RECENT SYNTHETIC DEVELOPMENTS AND REACTIVITY OF AROMATIC INDOLIZINES

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Abstract. Aromatic indolizines exhibit interesting biological and fluorescent properties, so interest in the chemistry of this class of compounds has increased over the last years. In this review, we present recent developments in the synthesis of the indolizine ring and discuss several aspects of its reactivity.

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1. Introduction

Indolizines are privileged compounds that have received considerable attention in modern organic synthesis. From a structural viewpoint, the indolizine core fits well into the class of heterocyclic π-electron-rich compounds that feature very dense and small architecture with many interesting properties including aromaticity, planarity, physiologically compatible polarity, protonation site, and fluorescence.

Although aromatic indolizines do not seem to occur in nature, interest in the biological and medicinal properties of these compounds has grown over the last years. As a result, various indolizine derivatives exhibiting different biological activities such as anti-inflammatory, anticaner, antimicrobial, and phosphatase inhibitory actions, among others, have been synthesized. The figure below summarizes the biological potential of the aromatic indolizine core (Figure 1).

![Figure 1. Biological activities related to the aromatic indolizine core.](image_url)

Recently, the synthesis of fluorescent π-conjugated molecules has attracted much attention because these molecules can be used as electroluminescent material for optoelectronic devices, dyes, sensors, and biomarkers. Hence, several substituted indolizines have been employed as bioprobes in pH and turn-on/off fluorescent sensors in the detection of lipid droplet accumulation, and in the detection of volatile organic compounds, and in cell labeling. Moreover, substituted indolizines have been used as organic sensitizer components for dye-sensitized solar cells and photoresponsive materials.

![Figure 2. Molecular structure and application of some fluorescent indolizines.](image_url)
Given the great importance of the aromatic indolizine core in numerous research and technological fields, in this chapter we describe recent developments in the synthesis of aromatic indolizines and discuss several aspects of their chemical reactivity.

2. Preparation of aromatic indolizines

Common strategies to prepare aromatic indolizines involve chemical manipulation of pyridine- and pyrrole-based substrates. In other words, aromatic indolizines can be prepared by a number of synthetic approaches including the Tschitschibabin reaction, cycloaddition reactions (1,3-dipolar cycloadditions), intramolecular cyclization, and cycloisomerization transformations as previously discussed in many reviews. Based on the increasing relevance of these compounds in various research and technological fields, here we focus on recently reported advances in the synthesis of functionalized aromatic indolizines from different starting materials.

2.1. From 2-alkylazarenes

First reported by Tschitschibabin, reaction of 2-alkylpyridines with α-halo ketones followed by cyclization of the quaternary salt is still a useful method to prepare indolizines. By exploring the precipitation of several pyridinium salts generated in acetone and the low solubility of the corresponding cyclized derivatives in water, Chai and co-workers developed a practical chromatography-free protocol to synthesize 2-substituted indolizines of type 4 (Scheme 1).

![Scheme 1](image_url)

Moreover, preparation of 3-acylindolizines by intermolecular cyclization of picolinium salts in the presence of DMF-Me₂SO₄ was reported in 2007. This approach allows the use of countless functional groups, such as methoxy, ester, cyano, nitro, and halogens, either on the pyridine moiety or on the other aryl group, to give an array of 3-acylindolizines (7) in good yields (Scheme 2).

Over the last years, direct benzylic C-H functionalization of 2-alkylazaarenes catalyzed by transition metals has received great attention. Interestingly, a combination of copper(II) acetate and nickel powder in the presence of 1,10-phenanthroline as ligand allows annulation of 2-alkylazaarenes with cinnamic acids.
Additional experiments have indicated that dehydrogenative coupling does not demand oxidants, and that copper(0) species may participate in the process. The methodology is compatible with various 2-alkylazaarenes and aryl-substituted α,β-unsaturated carboxylic acids, delivering the corresponding C-2 arylated indolizines (10) in moderate yields (Scheme 3).

2.2. From heterocyclic N-ylides

The use of heterocyclic N-ylides, especially pyridinium ylides, in 1,3-dipolar cycloaddition reactions with dipolarophiles is frequent during the synthesis of aromatic indolizines. Numerous electron-deficient alkenes, alkynes, and allenes have been used as reactive dipolarophiles, which has allowed target compounds with great structural diversity to be prepared.

Although α-halocarbonyl compounds are normally used to generate azinium salts, other electron-withdrawing functions bearing leaving groups at the α-position have been successfully employed as well. For example, polysubstituted indolizines of type 13 can result from reaction of 1-(1-cyanoalkyl) pyridinium salts with nitroolefins or diethyl azodicarboxylate (DEAD) under basic conditions. Absence of an alkyl
catalyzed cycloisomerization to afford 1,3-difunctionalized indolizines (25) from moderate to excellent yields (Scheme 7).
Entrapment of the acid generated during the intramolecular attack of the pyridine nitrogen at the copper-activated π-bond by bicyclic strong bases leads to an *in situ* oxidative alkynylation of the copper(I) intermediate with alkynyl bromide or alkynyl dibromide. This recently developed *tandem* aminocupration/alkynylation protocol enables preparation of interesting highly functionalized indolizines under mild conditions (Scheme 8).41

In the last years, great attention has been given to the development of sustainable and environmentally friendly chemical processes. In this context, biocatalysis has emerged as important tool for the synthesis of heterocyclic compounds,42-44 including indolizines.45 Moreover, it has been found that cycloisomerization of 2-pyridinyl-substituted propargylic esters can be carried out by a catalyst-free approach in water.46
Notably, no purification is required after the reaction is completed, which allows isolation of the corresponding functionalized indolizines of type 31 in similar or higher yields as compared to the strategies involving transition metal-promoted catalysis (Scheme 9).

Iodine-mediated 5-endo-dig cyclization of pyridine-substituted allylic esters is a viable approach to synthesize indolizines bearing functional groups at the pyrrolidine ring. The reaction takes place smoothly in CH₂Cl₂ at room temperature, to generate the 2-iodo-substituted indolizines in very high yields. Moreover, the iodide substituent is amenable to chemical manipulation, allowing fast derivatization by transition-metal cross coupling or radical-based reactions. A 5-endo-trig iodocyclization of the corresponding allylic esters (34) has also been reported. In this case, a base-catalyzed dehydroiodination gives the iodo-free 1,3-disubstituted indolizines (35) in good yields (Scheme 10).

By using an A³ tree-component approach, propargylic pyridines generated from coupling of 2-pyridine carboxaldehyde with secondary amines and terminal alkynes in the presence of a metal catalyst can undergo cycloisomerization, to give the corresponding aminooindolizines. Zinc iodide is a convenient catalyst for these reactions, leading to isolation of the products in good yields (Scheme 11).
2.4. From alkynyl pyridines

In 2001, Gevorgyan and co-workers reported the copper-assisted cycloisomerization of alkynyl amines as an efficient strategy to prepare pyrroles and pyrrole-containing heterocycles such as indolizines.52 A protocol involving the sequential palladium-copper-catalyzed cross-coupling of 2-bromo pyridine derivatives with propargyl amines or amides under cycloisomerization provides 3-aminoindolizines 43 (Scheme 12).53

Recently, a Lewis acid-catalyzed cyclocondensation protocol involving 3-(pyridine-2-yl)-propionates and enones has been developed to obtain ester-substituted indolizines derivatives that cannot be directly achieved by conventional methods. This protocol could also give a phosphonate-substituted indolizine. Titanium tetrachloride has proven to be a good catalyst for the reactions, which take place smoothly under mild conditions (Scheme 13).54
2.5. From 2-pyridylesters

Several recently developed strategies explore 2-pyridylacetates and unsaturated ketone derivatives as substrates for the synthesis of indolizines. For example, metal-catalyzed cyclization of 2-pyridylacetates with unsaturated ketones and chalcones can afford ester-substituted derivatives. In addition, metal-free [3+2] cyclization of 2-pyridylesters with chalcones catalyzed by iodine constitutes an interesting alternative to prepare tri-substituted indolizines as in gram scale (Scheme 14).

An intramolecular nucleophilic substitution of a benzylic iodide by pyridine nitrogen followed by proton elimination appears to be involved in the reaction mechanism. This reaction delivers 1-ester-substituted indolizines (57) bearing aryl or alkyl substituents at position C-3 in moderate to good yields (Scheme 15).

More recently, alkenes have proven to be convenient substrates to synthesize indolizines by I₂-catalyzed cyclization with 2-substituted pyridines in the presence of TMEDA and the oxidant r-butyldi peroxide (TBHP) (Scheme 16).
Furthermore, reaction of 2-pyridylesters or 2-pyridyalconitriles with various types of alkynes can afford di- and tri-substituted indolizines in a one-pot reaction catalyzed by silver carbonate (Scheme 17). In the case of terminal alkynes, cycloisomerization of 2-pyridyl-substituted propargyl intermediates, generated from reaction of pyridines with silver acetylides, produces indolizine rings.
For di-substituted alkynes, the reaction seems to proceed via intramolecular condensation of a vinyl carbocation entity.

Morita-Baylis-Hillman acetates (MBHAs) have been used to prepare functionalized heterocyclic scaffolds including indolizines. In this context, several tri-substituted indolizines bearing an ethyl acetate group at position C-3 can be prepared by using ethyl-2-pyridylacetate and 2-pyridylacetonitrile as substrates (Scheme 18).  

![Scheme 18]

2.6. From pyrroles

Pyrroles and indoles are particularly important substrates to prepare indolizines bearing functional groups at the pyridine ring. In this context, under controlled reaction conditions, the Stobbe condensation product from pyrrole-2-carboxaldehyde and dimethyl succinate affords 5-oxygenated indolizines with an ester group at position C-7. On the other hand, a base-mediated cycloisomerization of 2-acetylpiprole derivatives provides 8-oxygenated indolizines in high yields. Notably, subsequent reaction of the aldol-type cyclization products with electrophiles allows one-pot preparation of valuable synthetic intermediates such as O-acetates and O-triflates (Scheme 19).

![Scheme 19]

Interestingly, [4+2] annulation of pyrrole-2-carboxaldehyde with activated methylene compounds affords indolizines displaying a highly substituted pyridine ring. The reaction involves a Knoevenagel
condensation and an intramolecular aldol cyclization cascade reaction, to give the corresponding derivatives bearing alkyl, ester, ketones, cyano, and amino groups (Scheme 20).

Very recently, Liu and co-workers prepared functionalized indolizines through a gold(I)-catalyzed hydroarylation/cycloaromatization strategy. As shown in Scheme 21, reaction of α-(N-pyrrolyl)ketones with terminal or activated internal alkynes in the presence of 5 mol% of Ph3PAuNTf2 provides polysubstituted indolizines of type 72 in moderate to good yields.64

The palladium-catalyzed tandem reaction of multi-substituted 1,4-dibromo-1,3-butadienes with pyroles is also an interesting strategy to synthesize highly substituted pyridine-ring indolizines (Scheme 22).65 An electrophilic palladation with a base-assisted C-H bond activation step has been proposed as part of the reaction mechanism.

3. Reactivity of aromatic indolizines

Indolizines are heterocyclic π-electron-rich compounds that readily undergo electrophilic substitution but rarely suffer nucleophilic attack. The structural similarity of indolizines, pyrroles, indoles, and isoindoles (Figure 3) somehow makes their reactivity comparable except for a singular aspect: cycloaddition involving the entire π-system of indolizines.
Concerning electrophilic attack, the reactivity of indolizines concentrates at positions C-1 and C-3, preferably at position C-3. The stabilizing resonance energy of the pyridine moiety accounts for the observed selectivity and regioselectivity. Given the resonance hybrid shown in Figure 4, the energy required for charge separation is lower in c than in b, so c is a more stable resonance hybrid and contributes mostly by keeping electronic density at position C-3.

Conjugation also gives plausible evidence of the regioselectivity at position C-3. The reaction intermediate of an electrophilic substitution can give C-1 or C-3-substituted isomer structures (a and b respectively, Figure 5). The C-1 intermediate displays conjugation over the nitrogen atom, whereas the C-3 intermediate presents conjugation over the carbon atom. It is well known and widely accepted that better orbital overlap favors conjugation through the carbon atom over conjugation through the heteroatom.

Figure 3. Indolizine and compounds with similar structure and reactivity.

Scheme 22

Figure 4. Contributing resonance structures of the indolizine core.

Figure 5. Structures of N-assisted nucleophilic substitution intermediates with heteroatomic and homoatomic conjugation.
3.1. Protonation of aromatic indolizines

Indolizines are exclusively protonated at positions C-1 and C-3 of the indolizine scaffold, as illustrated in Scheme 23. To elucidate the acid-base behavior of alkyl-substituted indolizines, Fraser and co-workers conducted $^1$H-NMR studies to investigate the protonation site of the nucleus in trifluoroacetic acid solution. These authors showed that 2-methyl-, 1,2-dimethyl-, 2,6-dimethyl-, 2,8-dimethyl- and 1,2,3-trimethyl-indolizinium perchlorates only give 3H-indolizinium cations. However, in further studies, Fraser included a wider range of indolizines, to reveal that an alkyl group at position C-3 gives rise to a mixture of C-1- and C-3-substituted indolizinium salts. Relative proportions depend on the nature and position of the substituents. Regarding the C-3-substituted indolizines, even when position C-3 is alkylated, protonation of 3,5-dimethylindolizinium perchlorate occurs exclusively at C-3 position, which the authors attribute to intramolecular overcrowding.

![Scheme 23](image-url)

Armarego published $^1$H-NMR studies on the protonation of several structures, including additional indolizinium perchlorate structures, and extended the concept to aqueous solution, to find that 3-methyl-, 3,7-dimethyl-, 2,3,6-trimethyl-; and 2,3,7-trimethyl-indolizinium perchlorates are preferentially protonated at position C-1 in trifluoroacetic acid. However, in diluted hydrochloric acid solution (1.5 mol/L), the cations arise as a mixture of C-1 and C-3 protonated species. Anomalous protonation at position C-1 can be justified by steric hindrance posed by the 3-methyl group.

3.2. Nitrification of aromatic indolizines

Nitrification of 2-methylindolizines can result in substitution at position C-3 or C-1 depending on reaction conditions. In general, mild acidic conditions give 3-nitroindolizines, whilst strongly acidic conditions afford 1-nitroindolizines. Hickman and co-workers showed that treatment of indolizine, 2-methylindolizine, or 1,2-dimethylindolizine with nitric acid in excess acetic anhydride at -70 °C produces the corresponding 3-nitro derivatives in moderate yields with no isomer. More severe acidic conditions during treatment of 2-methylindolizine in a nitric/sulfuric acid mixture (HNO$_3$/H$_2$SO$_4$) preferentially generates 1-nitroindolizine. Nitration of 2-phenylindolizine in HNO$_3$/H$_2$SO$_4$ gives 2-(4-nitro-phenyl)indolizine, whereas nitration with nitric acid only generates 1,3-dinitro-2-phenyldiolizine in low yields. As mentioned in Section 3.1., $^1$H NMR studies have shown that position C-3 is the most basic site of the heterocycle and is preferentially protonated under acidic conditions. Therefore, it is quite reasonable that strongly acidic conditions
(HNO₃/H₂SO₄) favor protonation at position C-3, protecting this position from electrophilic attack.³⁷ Kinetic studies have confirmed that nitration and nitrosation of 1-methyl-2-phenylindolizine involves attack on the conjugate acid.³² Scheme 24 shows the reaction pathway for 2-methylindolizine and 2-phenylindolizine in mild and severe acidic conditions.

\[
\text{Scheme 24}
\]

In addition to synthetic methods based on direct nitration of the indolizine nucleus, oxidation of 3-nitroso-2-methylindolizine can provide 3-nitro-2-methylindolizine.³³

### 3.3. Nitrosation and diazo coupling of aromatic indolizines

The first report of direct insertion of a nitroso group into the indolizine nucleus dates from 1936 and is authored by Kondo and Nischizawa.³⁴ This insertion involves reaction between nitrous acid and 3-acetyl-2-methylindolizine, to generate the respective 1-nitroso derivative (Scheme 25a).

\[
\text{Scheme 25}
\]

Optimization of this transformation and its conduction in aqueous sodium nitrite with addition of acids (HCl or CH₃CO₂H) produces 1-nitroso-3-acetyl-2-methylindolizine, 1-nitroso-3-acetyl-2-phenylindolizine, 3-nitroso-2-methylindolizine, 3-nitroso-2-phenylindolizine, and 1-nitroso-2-methyl-3-ethyindolizine in good yields (> 80%). Under the optimized conditions, Hickman and co-workers³⁶ performed nitrosation of seven different indolizines, to obtain bright green crystalline solids in good yields in most cases. The crystals become red upon treatment with acidic solution; the exception is 3-nitrosoindolizine, which is stable in air at room temperature. Nitrosation of 1,2-dimethylindolizine does not give a crystalline product although the
reaction seems to proceed normally in this case, the author reported obtaining an “intractable tar” after concentrating the green extract in chloroform.

Azo-indolizines can result from electrophilic attack by diazonium salts at position C-3. For example, reaction of indolizines of type 87 with the neutral diazonium salt derived from 4-aminobenzoic acid affords the azo-derivatives (3-(4-carboxyphenylazo)indolizines) 89a and 89b in good yields (Scheme 25b). 69

3.4. Alkylation of aromatic indolizines

Preparation of alkyl-substituted indolizines from alkyl-substituted pyridine derivatives is more convenient than direct alkylation of the indolizine nucleus itself. 75 However, with respect to alkyl-functionalization at positions C-1 and C-3 of the indolizine nucleus, the Mannich reaction is very useful to obtain aminomethyl-indolizines. This multi-component reaction employs a non-enolizable aldehyde, a primary or secondary amine, and a C-1 or C-3 unsubstituted indolizine core. In this case, indolizine works as the originally enolizable carbonyl compound employed in the Mannich-type reaction. After formation of the iminium ion during reaction between the amine and the aldehyde, indolizine, in which the electron density concentrates at positions 1 and 3, attacks the electron-deficient carbon of the iminium ion, resulting in a 1- or 3-aminomethyl-substituted indolizine of types 91 and 93, respectively (Scheme 26). Attack at position C-1 is analogous to attack at position C-3.

Interestingly, despite the methylamino group provides the perspective for several chemical transformations, this functional group is strategic for the synthesis of bioactive indolizines. Scheme 27 shows ephedrine and methamphetamine as amino components of a Mannich-type reaction that uses 1,2-diphenylindolizine 94, in which the corresponding Mannich bases 96a,b display depressor activity in the central nervous system. 76
Conjugated addition is a powerful strategy for the functionalization of heterocyclic substrates and can be used to alkylate positions C-1 and C-3 of indolizines. A recent paper by Matviiuk and co-workers describes the selective C-3 addition of 2-phenylandolizine and 7,9-dinitropyrido[2,1-α]isoidole to N-substituted maleimides, as shown in Scheme 28.  

![Scheme 28](image)

3.5. Acylation of aromatic indolizines

Acylation can occur at position C-3 or C-1 of aromatic indolizines. However, acylation at position C-3 is favored. Acylation at position C-1 only takes place when position C-3 bears a substituent or when indolizine is treated with excess acylating reagent. Scholtz in 1912 was the first to acylate indolizines by heating indolizine and 7-methylindolizine with acetic anhydride in the presence of sodium acetate, to obtain the respective 3-acetyl derivatives. Heating the mixture of indolizines with acetic anhydride at higher temperatures affords 1,3-diacetylated products of indolizines.

The Friedel-Crafts reaction can be employed to acylate indolizines, large excess of AlCl₃ in CCl₄ gives 1,3-diacetyl-2-methylindolizine from 3-acetyl-2-methylindolizine. However, the 1,3-diacetylated product is obtained in very low yield in reactions that start directly from 2-methylindolizine (Scheme 29).

![Scheme 29](image)

3.6. Halogenation of aromatic indolizines

By the end of the 1940s, little attention was being given to the halogenation of indolizines and only few uncharacterized crystalline products had been reported. In 1977, halogenation of azaindolizines was achieved by using N-bromosuccinimide, to give the corresponding C-3- and/or C-1-substituted products. When the positions C-1 and C-2 were originally substituted in the starting indolizine rings, the pyridine nucleus became the target of attack. More recently, 5-iodo- and 5-bromo-indolizines were prepared after
regioselective lithiation at position C-5 and further reaction with the source of halogens, as shown in Scheme 30. As observed, both 5-bromoindolizines and 5-iodoindolizines could be obtained in high yields.\(^8\)

\[ \text{Scheme 30} \]

Xia and You successfully promoted regioselective halogenation (Cl or Br), mediated by Cu (II), at position C-3 of a series of 19 indolizines and obtained yields between 39 and 96%.\(^9\) The resulting haloindolizines were used in cross-coupling reactions catalyzed by palladium (Suzuki-Miyaura). Further details of this protocol will be discussed in the Section on “Coupling reactions of indolizines”.

### 3.7. Oxidation of aromatic indolizines

The indolizine core is easy to oxidize, but the reaction usually cleaves the nucleus. In 1932, Diels and Alder demonstrated that indolizine-trimethyl-1,2,3-tricarboxylate (108) can be oxidized to picolinic acid N-oxide (109) in a mixture of acetic acid and hydrogen peroxide (Scheme 31).\(^9\) Later, they applied this reaction in a structural elucidation and demonstrated that there was no nitro group in the six membered-ring product obtained from dimethyl 1-nitroindolizine-2,3-dicarboxylate (starting material).\(^1\)

\[ \text{Scheme 31} \]

Few studies have demonstrated oxidation of indolizine while keeping the nucleus intact. Reaction of 3,3'-methyleneindolizine with tetrachloro-1,4-benzoquinone leads to the 5,5'-bridged compound 111 (Scheme 32).\(^9\)

\[ \text{Scheme 32} \]
A work dated from 1995 showed the catalyzed oxidation of 2-phenyl-5,6,7,8-tetrahydroindolizine by oxygen under light, which gave 2-phenyl-8a-hydroxy-6,7,8,8a-tetrahydro-3(5H)-indolizinone with yields between 63 and 76% under mild conditions.\textsuperscript{93} Examples of the oxidation of hexahydroindolizines with ozone\textsuperscript{94} and of octahydroindolizines with osmium tetroxide\textsuperscript{95} have also been described.

3.8. Metalation of aromatic indolizines

Renard and Gubin were the first to report on the metalation of indolizines by regioselective lithiation of 2-phenylindolizine at position C-5. The reaction of the generated anion with different electrophiles led to expected functionalized derivatives as shown in Scheme 33.\textsuperscript{96}

![Scheme 33](image)

In 2005, Kuznetsov and co-workers updated the protocol established by Renard and Gubin and extended it to other electrophiles (e.g., I\textsuperscript{-} and CHO\textsuperscript{+}).\textsuperscript{97} Direct lithiation of 2-substituted indolizines followed by addition of electrophiles gave 5-substituted 121a-e indolizines in good yield (74-96%) as depicted in Scheme 34.

Over the last years, the mixed lithium-magnesium reagents,\textsuperscript{98-103} especially the amides TMP\textsuperscript{-}MgCl-LiCl\textsuperscript{104-106} and TMP\textsuperscript{-}Mg\textsuperscript{2}LiCl\textsuperscript{107-109} (TMP=2,2,6,6-tetramethylpiperidine) have emerged as alternative reagents for the functionalization of aromatic and heteroaromatic compounds even in the presence of sensitive functional groups.

Reaction of different metallic bases with 1-ester-substituted indolizines and consequent reaction of the corresponding anion with electrophiles afford many C-2 and C-5 difunctionalized indolizines. Metalation at positions C-2 and C-5 seems to be a dynamic equilibrium, and the nature of the base and of the electrophile seems to govern regioselectivity. In general, when the mixed lithium/magnesium amide TMP\textsuperscript{-}MgCl-LiCl is used as base, more reactive electrophiles afford substitution at position C-2, whereas less reactive electrophiles promote functionalization at position C-5 of the indolizine nucleus. Scheme 35 brings a proposal for the electrophile-controlled functionalization of 1-ester-substituted indolizines.\textsuperscript{110}
3.9. Palladium-catalyzed coupling reactions of aromatic indolizines

Palladium-catalyzed coupling reactions are among the most important reactions for the functionalization of aromatic and heterocyclic substrates.\textsuperscript{111-114} In 2004, Park and co-workers published the first work on the coupling reactions of indolizines catalyzed by palladium.\textsuperscript{115} At the time, the group developed an efficient protocol for arylation and heteroarylation of indolizines at position C-3. Mechanistic studies unequivocally reinforced that electrophilic substitution accounted for this transformation (Scheme 36).

\begin{align*}
\text{Ar} & \quad + \quad \text{R} \quad \overset{\text{Pd(OAc)}_2}{{\text{Ph}_3}} \quad \text{KOC,H}_2 \quad \text{MPP, 100°C} \\
& \quad \rightarrow \quad \text{Ar-R} \\
\end{align*}

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<th>Ar</th>
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<th>Pd(OAc)_2</th>
<th>KOC,H_2</th>
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Scheme 36
The authors used five distinct indolizines bearing different substituents at position C-2 in combination with five aryl bromides and PdCl₂(PPh₃)₂ as catalyst in aqueous alkaline solution, to obtain many 3-aryl coupled indolizines in reasonable to good yields (Scheme 36).

Kim and co-workers reported that the iodine-mediated 5-endo-dig cyclization of propargylic esters provides highly functionalized indolizines with an iodine substituent at position C-2. The resulting 2-iodineindolizines can be applied in Suzuki, Heck, and Sonogashira-coupling reactions, as shown in Scheme 37.⁴⁷

As mentioned in Section 3.8., Kuznetsov prepared a series of 5-Br- or I-indolizines via selective lithiation and applied these halogen derivatives in the Suzuki-coupling reaction with different aryboronic acids, to obtain a series of 5-arylindolizines in yields ranging from 32 to 97% (Scheme 38).⁸⁸

Highly regioselective synthesis of 12 bis-indolizines was achieved through C-H functionalization catalyzed by palladium; yields were reasonable to virtually quantitative (Scheme 39a, 34-99%). Application of this methodology was demonstrated by intramolecular oxidative coupling in the construction of macrocycles of type 139 (Scheme 39b).¹¹⁶

Halogenation of the indolizine nucleus at position C-3 and subsequent palladium-catalyzed coupling is also feasible. For example, Xia and You successfully promoted the copper(II)-mediated halogenation (Cl or Br) of 19 functionalized indolizines at position C-3 in yields varying from 39 to 96%. The resulting 3-
chloro-indolizines were further applied in Suzuki-Miyaura cross-coupling reactions that delivered 3-phenylindolizines in 82-95% isolated yields. Scheme 40 describes the general conditions.\(^{+9}\)

\[
\text{Pd(OAc)}_{2} \text{(cat.)} \quad \text{O} \quad (34-99%) \quad \text{d vinylarenes} \quad \text{gents containing a halogen atom} \quad \text{(cat.)}
\]

The regioselectivity \(\alpha\) has resulted in C-phenylindolizines in 82-95% isolated yields. Scheme 40 describes the general conditions.

A highly regioselective palladium-catalyzed oxidative coupling between indolizines and vinylarenes has resulted in C-3-substituted \(\alpha\)-vinylaryl-indolizines (145). In some experimental conditions, a mixture of \(\alpha\)- and \(\beta\)-aryl coupling products arises. However, in most cases the \(\alpha\)-isomer is the sole or the major product. The regioselectivity is attributed to the bidentate nitrogen-containing ligands (Scheme 41).\(^{117}\)

The synthesis of indolizines starting from reagents containing a halogen atom gives a halogen-substituted indolizine that is suitable for cross-coupling reactions. Zhou and co-workers prepared indolizine-\(\beta\)-D-glucopyranoside by such strategy and obtained a series of indolizine-\(\beta\)-D-glucopyranoside that can be applied as SGLT2 inhibitors (Scheme 42).\(^{118}\)
Palladium-catalyzed cross-coupling between 2-aryl-indolizines and aromatic halides through the Negishi-type reaction gives several 2,5-diaryl-indolizines. The 2-aryl-5-organozinc intermediate can be prepared by lithium/ZnCl₂ exchange and then coupled with aryl halides using Pd(Ph₃)₄ in catalytic amounts (Scheme 43).¹¹⁹

![Scheme 43](image)

3.10. Aromatic nucleophilic substitution

Nucleophilic attack at the indolizine nucleus generally occurs at position C-5 in compounds containing an electron-withdrawing group as substituent. When 8-nitroindolizine is treated with secondary amines, 5-amino-8-nitroindolizoline arises.⁷³

Babaev and co-workers designed a successful protocol to convert 2-aryl-6-cyano-7-methyl-5-indolizinones to 2-aryl-5-chloro-6-cyano-7-methylindolizines. The strategy can be used to synthesize C-5-substituted indolizines of type 154 from different nucleophiles in good yields, as presented in Scheme 44.¹²⁰

![Scheme 44](image)

3.11. Reduction of aromatic indolizines

Reduction of the indolizine core represents an important strategy to synthesize alkaloids. In 1912, Scholtz was the first to report this reaction by using elemental sodium as reducing reagent.⁸⁴ However, he assumed that the obtained compound was not a reduced derivative but a ring disruption product (Figure 6, structure a). Later, in 1946, Borrows and Holland proposed that reduction of indolizine with elemental sodium afforded the dihydro-indolizine derivative (Figure 6, structure b).⁷³ In general, the metal-assisted reduction products largely depend on the substitution pattern of the indolizine nucleus. Although the six-membered ring is more susceptible to hydrogenation, Diels and Meyer reported the selective reduction of the five-membered ring by treatment with platinum oxide, to isolate the tetrahydro derivative (Figure 6, structure c).⁸⁴ Under more drastic conditions (high temperatures and pressures), total reduction can be achieved in the presence of Raney nickel.⁸⁰ By using the same Raney nickel or platinum catalysts at ambient temperature and pressure, it is also possible to reduce the six-membered ring selectively (Figure 6, structures d and e).⁸¹ Reduction of 2,5-diphenylindolizine with rhenium heptasulfate affords the fully saturated 2,5-diphenyloctahydroindolizine nucleus (Figure 6, structure f).¹²¹

Moreover, in 2005 Kim and co-workers established a protocol regarding the regioselective partial reduction of indolizines under Birch conditions, as shown in Scheme 45.¹²²
Finally, Ortega and co-workers recently established a methodology based on the use of a ruthenium-NHC catalyst in the asymmetric/regioselective hydrogenation of indolizines, to obtain indolizine alkaloids in excellent yields and expressive enantiomeric ratio (Scheme 46).\textsuperscript{123}

4. Conclusion

Since the first reports on the synthesis of aromatic indolizines and the description of their properties, the chemistry related to this heterocycle has seen tremendous development. In part, such advances lie on the relevant biological potential attributed to the indolizine ring, which has encouraged synthetic chemists to prepare libraries aiming at identifying new lead compounds. Besides the biological activities, the fluorescence properties of the indolizine core have also contributed to the increasing interest of the scientific community in the synthesis of structurally diverse indolizine derivatives.

The attractive properties of indolizines have also propelled the development of innovative preparation procedures. Strategies involving the use of more structurally elaborated starting materials and transition-metal catalyzed cyclizations have contributed to the synthesis of increasingly complex indolizines. Notably, almost all the reagents and reactions related to the nitrogen-containing aromatics are equally applicable to
the construction of architected indolizines including very classical procedures such as nucleophilic and electrophilic aromatic substitution, metalation, oxidation, and reduction as well as metal-assisted coupling reactions and recently developed C-H activation protocols.

In summary, knowledge about the synthesis and reactivity of aromatic indolizines accumulated over the last decades allied to the recent developments in target-oriented synthesis bring excellent perspectives for the scientific and technological applications of these compounds.

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