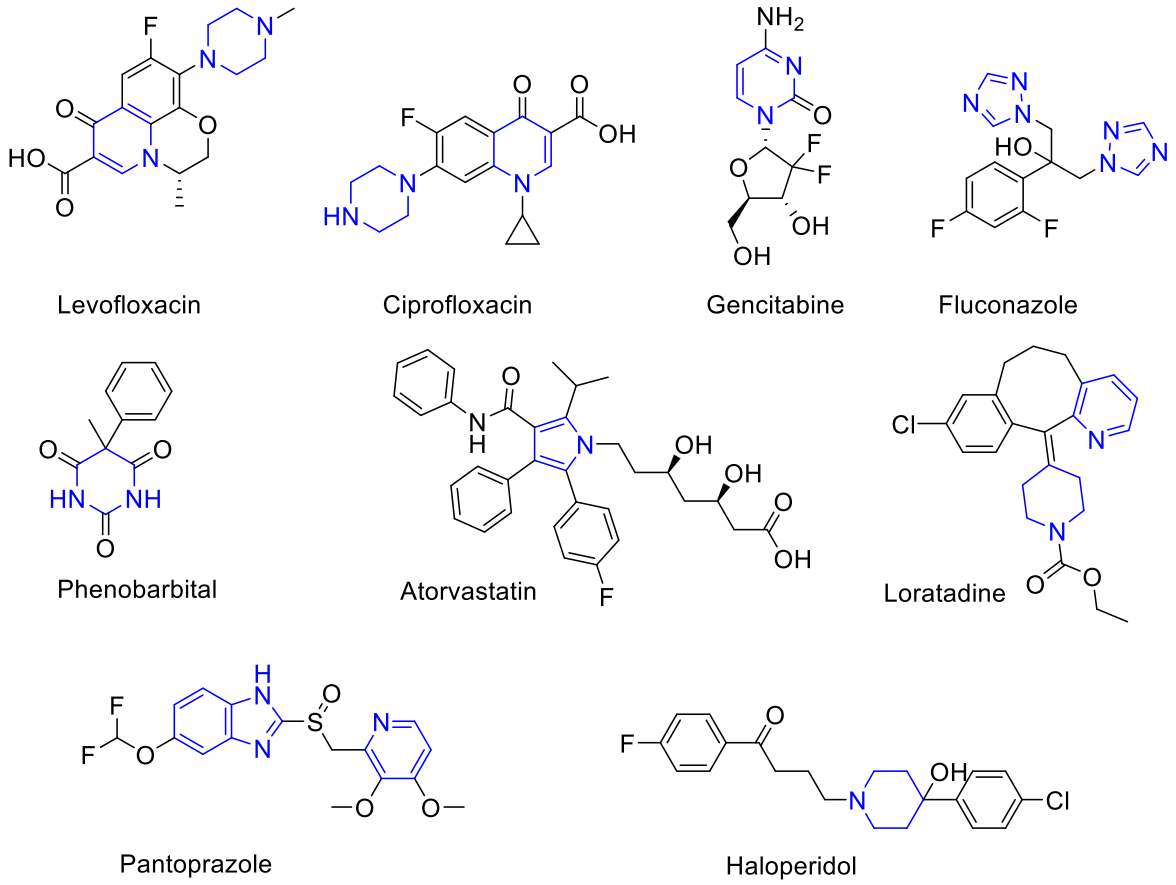


Figure 4. Pharmaceutical drugs containing N-heterocycles in their structures.

Another important class of molecules that contain *N*-heterocyclic core in their structures are alkaloids. Alkaloids such as those which contain an indole core are mainly found in plants *Apocynaceae* (genera *Alstonia*, *Aspidosperma*, *Rauvolfia* and *Catharanthus*), *Rubiaceae* (*Corynanthe*), *Loganiaceae* (*Strychnos*) and some fungi (*Psilocybe cubensis*, *Ergot* and *Bufo alvarius*)(HESSE, 2002) . The biological activity of many of these compounds has been well understood for centuries.

For example, reserpine, an alkaloid first isolated from *Rauvolfia serpentine* it was largely used as medicine to treat snake bites and insanity in India around 1000 B.C. Nowadays, it is known that this substance has an antihypertensive effect and more recently some studies have showed that it can also be used for relief of psychotic symptoms associated to schizophrenia (Figure 5) (HOENDERS et al., 2018).

Ibogaine, present in the roots of the perennial rainforest shrub Iboga was commonly used for medicinal and ritual purposes within African spiritual traditions of the Bwiti. A recent research conducted by Brazilians researchers at Federal University of São Paulo (UNIFESP) has showed that this drug can help in drug addiction (cocaine, crack and others) (CHAGAS et al., 2014). However, its efficacy has been hard to prove,

since negative side effects have been reported on administration of this drugs, which has led to it being prohibited for use in certain countries (Figure 5) (BROWN, 2013).

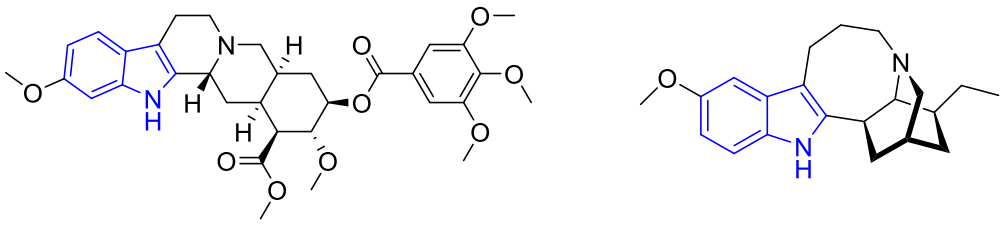


Figure 5. Examples of alkaloids with biological activity.

1.3 Indolizines

Among the most important *N*-heterocyclic compounds in drug development field are the indolizines (JOULE; MILLES; SMITH, 2000).

Indolizine is a *N*-fused bicyclic compound which is the combination of a 6-membered ring (π-deficient) and 5-membered ring (π-excessive) (Figure 6).

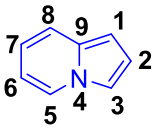


Figure 6. Indolizine ring.

It possesses a delocalized 10π-electron system and nitrogen atom has influence in both rings. The 5-membered ring resembles the reactivity of a pyrrole being suitable to electrophilic substitutions reactions while the 6-membered ring resembles the reactivity of a pyridine ring. Despite this mixture of properties, indolizines are considered a π-excessive ring and promptly undergo electrophilic substitutions (KATRITZKY, A. R.; RAMSDEN, C. A.; JOULE, J. A.; ZHDANKIN, 2010).

Indolizine is also an important bioisostere analogue of indole being considered as privileged structure with application in pharmaceutical, agrochemical and material sciences field. In addition to the natural products, in the last few years several research groups have been reported synthetic derivatives with different biological activities (against tuberculosis, leishmaniasis, antifungal, antiviral, antibacterial, antitumor properties, analgesics, anti-inflammatory agents, calcium channel blockers and inhibitors of 15-lipoxygenase) (MEDDA et al., 2003; DE BOLLE et al., 2004; TEKLU et al., 2005; JAMES et al., 2006; DARWISH, 2008; SHEN et al., 2010; HAZRA et al., 2011; LINGALA et al., 2011; SHARMA; KUMAR, 2014) (Figure 7).

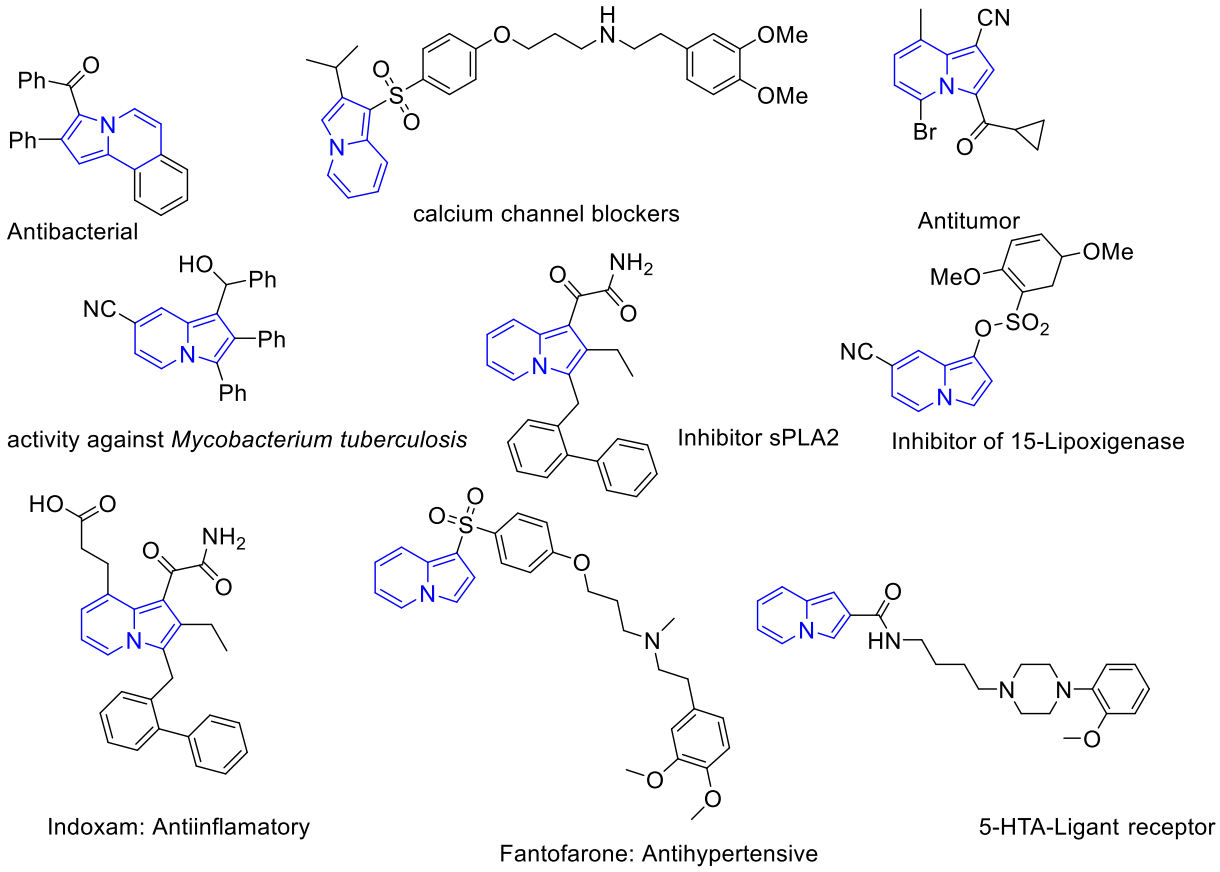


Figure 7. Examples of bioactive indolizines.

Although the occurrence of the indolizine ring system in natural products is quite rare, its partially and fully hydrogenated derivatives are common in nature and some of them present interesting biological activities. For example, Camptothecin is a natural product isolated from a Chinese tree *Camptotheca acuminate* (BUTA; NOVAK, 1978) which selectivity inhibits DNA tropomerase I (HERTZBERG; CARANFA; HECHT, 1989) (Figure 8). (+)-Castanorpermum, (+)-lentiginosine and (+)-swainsonine are examples of fully saturated indolizines (known as indolizidinone alkaloids) which are potent glycosidase inhibitors (Figure 8) (WATSON et al., 2001).

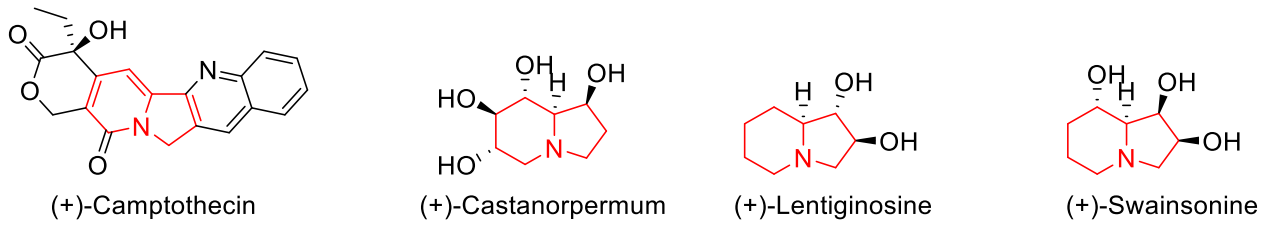


Figure 8. Examples of partially and fully indolizine derivatives found in nature.

Despite of all medicinal chemistry relevance, recently many research groups have been dedicated to the synthesis of fluorescent *π*-conjugated indolizines derivatives due to their application as dyes (KUMAR et al., 2013; OOYAMA et al., 2013), bioprobes (KIM; LEE; PARK, 2011; JEONG et al., 2012; CHOI et al., 2014), electroluminescent material for optoelectronic (WAN et al., 2012; WANG et al., 2013), biomarkers (OLIVEIRA et al., 2010; LIU et al., 2012) and sensors (DELATTRE et al., 2005; LUNGU et al., 2005; MORO et al., 2013).

For example, Sung and co-workers (SUNG et al., 2017) have developed a new fluorescent mitochondrial probe for monitoring mitochondrial integrity under the live cell condition (Figure 9). It is known that cancer cells have different patterns in mitochondrial morphology and because of that the design of probes which can cross the cellular membrane of a cancerous cell can help in cancer phenotype identification and in the measurement of the drug, due to the accumulation of the probe at the mitochondrial membrane (ALIROL; MARTINOU, 2006; BLANCHET et al., 2015; GIEDT et al., 2016).

In this study they were able to show that simple changes in the chemical structure of organic fluorophores can cause a significant difference in the cellular staining ability as well as photophysical properties of organic fluorochromes. For example, the introduction of an olefin spacer between pyridinium moiety and indolizine fluorophore caused significant differences in the absorption, emission wavelength and mitochondrial staining ability of bioprobes.

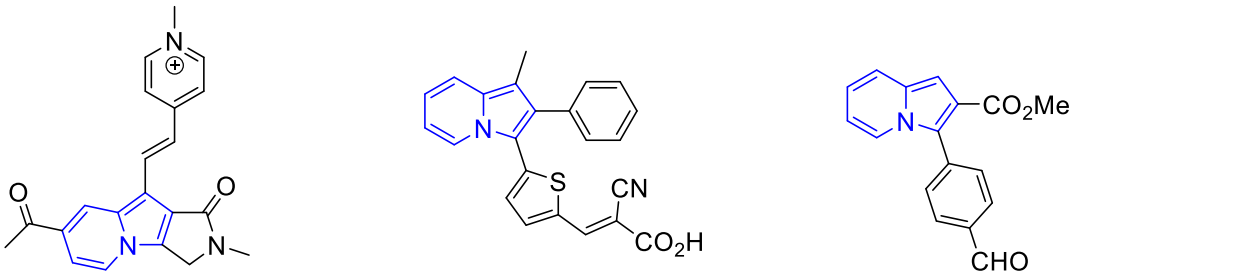


Figure 9. Examples of fluorescent *π*-conjugated indolizines derivatives.

1.4 Indolizine: Synthesis

Indolizine scaffold can be synthetized through several different approaches (SADOWSKI; KLAJN; GRYKO, 2016), however, most of used protocols are based in the annulation of pyridine or pyrrole-based substrates to indolizines (Figure 10).

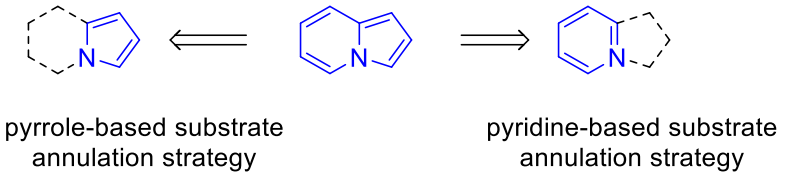


Figure 10. Approaches to indolizine framework.

The annulation of pyridines is the most used strategy for the synthesis of indolizines, being relevant to highlight two approaches: (a) intramolecular cyclization of 2-akylpyridines with anhydrides (Scholtz reaction) or α-haloketones (Tschitschibabin or Chichibabin reaction) and (b) 1,3-dipolar cycloadditions of pyridinium salts with alkenes or alkynes (SINGH; MMATLI, 2011; VEMULA; VURUKONDA; BAIRI, 2011; SHARMA; KUMAR, 2014; KIM et al., 2015) (Figure 11).

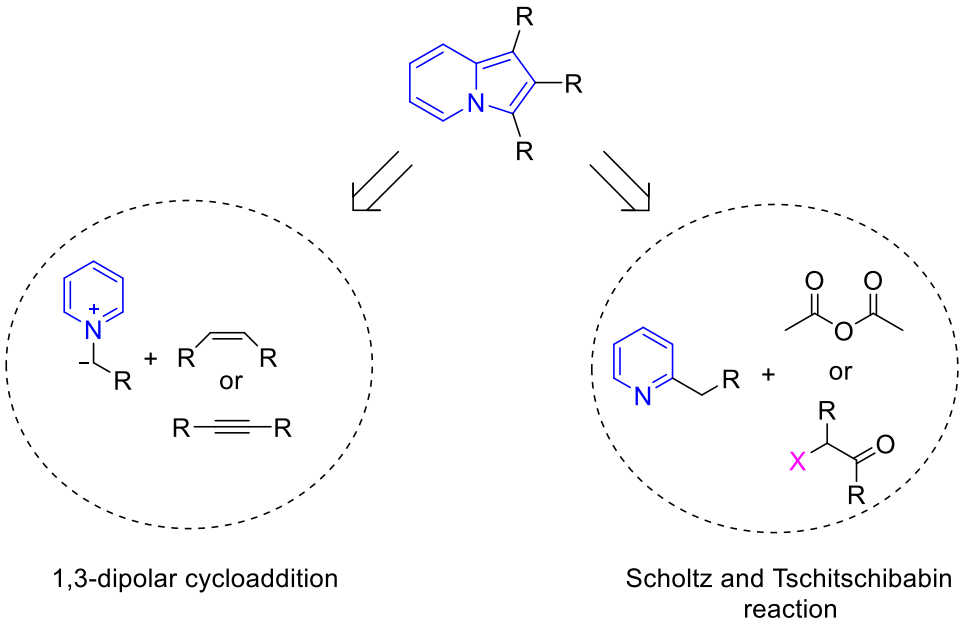
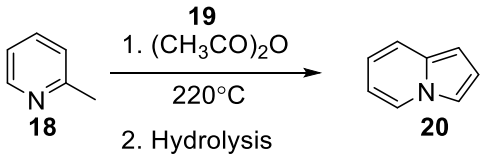


Figure 11. Traditional synthesis of indolizine using pyridines.

In 1912 Scholtz described for the first time the synthesis of indolizine **20** through reaction between 2-methyl-pyridine **18** and acetic anhydride at 220 °C followed by a hydrolysis step. However, this approach is no longer used because of the low yield,

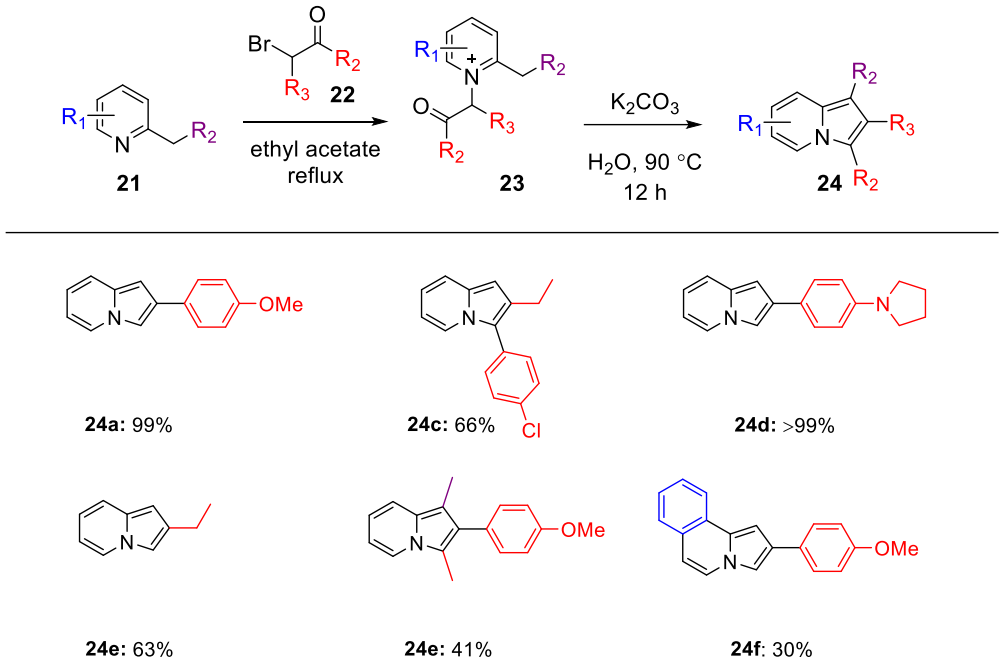
the difficulty in preparing functionalized derivatives and the requirement of high temperatures (SCHOLTZ, 1912) (Scheme 1).



Scheme 1. Scholtz reaction.

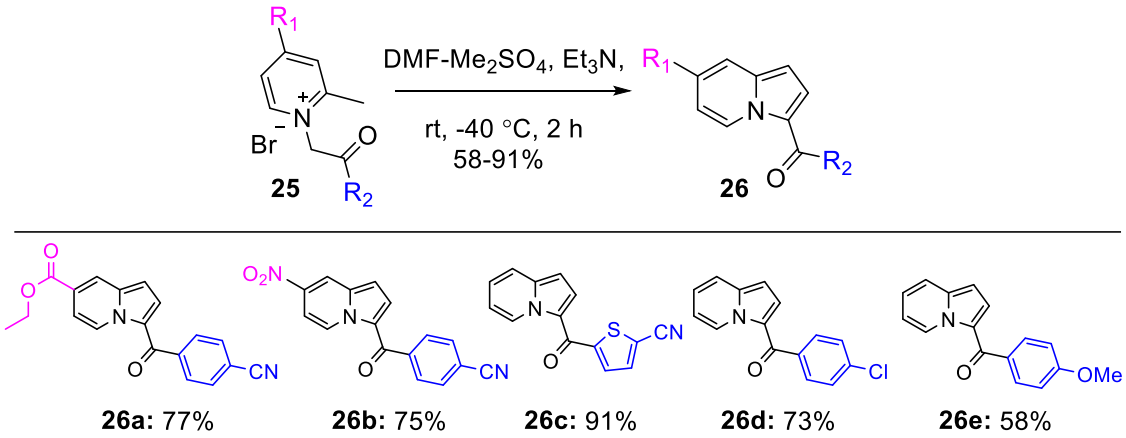
On the other hand, Tschitschibabin's strategy was first reported in 1927 and remain the simplest and most efficient way to prepare 2-alkyl or aryl indolizines. In this approach, pyridine is converted into its corresponding quaternary salt **23** by reaction with α-haloketones **22**. Then, after an intermolecular cyclization mediated by base (K_2CO_3), 2-alkyl or aryl indolizines were obtained in good yield. Chai and co-workers have demonstrated the efficiency of this approach through the synthesis of novel 2-arylated indolizines of type **24** using several pyridinium ylides in a chromatography-free protocol (TSCHITSCHIBABIN, 1927; CHAI et al., 2003).

Different kind of bases can be used including inorganic salts such as carbonates and bicarbonates in aqueous medium. The yield for this reaction are reasonable, however, the electron-withdrawing nature of the α-haloketone and the presence of bulky substituents in the pyridine ring (R_1 and R_2) may slower the intramolecular cyclization or leave the nitrogen less accessible to the *N*-alkylation (Scheme 2, compound **21** to **23**) leading to low yield (CHAI et al., 2003) (Scheme 2).



Scheme 2. Tschitschibabin approach adapted by Chai and co-workers.

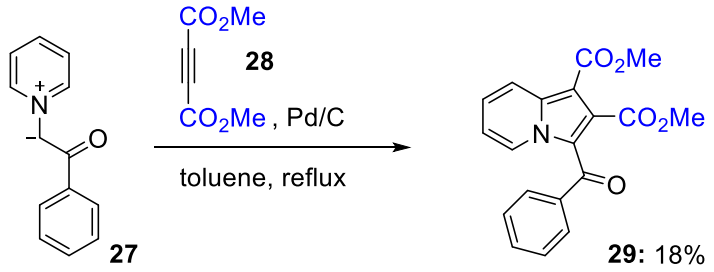
In 2007, Przewloka and co-workers reported the synthesis of an array of 3-acylindolizines in the presence of DMF·Me_2SO_4. This methodology exploits the use of pyridines and α-haloketones substituted with several functional groups such as methoxy, cyano, nitro, halogens and heteroaryl (PRZEWLOKA et al., 2007) (Scheme 3).



Scheme 3. Synthesis of 3-acylindolizines.

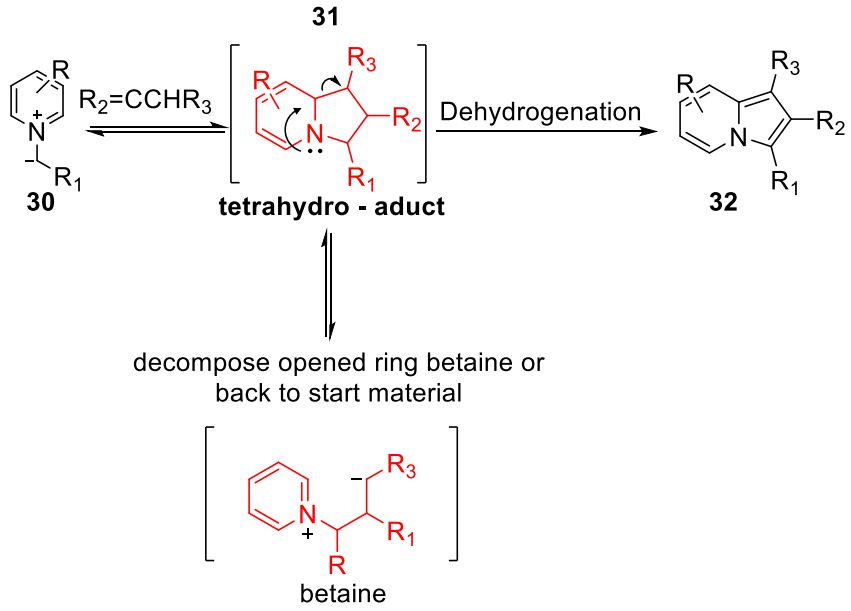
Another stablished approach for the preparation of functionalized indolizines is 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient dipolarophiles. In 1961 Boekelheide demonstrated the preparation of 1,2,3-trisubstituted indolizines **29**

by reaction between pyridinium ylide type **27** with an activated alkyne **28**, using toluene as solvent in the presence of Pd/C (GALBRAITH et al., 1961) (Scheme 4).



Scheme 4. Synthesis of 1,2,3-trisubstituted indolizines.

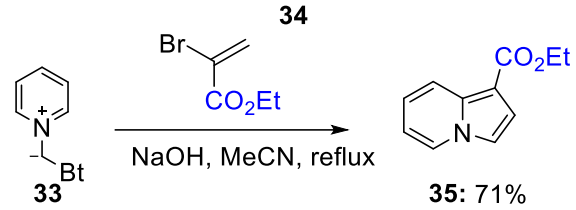
Since then, numerous methodologies using different kind of activated alkynes and alkenes as dipolarophiles have been reported. According to the cycloaddition mechanism, there is formation of an unstable tetrahydro-adduct intermediate **31** which decomposes to form ring opened compound called betaines or starting materials (Scheme 5) (TSUGE; KANEMASA; TAKENAKA, 1985).



Scheme 5. Decomposition of tetrahydro-adduct intermediate to betaine or starting material.

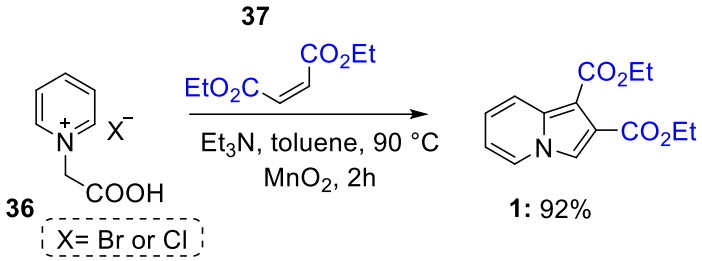
Because of the formation of this instable intermediate **31** when activated methylenes are used as dipolarophiles, it is necessary that they contain in their structure a good leaving group or the use of an oxidizing reagent during the reaction. Katritzky and co-workers have used α-bromo-α,β-unsaturated esters or nitrile as

dipolarophiles to prepare indolizines of type **35**. Through a base-assisted elimination of bromo substituents or benzotriazole (Bt) from the corresponding cycloadduct they were able to prepare C-1 substituted indolizines with different groups (Scheme 6) (KATRITZKY et al., 1999).



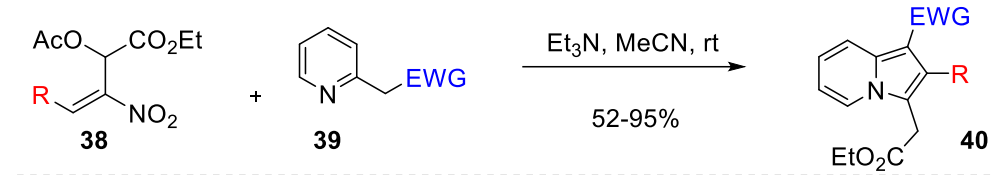
Scheme 6. Synthesis of ethyl indolizine-1-caboxylate.

In 2000, Zhang and co-workers reported the synthesis of 3-unsubstituted indolizines through a 1,3-cycloadditon/oxidation step between activated alkenes and carboxylic acid substituted pyridinium salts **36**. In the absence of good leaving groups in the alkene structure, it was necessary the use of an oxidant in order to promote *in-situ* dehydrogenation of the unstable tetrahydro-adduct. After trying several commercial oxidizing agents, they achieve best results when using MnO_2. For example, by using this strategy they were able to prepare indolizine **1** in 92% yield (Scheme 7) (ZHANG et al., 2000).



Scheme 7. Synthesis of dimethyl indolizine-1,2-dicarboxylate.

Furthermore, another interesting strategy to prepare indolizines bearing groups at pyrrole ring is using Morita-Baylis-Hillman acetates (MBHAs). In this context, Zhu and co-workers were able to react MBHAs with ethyl 2-pyridylacetate and 2-pyridylacetonitrile to obtain several trisubstituted indolizines in moderate to good yield **40** (Scheme 8) (ZHU et al., 2013).



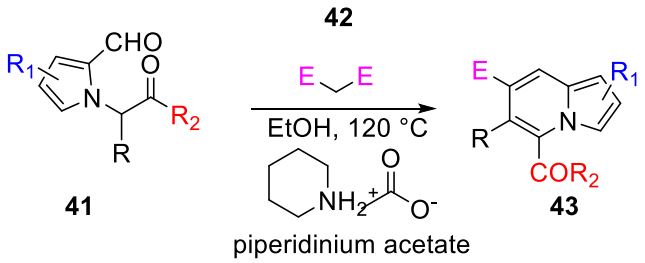
EWG = CO_2Et or CN

R= Ph, 4-Cl-Ph, 4-Cl-Ph, 4-F-Ph, 4-F-Ph, 4-Br-Ph, 3-Br-Ph, 2-Br-Ph, 3-CF_3-Ph, 4-OCH_3-Ph, 4-OAc-Ph, 4-$N(CH_3)_2$-Ph, 2-Furyl

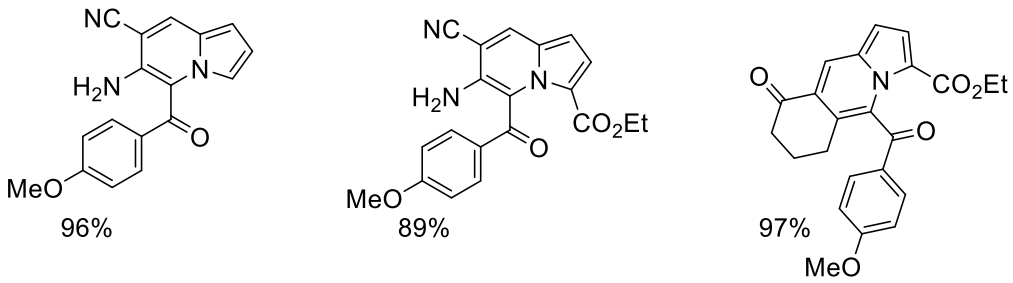
Scheme 8. Synthesis of trisubstituted indolizines from MBHA adduct.

However, these are not the only strategies that can be used to prepare indolizines using pyridine-like substrates. There are also multi-components reactions, cyclodimerizations catalysed by metals or metal free reactions, iodine-mediated direct oxidative cyclization between 2-alkylpyridines and enolizable aldehydes, annulation of propargylic alcohols with pyridine derivatives and others (GOFF, 1999; KIM et al., 2007; CUNHA; DE OLIVEIRA; VASCONCELLOS, 2013).

Despite of the majority strategies to prepare indolizines have been based on pyridine derivatives, recently have been a rising number of approaches using pyrrole-like substrates. In 2013, Kim and co-workers proposed an annulation process that involved a Knoevenagel reaction followed by an intramolecular aldol cyclization which make possible the construction of much more diversified molecules bearing a variety of substituents groups in both rings (KIM; JUNG; KIM, 2013) (Scheme 9).

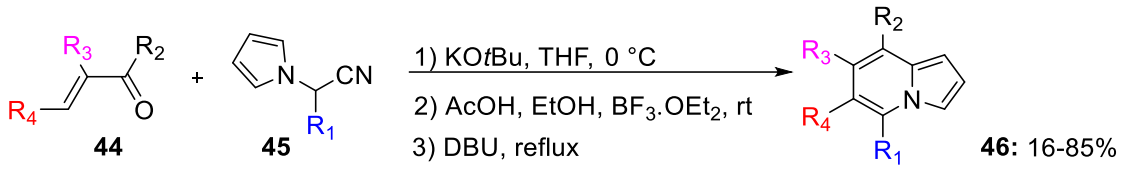


E= electron-withdrawing group



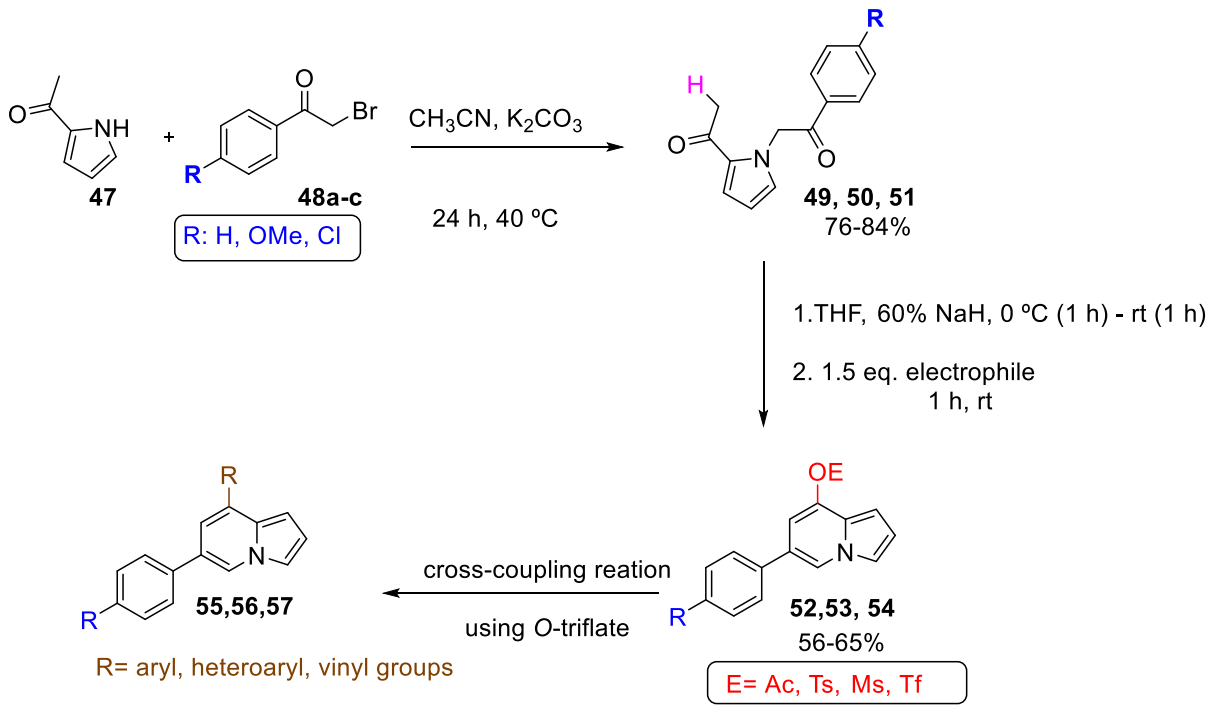
Scheme 9. Synthesis of polysubstituted indolizines involving Knoevenagel approach.

Later, Kucukdisli and Opatz through an one-pot conjugated addition/cyclodehydration/dehydrocyanation sequence involving α,β-unsaturated ketones or aldehydes **44** and 2-(1H-pyrrol-1-yl)nitriles **45** have prepared a number of indolizines fully substituted at pyridine ring (Scheme 10). (KUCUKDISLI; OPATZ, 2012).



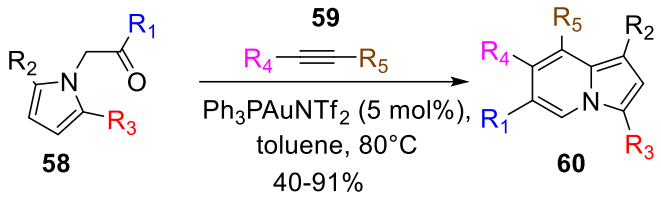
Scheme 10. Synthesis of indolizines fully substituted at pyridine ring.

At the same time, Kim and co-workers have demonstrated preparation of 6,8-dissubtituted indolizines through a based-mediated cyclodimerization of 2-acetylpyrrole derivatives. In this approach, they were able to isolate valuable synthetic intermediates such as *O*-triflate and *O*-acetate indolizines which after undergone Suzuki-Miyaura cross-coupling, Heck coupling, Friedel-Crafts acylation and Vielsmeier-Haack formylation led to the preparation of more complex indolizine derivatives (Scheme 11) (LEE; KIM, 2013).



Scheme 11. Synthesis of 6,8-dissubtituted indolizines through a based-mediated cyclodimerization of 2-acetylpyrrole derivatives.

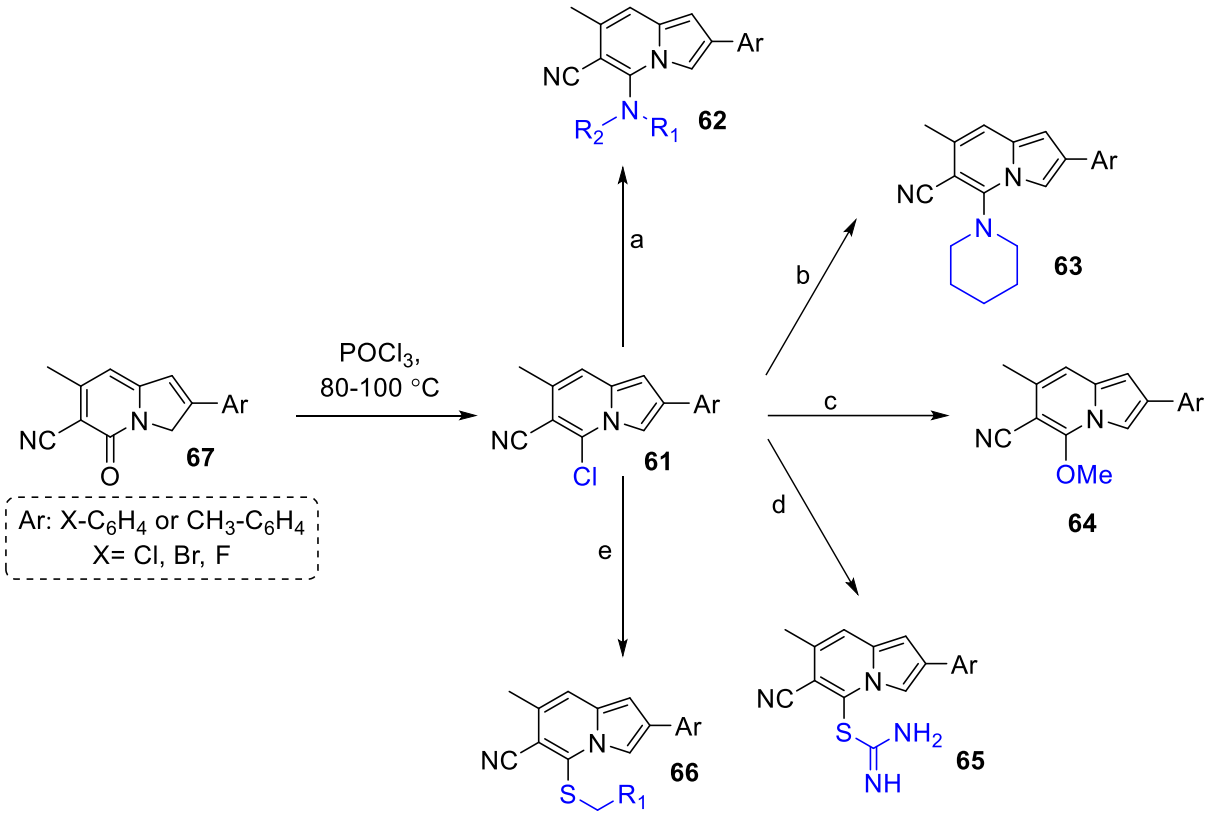
More recently, Liu and co-workers have reported the synthesis of polysubstituted indolizines type **60** using gold catalyst to promote an efficient hydroarylation / cycloaromatization. In this work they used α-(*N*-pyrrolyl)ketones **58** and terminal or activated alkynes **59** in the presence of 5 mol% of $Ph_3PAuNTf_2$ (Scheme 12) (LI; XIE; LIU, 2016).



Scheme 12. Synthesis of polysubstituted indolizines through hydroarylation / cycloaromatization catalysed by gold.

1.5 Reactivity of Indolizines

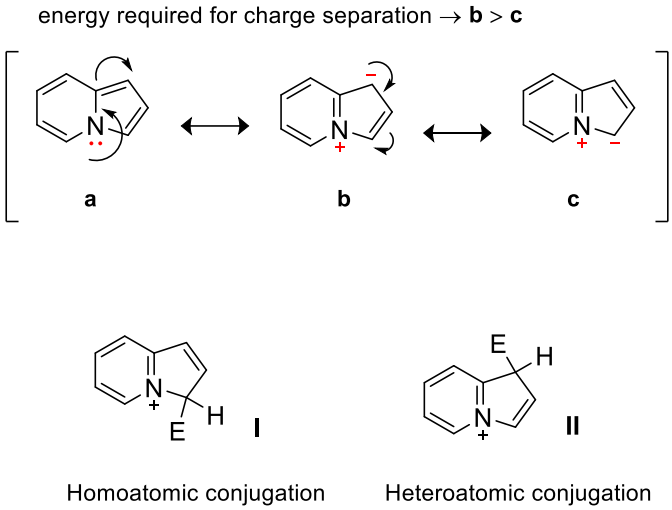
Indolizines belong to the class of *N*-fused heterocyclic *π*-electron-rich type and because of that promptly undergo electrophilic substitution, but in specific cases they can suffer nucleophilic attacks. For example, Babaev and co-workers have shown a protocol were indolizines bearing electron-drawing groups at C-6 position are susceptible to nucleophilic attacks. In this work, firstly, they were able to convert 2-aryl-6-cyano-7-methyl-5-indolizinones **67** to 2-aryl-5-chloro-6-cyano-7-methylindolizines **61**. Then, reacting these 5-chlorinated derivatives with several nucleophiles indolizines type **62-66** were synthetized in good yield (Scheme 13) (BABAEV; VASILEVICH; IVUSHKINA, 2005).



a) NHR_1R_2, rt. b)piperidyl,rt. c)MeONa;MeOH. d) $(NH_2)_2CS$. e) $HSCH_2CO_2Et$, EtOH, NaOH, rt.

Scheme 13. Nucleophilic attack in indolizines bearing electron-drawing groups at C-6 position.

Regarding to electrophilic substitution attack the most reactivity position at indolizine ring is C-3 followed by C-1. C-3 position is more reactive due to two factors: (a) C-3 position holds electronic density and (b) After a nucleophilic attack the C-3 isomer formed can display conjugation over carbon atom (better orbital overlap for conjugation purpose) (Scheme 14, I) while C-1 isomer displays over nitrogen atom (Scheme 14, II) (FRASER; MCKENZIE; REID, 1966a).



Scheme 14. Resonance structures for indolizine moiety.

Furthermore, indolizines can be protonated at C-1 and C-3 position, alkylated through a Mannich-type reaction, acylated at C-3 position through a Friedel-Crafts reaction, C-1 or C-2 halogenated using *N*-bromosuccinimide or C-5 halogenated (when C-1 and C-2 positions are blocked) via regioselective lithiation and can suffer nitration, nitrosation and diazo coupling or oxidation leading to derivatives with or without nucleus cleavage (BORROWS; HOLLAND; KENYON, 1946a, 1946b; ARMAREGO, 1966; FRASER; MCKENZIE; REID, 1966; HARRELL, 1970; GRECI; RIDD, 1979; LINS; BLOCK; DOERGE, 1982; KATRITZKY; REES, 1984; ROSEMARY, 1994; MULVEY et al., 2007; KUZNETSOV; BUSH; BABAEV, 2008; MATVIIUK et al., 2014).

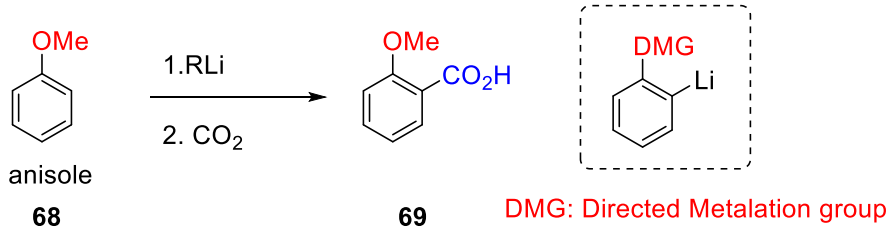
In addition, more complex structure or fluorescent compounds can be prepared through directed metalation approach or palladium-catalysed coupling strategies (AMARAL et al., 2014a, 2015).

1.6 Directed Metalation reaction

The regiocontrolled insertion of different groups into an aromatic and hetroaromatic ring is one of the biggest challenges in organic chemistry. In this kind of manipulation, it is required to have the ability to find the best reactional condition in the presence of frequently sensitive or reactive groups. Besides, even if it is possible to manage these inconvenient in some cases the challenge is pushing the insertion into the desired ring position.

In 1939 and 1940, Gilman and Wittig independently reported the *ortho*-metalation of anisole using PhLi or *n*-BuLi, respectively. As consequence of these studies, the

new concept that some functional groups (called directed metalation groups - DMG) could promote metalation to specific positions (usually *ortho* DMG) started to be investigated (Scheme 15) (GILMAN; BEBB, 1939; WITTIG; PIEPER; FUHRMANN, 1940).



Scheme 15. *Ortho*-metalation of anisole using lithium bases by Gilman and Wittig.

Over the subsequent years researchers such as Hauser (1964), Gronowitz (1968), Gschwend (1976), Meyers (1975), Comins (1983), Beak (1977), Snieckus (1989 and 1999) and others showed that amides, sulfonamides, ozaxolinyl groups, carbamates, esters and oxide phosphines groups can act as good DMGs leading to successful regioselective functionalization of numerous aromatic and heteroaromatic compounds (GREEN; CHAUDER; SNIECKUS, 1999; SCHLOSSER, 2005).

DMGs can direct the metalation to the ortho position due to (a) the ability of the heteroatom present in the DMG be able to effectively coordinate with the metal (lithium) in other to settle a complex-induced proximity effect (CIPE) and promote the directed deprotonation of the substrate or (b) through a inductive effect that lower the pKa value of the adjacent proton (Figure 12) (MONGIN; QUÉGUINER, 2001; CHEVALLIER et al., 2012). It is also important that the DMG group does not react with the base by a nucleophilic attack.

DMG: Directed metalation group

Chelation in the transition state

Acid-base (inductive) mechanism

Figure 12. CIPE effect.

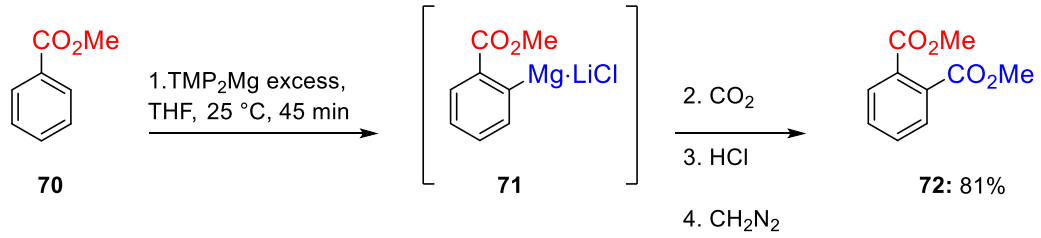
The most common base used in DoM (directed ortho metalation) are the alkyl lithium such as *s*-BuLi, *n*-BuLi and *t*-BuLi. Best results were observed using dry THF or Et_2O as solvents in the presence of TMEDA.

As TMEDA is a good ligand for metals, when in presence of lithium bases the nitrogen present in its structure can coordinate to lithium, forming a cluster of higher reactivity than the normal tetramer and hexamer forms of these bases.

Despite the success of this methodology, the use of lithium bases has some inconvenient such as (a) it is necessary work at low temperatures to achieve regioselectivity, (b) organolithium intermediate formed are very reactive and can led to the formation of undesired side products, (c) lithium bases normally do not tolerate sensitives groups such esters, cyano, ketones, aldehyde, amides, thus it is difficult to apply DoM in substrates bearing these functional groups without previously protection, (d) due to the low stability of this bases in THF at room temperature, they needed to be generated *in-situ* (EATON; MARTIN, 1988; RAPPOPORT; MAREK, 2008). These drawbacks are especially critical in the industry environment, where robust synthetic protocols are needed for process developments.

In 1947, Hauser and Walker reported the preparation of magnesium dialkyl- (R_2NMgX) and bisdialkylamides $(R_2N)_2Mg$ as an alternative to lithium bases. Later, Eaton and co-workers described the *ortho*-metalation of the methyl benzoate **70** using the magnesium diamide TMP_2Mg. In this approach they used excess of TMP_2Mg to form the intermediate **71** which was reacted with carbon dioxide followed by

diazomethane leading to the preparation of **72** in 81% (Scheme 16) (HAUSER; WALKER, 1947; EATON; LEE; XIONG, 1989).



Scheme 16. *Ortho*-metalation of methyl benzoate **70** using TMP_2Mg.

In the following years, the reactivity of these magnesium amides was investigated in the metalation of indoles, thiazoles and pyridines. Despite appearing as an interesting strategy for the functionalization of those substrates, these bases tend to form clusters in organic solvents and because of this the use of large amounts of base was crucial for the reaction success.

In 2006, Knochel and co-workers announced a new class of mixed Mg/Li, Zn/Li and Zn/Mg/Li bases (KRASOVSKIY; KRASOVSKAYA; KNOCHEL, 2006; CLOSOSKI; ROHBOGNER; KNOCHEL, 2007; CLOSOSKI, G. C.; ROHBOGNER, C. J.; KNOCHEL, P. KRASOVSKIY, A., KRASOVISKAYA, 2008; WUNDERLICH et al., 2010) (Figure 13). This combination of hindered bases (less nucleophilic) with LiCl allow the preparation of more soluble and stable bases in THF (standard solvent used in metalation reactions). Besides, selectivity can be achieve working at higher temperatures (25-45 °C) when compared with alkyl lithium bases.

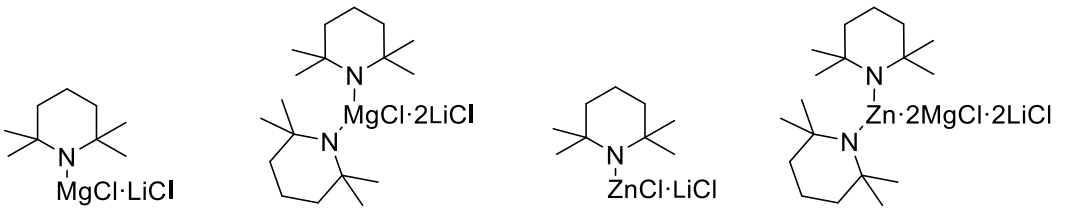
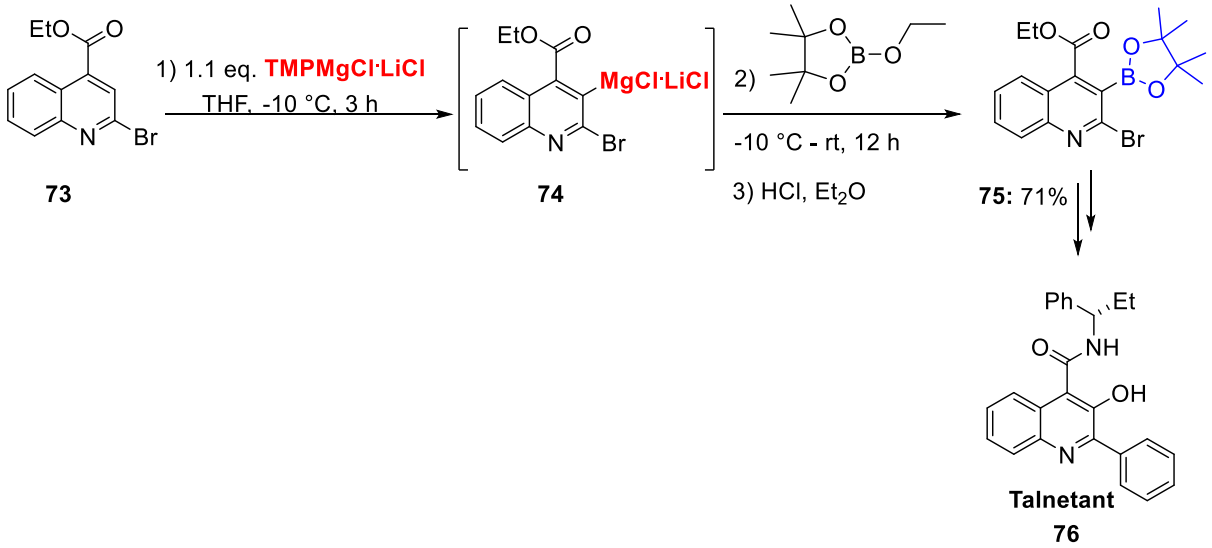


Figure 13. Mixed Mg/Li, Zn/Li and Zn/Mg/Li bases.

Boudet and co-workers have demonstrated the applicability of this approach in the synthesis of Talnetant, a selective antagonist of NK3 receptor produced by GlaxoSmithKline. In this work, quinoline **73** bearing a sensitive group (ester) was selectively deprotonated using 1.1 equivalent of TMPMgCl·LiCl. After deprotonation,

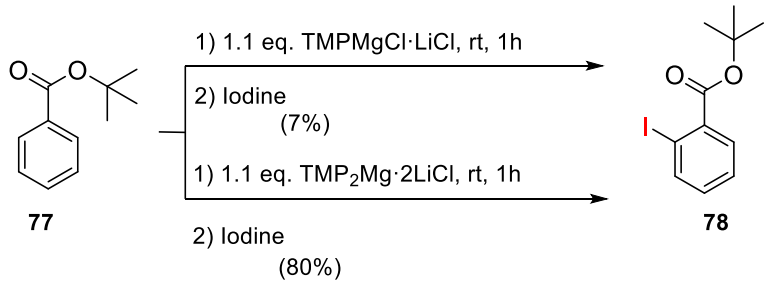
the intermediate **74** was reacted with 2-ethoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane led to the key compound **71** in 71% isolated yield (Scheme 17) (BOUDET; LACHS; KNOCHEL, 2007).



73 74 **76**

Scheme 17. Synthesis of Talnetant.

Even though, the relevance of this new kind of mixed Li/Mg bases in the metalation of a range of unsaturated substrates and the advantages over alkyl lithium bases, some moderately activated substrates gave unsatisfactory results. This is the case of tert-butyl benzoate **77** in which when reacting with TMPMgCl·LiCl followed by quench with iodine gave *tert*-butyl 2-iodobenzoate **78** in 7% yield only. On the other hand, using the new magnesium bisamide complexed with LiCl, first reported by Clososki and co-workers, the desired product **78** was obtained in 80% yield (Scheme 18) (CLOSOSKI; ROHBOGNER; KNOCHEL, 2007).

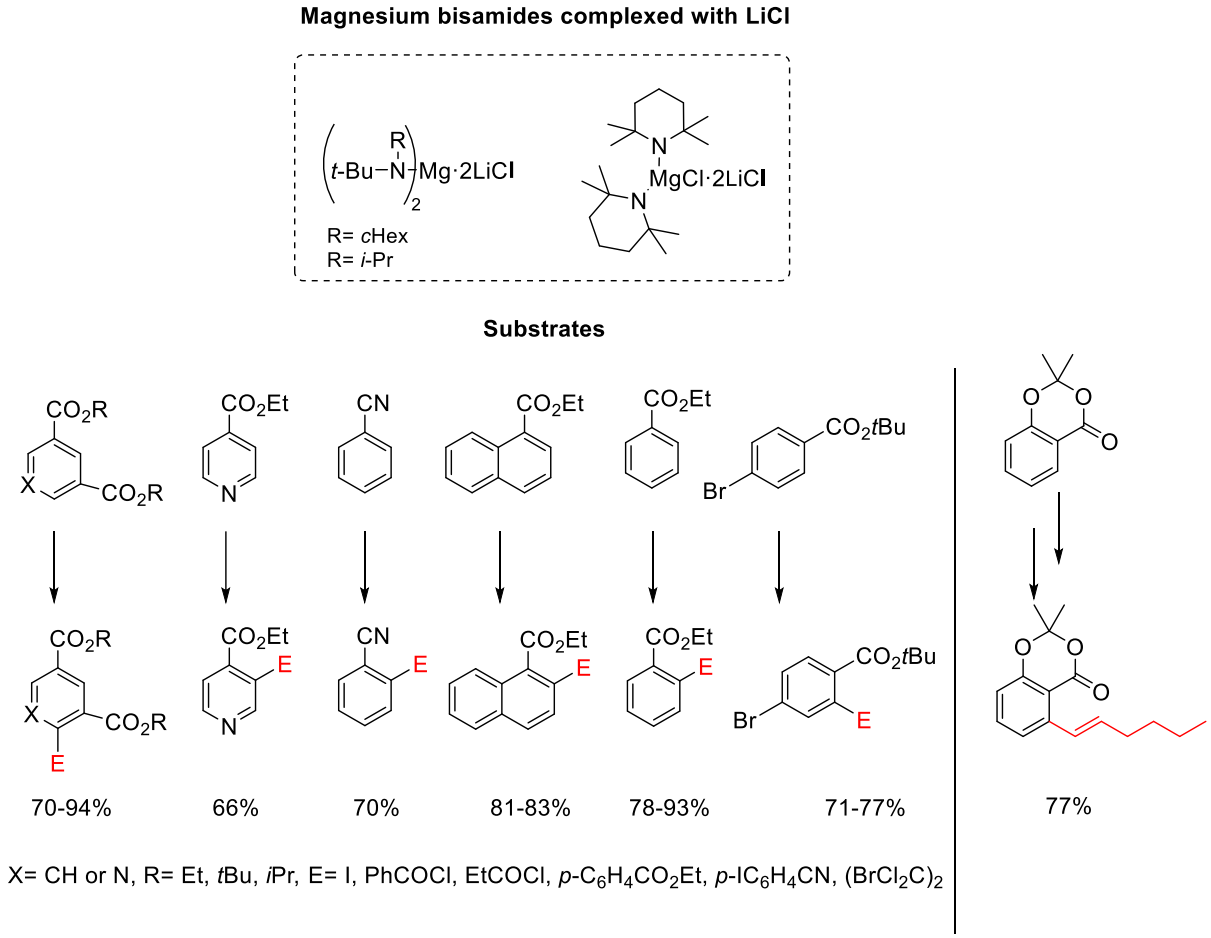


77 **78**

Scheme 18. TMPMgCl·LiCl versus $TMP_2Mg·2LiCl$ in the metalation reaction of *tert*-butyl 2-iodobenzoate.

In this same work the authors prepared another two magnesium bisamides complexed with LiCl (Scheme 19). They also were able to conclude that (a) these new

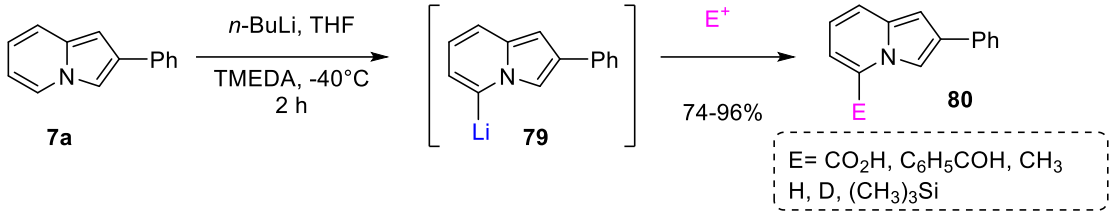
bases can tolerate sensitive functional groups (ketones, cyano, carbonates and bis(dimethylamino) phosphonate groups) (b) they are more powerful then magnesium amide mixed with LiCl and (c) they were capable of promote regioselective metalation of ester-substituted pyridines.



Scheme 19. Examples of substrates that were capable of being reacted with magnesium bisamides complexed with LiCl.

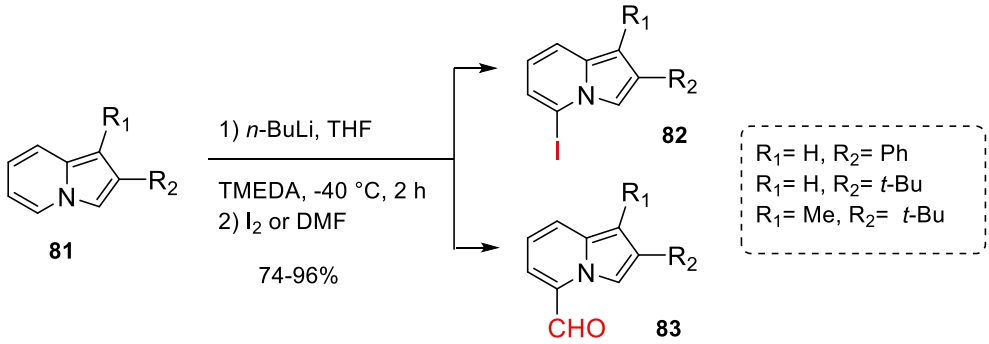
1.7 Metalation of indolizine

In 1992 Renard and Gubin reported for the first time, the regioselective lithiation of 2-phenylindolizine using *n*-BuLi. In this work, they were able to react the C-5 lithiated indolizine intermediate **79** with some electrophiles such as CO_2, benzaldehyde, iodomethane, HCl, D_2O and $(CH_3)_3SiCl$ to obtain C-5 derivatives **80** in good yield (Scheme 20) (RENARD; GUBIN, 1992).



Scheme 20. Regioselective lithiation of 2-phenylindolizine.

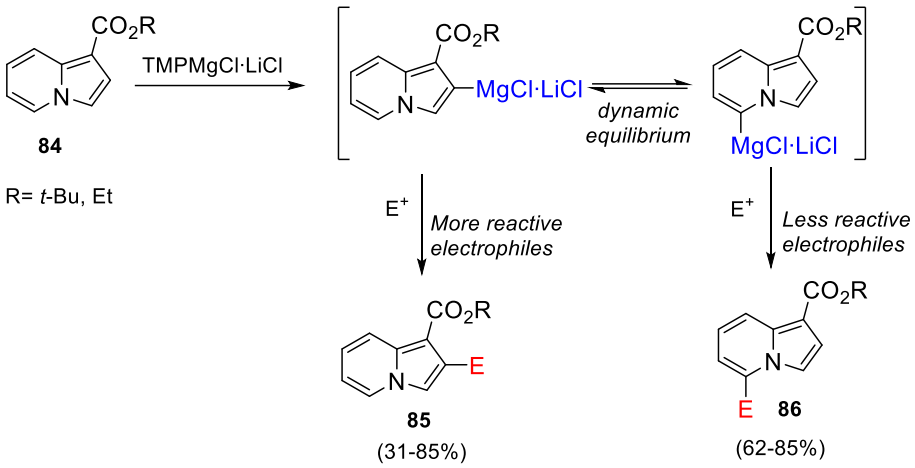
Then, in 2005 Kuznetsov and co-workers, based in the Renard and Gubin work, demonstrated that 2-substituted indolizines bearing alkyl and phenyl groups, after undergo directed metalation can led to the preparation of iodine and formyl derivatives in good yield (Scheme 21) (KUZNETSOV et al., 2005).



Scheme 21. Lithiation of 2-substituted indolizines followed by reaction with iodine and DMF.

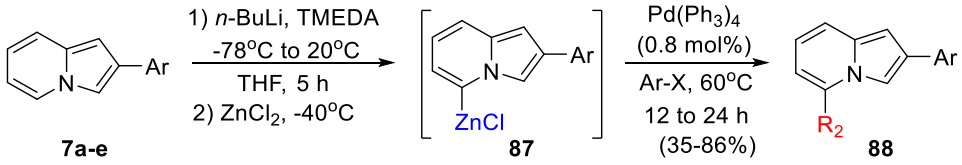
Later, Amaral and co-workers have developed a new base-controlled protocol in which 1-sustituted indolizines were successfully functionalized through reaction with LDA and Mg amides complexed with LiCl, followed by reaction with different electrophiles. In this study, they showed that seems to be a dynamic equilibrium between C-2 and C-5 positions when using TMPMgCl·LiCl and the nature of the electrophiles appears to carry out regioselectivity. More reactive electrophiles afforded C-2 substitution **85** while less reactive electrophiles conduct to C-5 derivatives **86** (Scheme 22) (AMARAL et al., 2015).

They also synthetized aryl and heteroaryl derivatives using Negishi cross-coupling strategy.



Scheme 22. Base controlled approach for 1-substituted indolizines using Li/Mg amides complexed with LiCl.

In another work, Amaral and co-workers have demonstrated the efficiency of Palladium-catalysed cross-coupling reaction between aromatic halides and 2-arylindolizines. In the first step, 2-arylindolizines **7a-e** were lithiated using *n*-BuLi. Then, they promoted an lithium/$ZnCl_2$ exchange and the 2-aryl-5-organozinc intermediate **87** could be coupled with aryl halides using catalytic amounts of $Pd(Ph_3)_4$ (Scheme 23) (AMARAL et al., 2014).



Scheme 23. Lithiation of 2-arylindolizines followed by Negishi cross-coupling reaction.

Given the importance of indolizine scaffold in different fields, in this thesis we will discuss strategies to prepare functionalized indolizines with potential application in medicinal chemistry and material science.

2. Conclusion

In this work, we have performed a comprehensive study on the functionalization of the indolizine ring by using metalation and C-H borylation strategies. Based in our results, the mixed magnesium-lithium base TMPMgCl·LiCl proved to be an excellent reagent for regioselective functionalization of indolizines bearing strong directing metalation groups, such as esters and 2-oxazolines. Reaction of the organomagnesium intermediates with several electrophiles allowed the isolation of a number of functionalized derivatives in reasonable to good yields. We could also note that some electrophiles appear to be able to disrupt the chelation between DMG and the magnesium base complexed with LiCl (TMPMgCl·LiCl) leading to C-5 derivatives for substrate **1**. In the case of the 2-oxazoline substituted substrate, the highly nucleophilic reagent *n*-BuLi could be used as metalating agent, allowing the selective deprotonation of the most acidic hydrogen and further isolation of C-5 functionalized derivatives in good yields. This base dependent control offered by the 2-oxazoline as DMG should be highlighted and possibly will find further applications in organic synthesis.

In the second part of this work, the lithiation of 2-arylindolizines led to the synthesis of five new 5-formyl-2-aryl indolizine derivatives in good yield. This methodology allowed to the preparation of other 15 new 5-substituted derivatives containing ester, carboxylic acid and amide groups in good yield as well. Due to the fluoresce exhibited for these compounds they had their photochemical and photophysical properties evaluated.

The maximum absorption in the UV-vis region observed were in the range of 257-457 *nm* and the maximum fluorescence emission were in the range of 485-549 *nm*. These compounds were evaluated in methanol and DMSO, the values of quantum yield were higher for the 5-ester derivatives (**9a-e**) and relatively lower for the aldehydes (**8a-e**). The emission decay profiles were fitted to one or two exponential curves depending on the functional group. In general, compounds in DMSO showed higher Stokes shift values, quantum yield and lifetime, compared to results in methanol. Among the groups, lower values were registered for aldehyde compounds (**8a-e**). Interestingly, it is also noticed that in all groups, the compounds containing 2-phenyl group (**8a**, **9a**, **10a**, and **11a**) presented higher efficiency for fluorescence emission with longer average lifetime.

Regarding to the C-H borylation, we could find a reactional condition that despite low yield and less selectivity, when compared with the metalation protocol, led to C-3 and C-5 arylated derivatives for indolizine **12** and C-5, C-6 and C-5,6 arylated derivatives for indolizine **1**. We could conclude with this study that the C-H borylation reaction it is possible for substituted indolizines, however it necessary more investigation using different catalyst and ligands in order to achieve site-selectively. Nonetheless, the results achieve in this study still important since to the best of our knowledge this was the first study on C-H activation/borylation using indolizines as model substrates.

Overall, this work allowed the expansion of our knowledge in the reactive of substituted indolizines and the development of new approaches that, in the future, can help in the construction of more complex derivatives.

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