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Dearomatization Reactions of Indoles to Access 3D Indoline Structures

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Abstract This account summarizes our involvement in the development of dearomatization reactions of indoles that has for origin a total synthesis problematic. We present the effort from our group to obtain 3D-indolines scaffold from the umpolung of N-acyl indoles via activation with FeCl₃, to the oxidative spirocyclization of N-EWG indoles and via the use of electrochemistry.

Key words Indole, dearomatization, indolines, FeCl₃, radical chemistry, electrochemistry

Introduction
Indoline derivatives are three dimensional structures of interest in the context of drug discovery.¹ In this context, the overall purpose of our research program is the development of new synthetic methods for the dearomatization of the indole nucleus to access such structures (Scheme 1).² A dearomative process allows to transform a plain and achiral compound into a chiral scaffold.³

The starting point of our endeavors in this research field was our desire to perform the total synthesis of ent-azonazine (4),⁴ a benzo[furoindoline]-containing natural product which biosynthesis implies the oxidative coupling of the indole and phenol parts of diketopiperazine 3 (Scheme 2). Inspired by the impressive Harran’s total synthesis of diazomamide A (2) via benzo[furoindoline 2 from tripeptide derivative 1,⁵ we planned to perform a bioinspired dearomative oxidative cyclization mediated by a hypervalent reagent such as PIFA or PIDA.⁶ This procedure involved the oxidation of the phenol into a highly electrophilic phenoxenium species which is immediately attacked by the nucleophilic indole. Unfortunately, all our attempts met with failures leading to mixtures of intractable oxidized products. Yao was more persistent than us. Few years after our attempts, his research group was able to achieve the oxidative cyclization of tryptophan-tyrosine diketopiperazine 3 leading to over-oxidized benzofuroindoline 5 which was eventually converted into ent-azonazine (4).⁷
towards the benzofuroindoline core of diazonamide A and azonazine.

The Harrran’s oxidative coupling between indoles and phenols mediated by PIDA is unfortunately quite substrate dependent. Not only the oxidative cyclization of diketopiperazine 3 toward azonazine (4) is capricious, but an intermolecular version also invariably failed in our hands.

While our incapacity to form the benzofuroindoline framework of azonazine was frustrating at that time, it was retrospectively an opportunity. It encouraged us to initiate a new research program which led us to investigate alternative dearomatization reactions of indoles.

After having considered various tactics without success, we turned our attention towards the reversion of polarity of indoles (Scheme 3). Rather than using the innate C3-nucleophilicity of indoles, our deearomatization strategies mainly relies on an umpoling process leading to the generation of electrophilic indolenium derivatives which can be further functionalized.9

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**Scheme 3 Generation of electrophilic indoles.**

**Innate Reactivity of Indoles**

**C3-nucleophilicity**

**Umpoling of Indoles**

**Electrophilic Indoles**

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1. **Activation of N-acyl indoles with FeCl3**

1.1 **Hydroarylation of N-acyl indoles**

In our effort toward the synthesis of azonazine, we aimed to discover a general method to achieve a regioselective dearomatization introduction of aryl groups at the C3-position of indoles10 and eventually to access benzofuroindolines. As we already discussed it in a previous Synpact article,24 we were inspired by a report from Nakatsuka and co-workers, which described the regioselective C3-hydroarylation of N-Ac indoles 6 into 3-arylindolines 8 mediated by a large excess of AlCl3 with the creation of one stereogenic center in a racemic form (Scheme 4).10 Very interestingly in this reaction, the C3-position of N-Ac indole 6 could be formally considered as electrophilic.9 This work was published in a journal10a which is not widely access by the community of synthetic organic chemists and was unfortunately unnoticed despite its very high synthetic potential. Nevertheless, this method seemed well suited to access benzofuroindolines 11. Unfortunately, the reaction could not proceed with phenols 9 as nucleophiles in presence of AlCl3 as the promoter. Investigation of various Lewis acids resulted in the discovery of FeCl3 as a very potent mediator of the hydroarylation of N-Ac indoles 6 by phenols 9,11 The 3-(2-hydroxyphenyl)-N-Ac-indolines 10 obtained were then converted into benzofuroindolines 11. Since the direct oxidation of 10 did not lead to the corresponding N-Ac benzofuroindolines, we removed the acetyl group in acidic conditions. Subsequently, oxidation of the indoline with TPAP and NMO or diisopropylazodicarboxylate (DIAD) led directly to the expected benzofuroindolines 11 in which indeed the fused benzofuran and indoline parts are cis.

The development of a catalytic enantioselective version of this hydroarylation reaction is highly desirable. However, it is a difficult task that we are currently investigating. In the meantime, we relied on the use of a N-acyl chiral auxiliary derived from proline on 12 that delivered a modest diastereoselectivity. Nevertheless, after separation, the major diastereoisomer 13a could be converted into a benzofuroindoline 11a with a 94% ee.

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**Scheme 4 Regioselective hydroarylation of N-acylindoles by phenols inspired from Nakatsuka and co-workers.**

Since a limited number of substrates were investigated by Nakatsuka and since we found that FeCl3 is a better promoter than AlCl3, we decided to perform a thorough investigation of the hydroarylation of N-Ac indoles 6 (Scheme 5).12 Various electron-rich arenes such as anisole, thioanisole, trimethoxybenzene, toluene, xylene or naphtalenes could be employed as the nucleophilic entity leading to 3-arylindolines 8. Very interestingly, we were also able to add some heterocyclic aromatic nucleophiles including N-Ts indole, 3-methylbenzofuran and thiophene derivatives. Concerning the substitution of the indole moiety, both electron-donating groups, halogens and electron withdrawing groups on the benzene part are tolerated. It is noticeable that the reaction is faster with electron-donating groups: while the reaction is finished less than 1 hr with a methoxy group at the C5-position, 48 hrs are necessary for a nitro group at the same position. The C3-position tolerates phenyl, benzyl as well as alky1 substituents with functional groups such as ester or bromide. However, the presence of a nitrogen-containing group on the C3-alkyl chain completely inhibits the reaction.
We recently extended this method to an intramolecular version (Scheme 6). 3,3-Spiroindolines 15, which are molecules of biological interest, were obtained when the arene nucleophile is attached at the C3-position of indole 14 by a three carbons-tethered. In contrast, a shorter tether in 16 led to a C2-hydroarylation and to cis-tetracyclic compounds 17.

We then gathered mechanistic insights of this general hydroarylation reaction which requires 2 equivalents of FeCl₃. In situ IR analysis and the isolation of a FeCl₃-(skatole N-Ac)₂ complex suggests a pre-activation of the carbonyl of N-Ac skatole by FeCl₃ such as in 1a via respective collaborations with Alejandro Perez-Luna from Pierre and Marie Curie University of Paris-6 and Nourredine Ghermani of the Faculty of pharmacy of Université Paris-Sud (Scheme 8). This activation would probably increase the delocalization of the nitrogen lone pair into the carbonyl system. Thus the nitrogen lone-pair would be less delocalized into the enamide system and therefore the electron density at the C3 position would decrease. High resolution X-ray diffraction of the FeCl₃-(skatole N-Ac)₂ complex and of N-Ac skatole allowed us to experimentally observed that the coordination of FeCl₃ to the acetyl group could induce the reversal of polarity of the C3-position. In addition, a Hammett’s study which takes into account the electronic parameters of the substituents in position 5 and 6 suggests the existence of positive charges on the indolic nitrogen and the C3 position of the indole.

The kinetic isotopic effect (KIE = 1 for toluene vs toluene-d₈ as nucleophile), indicates that the rupture of the CH bond of the nucleophile is not the rate determining step of the reaction which seems in agreement with a Wheland type intermediate and a Friedel-Crafts type mechanism (very fast CH cleavage).
After formation of a complex such as I between FeCl₃ and N-Ac indole 6 resulting in the umpoling of the C3-position of the indole nucleus, we thought that a second FeCl₃ molecule would activate the C2=C3 double bond, however this mechanistic pathway was invalidated by DFT calculations performed by Vincent Gandon from our institute. It was rather suggested that it is a proton which activates the C2=C3 double bond (II) to induce the attack of the aromatic nucleophile and the creation of a Wheland intermediate III. The reaction is probably initiated by traces of HCl from the hydrolysis of FeCl₃ in air. Then aromatisation of the Wheland intermediate would stoichiometrically deliver a proton and IV.

NBO charge calculations by DFT have shown that in the case of a 3-substituted indole, the C2 position becomes the most nucleophilic upon formation of complex Ia between the acetyl and FeCl₃. Thus the proton will be introduced in position C2, activating the C2=C3 double bond, however this pathway would be performed with triflic acid instead of FeCl₃ (Scheme 9).

In situ IR, NMR or mass spectrometry studies suggest a mechanism similar to the one with FeCl₃: one proton will activate the acetyl of indole and another proton will activate the C2=C3 bond (V). DFT calculations have determined that the transition state for the protonation of the indole leading to carbocation V in presence of TOH has an energy barrier similar to the one leading to IIa in presence of FeCl₃.

An initial screening of Brønsted acids such as HCl proved to be unsuccessful to perform this hydroarylation process. Unfortunately, at that time, we did not envision strong enough Brønsted acids. Inspired by the mechanistic hypothesis with FeCl₃, we recently discovered that all of our hydroarylation reactions of N-Ac indoles 6 could be performed with triflic acid or sulfuric acid instead of FeCl₃ (Scheme 9).¹⁸ In situ IR, NMR or mass spectrometry studies suggest a mechanism similar to the one with FeCl₃: one proton will activate the acetyl of indole and another proton will activate the C2=C3 bond (V). DFT calculations have determined that the transition state for the protonation of the indole leading to carbocation V in presence of TOH has an energy barrier similar to the one leading to IIa in presence of FeCl₃.

1.2 Difunctionalization of N-Ac indoles

In order to achieve a direct oxidative coupling between indoles and phenols, we decided to take advantage of the singular reactivity of N-Ac indoles 6 activated by FeCl₃.

In fact, just after we published the regioselective hydroarylation of N-Ac indoles by phenols, the group of Lei reported the oxidative coupling of electron-rich phenols 20 with styrenes 21 (Scheme 10).¹⁹ In the presence of DDQ and FeCl₃, phenol is oxidized into carbon-centered radical intermediate VI. These conditions appeared to us to be perfectly compatible with the activation of N-Ac indoles by FeCl₃. The phenoxyl radical VI is added regioselectively in position C2 of 3-substituted-N-Ac indoles 1a activated by FeCl₃ in order to form benzofuro[3,2-å]indolines 23 (Scheme 10).²⁰ The latter cis-fused framework is related to the natural product phalarine and is regiosomeric to the benzofuro[2,3-å]indolines obtained in our two stages process of scheme 4. Interestingly, with N-Ac indoles equally substituted at the C2 and C3 positions, regioisomeric benzofuro[2,3-å]indolines 24a and 24b were obtained.

It should be noted that this work was recently reinvestigated by the Lei group in electrochemical conditions with improvements of yields and scope of 23 (Scheme 11).²¹ The reaction proceeds via direct oxidation of the indole nucleus at the anode without the need of FeCl₃ and DDQ.

Eventually, the Jia group performed a similar transformation with PIDA as oxidant to achieve the total synthesis of phalarine (Scheme 11).²² In this case, it is likely that phenol 25 is oxidized into an electrophilic reagent. The benzoyl group on the indole nitrogen of tetrahydro-β-carbazole 26 is crucial to obtain the optimal yield of the desired regioisomer 27.
In order to increase the diversity of the 3-functionalized indolines that we could obtain by the FeCl₃ activation of N-Ac indoles, instead of electron-rich arenes, we investigated other π-nucleophiles such as allylsilanes. We have thus, performed in 2018 an unexpected 2,3-diallylation of N-Ac indoles with FeCl₃ (Scheme 12).

Scheme 12 FeCl₃-mediated diallylation of N-acetyl indoles.

In fact, we expected to obtain C3-monoallylated indolines 31. This method would have been complementary to the C2-allylation of indoles with allylboranes in presence of a Lewis acid via isomerisation of the enamine part of indole into imine VIII delivering 30.34 Surprisingly, the monomallylated compound 31 was never observed from allyltrimethylsilane 32 and N-Ac indole 6 in presence of FeCl₃. Instead, we noted the formation of the 2,3-diallylated indolines 33 (Scheme 12). In order to ensure decent yields, we used a large excess of the allylsilane 32 and of the iron promoter in a sealed vessel and we studied the scope of this diallylation reaction.

On the indole nitrogen, other electron-withdrawing groups than the acetyl, were tolerated such as formyl and ethyloxy carbonyl functions. Diallylated indolines 33 were still obtained with hindered alkyl or aryl substituents at the C3-position. Electron-donating groups and fluoride on the benzene part of the indole afforded the expected diallylated indolines 33. Unfortunately, in the presence of electron-withdrawing groups the diallylation did not proceed. As demonstrated by X-ray analysis, trans-diallylated indolines 33 were isolated as the major isomers starting from 3-substituted indoles. In contrast, cis-diallylated indolines 34 were synthesized from 2,3-disubstituted indoles.

The synthetic potential of the diallylated indolines obtained by this reaction was then demonstrated by applying different transformations to the olefins including a Heck reaction or a reduction of the two double bonds or the selective hydration of one of the alkene (not shown). In particular, the ring-closing metathesis was investigated and delivered cyclic compounds in good yields from the cis or trans indolines leading to tricyclic or tetracyclic indolines 35 and 36 (Scheme 12).

From a mechanistic point of view, several hypotheses are possible to explain this dearomative diallylation (Scheme 13).

Scheme 13 Mechanistic proposal for the FeCl₃-mediated diallylation of N-acetyl indoles.

In contrast with our previous hydroarylation, no protons are released stoichiometrically during the reaction in order to activate the C2=C3 bond. Here, we could hypothesize that the activation of the double bond was promoted either by FeCl₃ or by a trimethyl silyl cation generated by the reaction between allyltrimethylsilane 32 and FeCl₃. This activation would lead to the formation of carbocation IX at C3, which can be trapped by allylsilane 32 to form intermediate X. From this point, we can postulate several scenarios. Two single electron transfer (SET) oxidations of X with FeCl₃ would delivered iminium XI which could react with a second molecule of allylsilane 32 to lead to 2,3-...
diallylated indoline 33. Alternatively, oxidation of allylsilane 32 with FeCl₃ would lead to allylic cation XII which would be attacked by the carbon-metal bond of X.

While studying reaction between alkenes and N-Ac indoles activated by FeCl₃, we were surprised to observe in two occasions a formal [2+2] cycloaddition with the C2=C3 double bond of the indole nucleus. During the synthesis of spirocyclic indolines in 2016 (cf Scheme 6), we replaced in one occasion the arene by a terminal olefin.¹⁴ We thought that a one-type reaction would occur via XIII and would lead to spirocyclic-cyclohexenylindoline 38. It was again surprising to us to obtain cyclobutanic indoline 39, yet a spirocycle, but with a fused 5,4,5-tricyclic skeleton which structure was unambiguously verified by X-ray analysis (Scheme 14). It should be noted that You and Zheng described latter on a related reaction under light irradiation.²⁵ We observed the second case of a [2+2] annulation during the reaction of N-Ac cyclopentaindole 40 and allylsilane in 2018.²³ Along with the diallylated compound 34a which was the minor compound, we obtained 34% of cyclobutane 41. We postulated that after activation of the C2=C3 bond and attack of the trimethylallylsilane, the [β-silyl] carbocation XIII could be intramolecularly intercepted by the nucleophilic carbon at C3 before elimination of the trimethylsilyl cation, eventually leading to 41.

The unexpected observation of this first [2+2] annulation encouraged us to dive further into cycloaddition reactions of N-Ac indoles activated with FeCl₃. A great number of reports dealing with cycloadditions/annulations applied to the innate C₃-nucleophilic character of indoles has been described in the literature.²⁴ In these studies, the C₃-position of the indole adds to the electrophilic atom of a dipole or a diene, and the C2 indole position is intercepted by the nucleophilic part of the dipole or diene. With our “umpolung of indoles” in mind, we aimed to invert this innate regioselectivity of cycloadditions. At this point, we started a collaboration with Xavier Moreau and Vincent Coeffard at the Université of Versailles and Isabelle Chataigner at the Université of Rouen, both in France. One of our idea was to exploit the expertise of Xavier Moreau and Vincent Coeffard in organocatalyzed [4+2] cycloadditions of dienals 42 to and to merge it with N-Ac indoles activated by FeCl₃ in order to obtain Diels-Alder cycloadducts 43 in an enantioselective form via trienamine intermediate XIV (Scheme 15). Once again, an unexpected event occurred when the experiments were performed in Versailles in the team of Xavier Moreau.²⁰

The [4+2] cycloadduct 43 was never observed. Instead unexpected dearomatized products were formed. It turned out that the proline-derived catalyst was useless and 2 equivalents of FeCl₃ were necessary to promote the reaction. It took us some times to resolve the structures of the compounds obtained which we eventually attributed to regiosomeric tetracyclic furiondolines 44 for the major compound and 45 for the minor isomer which were both obtained as single diastereoisomers. A trans-relationship between the two ring junctions was observed for 44, while a cis-relationship was noticed for 45. At first sight, we were puzzled by the mechanism of this reaction which involved the formation of 2 cycles, 3 bonds and 4 stereocenters. Then we realized that 44 and 45 were the product of a formal (3+2) cycloaddition between N-Ac indole and dipole XVII. The latter would arise from an interrupted iso-Nazarov cyclization.²⁹ According to our proposed mechanism, FeCl₃ plays a double role in this reaction: activation of the N-Ac indole and of the dien. For instance, in 2014 Mischne showed the ability of FeCl₃ to promote interrupted vinylogous iso-Nazarov reactions.³⁰ The complexation by the carbonyl group of the dien would induce
the formation of a cyclic oxallyl cation XVI via a stereospecific 
conrotatory 4π electrocyclization of XV. Instead of the 
elimination of a proton to yield cyclopentadienone XVIII and then 
cyclopentenone 46, oxallyl cation XVII reacts with the activated 
N-Ac indole dipolarophile Ia. As the major pathway the new C2-
nucleophilic position of the indole adds to the carbocation of XVII 
and the resulting electrophilic C3-position of the indole is 
trapped by the oxygen atom of the dipole. Furthermore, minor 
cycloadduct 45 was produced from the classical reactivity of 
indoles in cycloadditions. We have therefore performed a domino 
interrupted iso-Nazarov/dearomative (3+2)-cycloaddition of 
electrophilic indoles promoted by FeCl3 (Scheme 15). Good yields 
and regioselectivities were obtained with substituents such as 
halogens (F, Cl, Br) or electron-donating groups on the benzene 
part of the indole. Then, we have shown that the nature of the 
substituent borne by the γ position of the 2,4-dienal 42 is 
important for this transformation. The best yields were obtained 
with a phenyl group at this position. Replacement of the latter 
with by a methyl led to a decrease of the yield, while a hydrogen 
led to no cycloaddition. Indeed, stabilization of carbocation 
intermediates XVI and XVII is increased with a phenyl group over 
a methyl group or a hydrogen. It should be noted that our 
consortium has also discovered that allenyl substituted by an 
electron-withdrawing groups could react in a [4+2] cycloaddition 
with cyclopentadienyl XVIII (not shown).31

2. Radical-Mediated Dearomatization of Indoles for 
the Synthesis of Spirocyclic Indolines

After demonstrating that the dearomatization of indoles could be 
effected via the generation of electrophilic indole intermediates, 
we turned our attention to study a radical-mediated approach. 
Two types of radical were chosen, perfluorinated-carbon and 
phosphonyl radicals, in order to introduce functional groups, 
which present unique biological properties.

Modified Minisci-type reactions constituted a strategy of interest 
for the functionalization of heteroarenes and indoles.32 
Generation of a free-radical intermediate in oxidative conditions 
is followed by its addition at the C2-position of indoles with 
the formation of a new bond (Scheme 16). Further oxidation of the 
radical XIX formed at C3 lead to carbocation XX. Indeed, fast 
amination generally yields functionalized indole 48. In our 
interrupted Minisci-type strategy, we desired to intercept 
carbocation XX with a nucleophile before the elimination of the 
proton from the C2-position which would give us access to 
indoline 47. It was in fact inspired by our work on the synthesis 
of benzofuro[3,2-b]indolines via the addition of a phenoxyl 
radical to N-Ac indoles in presence of FeCl3 (cf Scheme 10).20 
Therefore, our first thought was to take advantage of the unique 
reactivity of FeCl3-activated N-Ac indoles intermediates Ia to add 
a diverse array of radicals at the C2-position of indoles. It turned 
out that FeCl3 was not needed. As a precedent, Shi demonstrated 
that it was possible to add azide radicals into indoles 49 with a 
nucleophilic entity on the C3-position which can trap the 
carbocation at C3 leading to 2-azido-3,3-spirocyclic indolines 
50.33

Following this concept, a diastereoselective dearomative 3,3-
spirocyclization of indoles was reported by deploying the 
adition of trifluoromethyl radical XI at the C2 position of 
indoles 49.34 This radical was generated from the oxidation of 
sodium trifluoromethylsulfinate 51, also known as the Langlois’ 
reagent,35 with ceric ammonium nitrate (Scheme 17). The sodium 
1,1-difluorethylsulfinate could also be used to introduce a 1,1-
difluoroethyl group. The spirocyclization proceeds with primary 
and tertiary alcohols, carboxylic acids and sulfonamide as 
internal nucleophiles with a complete trans diastereoselectivity 
between the trifluoromethyl group and the nucleophilic entity of 
2-trifluoromethyl-3,3-spiroindolines.52 Different functional 
groups on the benzene ring and electron withdrawing groups on 
the nitrogen of the indole nucleus were well tolerated. We have 
thus merge a spirocyclic indoline with a fluorinated functionality 
which are both biologically relevant entities. Yu and Lan reported a 
concomitant and related transformation with the Togni's reagent 54 
instead of the Langlois’ reagent from gramines 53 and 
CO2 to obtain spirocyclic carbamates 55.36

In an analog manner, we have recently published the synthesis of 
2-phosphono-3,3-spiroindolines 57 by using phosphites 56 as 
source of phosphonyl radicals XXII in presence of manganese 
triacetate as oxidant.37 This method allows to embedded into a 
spirocyclic indoline framework, α-aminophosphonates which 
are important biological compounds. This transformation with 
a broad array of phosphonyl radicals works with an excellent 
trans diastereoselectivity with moderate yields (22-60%) and permits 
only alcohols as nucleophile (Scheme 17). It should be noted that 
these 2-phosphonindolines 57 are quite sensitive to acid or 
basic conditions and tends to aromatize via elimination of the 
acidic hydroxy at the C2 position.

Worthy of note, Wang and collaborators described the synthesis of 
related 3,3-spirocylic indolines via the intramolecular 
addition of radicals, generated by photoredox catalysis, to the 
C3-position of the indole, followed by the trapping of a C2-
carbocation by a nucleophile.38

Scheme 16 Radical-mediated functionalization versus dearomatization of indoles.
3. Electrochemical Dearomatization of Indoles

3.1 Direct electrochemical oxidation of indoles

While these radical mediated dearomatization of indoles were efficient methods to access three-dimensional indoline frameworks, they suffer from the use of excess amounts of oxidative reagents. Indeed, in the last decade, photoredox catalysis has emerged as an efficient method to generate radical intermediates in more sustainable conditions and is employed in indole dearomatization. On the other hand, electrochemistry also became over the last few years, a powerful synthetic tool in organic chemistry to avoid the use of stoichiometric amounts of oxidants or reductants. The selective difunctionalization of alkenes is an important application of electrochemistry, and related electrochemical dearomative process has been less studied.

As mentioned above, in 2017 Lei and co-workers deployed electrochemistry to improve our oxidative coupling between N-Ac indoles and phenols (Scheme 11). In this transformation, the N-Ac indole is considered to be oxidized at the anode into a radical cation. Therefore, due to our expertise in indole dearomatization, we were interested to also enter the field of electrochemically-induced deaorative process. Since we had no experience of electrochemistry, our endeavor was facilitated by the recent commercially availability of ElectraSyn 2.0, an easy-to-handle apparatus for electrosynthesis. We decided to trap indolyl radical cations generated at the anode by different nucleophiles in order to obtain difunctionalized indolines (Scheme 18).

This approach allowed us to develop an efficient and general electrochemical 2,3-difunctionalizations of indoles (Scheme 18). Building from the work of Royer, the formation of two C-O bonds was first studied by using methanol as co-solvent with acetonitrile in an undivided cell with a constant current between a graphite anode and a platinum-plated cathode. Based on different control experiments, the mechanism proposed for this electrochemical 2,3-dialkoxylation involves an anodic oxidation of the N-substituted indole into radical cation intermediate which can be intercepted by a alkoxide anion, produced by a cathodic reduction. Subsequent single electron transfer led to iminium ion and then to the 2,3-dialkoxyindolines.

Good yields of dimethoxyindolines were obtained in favor of the trans-diasteromeric. The electrolysis can also be performed with different alcohols like ethanol, allyl alcohol, cyclopropyl methanol, homopropargyl alcohol and ethylene glycol (Scheme 18). Various electron-withdrawing groups on indole nitrogen are tolerated in this transformation.

Concerning the electronic effects on the benzene part of the indole, both electron donating and electron-withdrawing groups...
afforded the expected dialkoxylated indolines 60. This reaction Proceeds well with alkyl groups or phenyl substituents at the C3 position and can preserve different functional groups on the C3-side chain. Interestingly, no intramolecular trapping was observed from tryptophol and tryptophan derivatives (two carbons on the C3-side chain). In contrast, we have observed that starting from homotryptophol or homotryptamine derivatives (three carbons on the C3-side chain) led to intramolecular trapping by the appended nucleophile. Methoxy-tetrahydropyranoindoline 62 as the major product\(^5\) with some 3,3-spirocyclic-2-methoxy indoline 63 were obtained in the case of an alcohol as the intramolecular nucleophile. An inversion of the regioselectivity was observed with a sulfonamide as internal nucleophile since trans-3,3-spirocyclic-2-methoxy-indolines 61 were selectively obtained.\(^4\)

On an other side, when we applied the same electrochemical conditions to tetrahydrocarbazoles, \(\alpha\)-monomethoxylated indoles 64 were isolated instead of the 2,3-dimethoxylation products. It seems obvious that after the deammativive 2,3-dimethoxylation, elimination of one methoxy lead to enamide XXVII which allylic nucleophilic substitution by methanol occurs.

In order to improve the diversity of this process, the formation of two C-N bonds was then achieved by using trimethylsilyl azide as nucleophile (Scheme 19).

This electrochemical diazidation reaction gave selectively trans-2,3-diazide indolines 65 with good yields from 3-substituted indoles.\(^45,49\) In the case of N-Ts tetrahydrocarbazoles or cyclopenta indole, the deammatized cis-products 66 were isolated. As synthetic applications, we have shown that this diazide compounds can be reduced to amines or engaged in a double click reaction to obtain triazoles (not shown). It should be mentioned than Lin reported in 2017, a general electrochemical diazidation of alkenes, from which one example of deammatization of N-Ts indole was reported via the metal-catalyzed addition of an azide radical to the double bond.\(^50,55\) Other research groups have also further performed deammativative difunctionalization of N-acyl indoles via electrochemically-generated radical cation intermediates.\(^52\)

It is known that 3-unsubstituted indoles could be halogenated into 3-haloindoles by electrosynthesis in presence of halides.\(^53,54\) It inspired us to generate \(\textit{in-situ}\) an electrophilic bromine reagent via the anodic oxidation of a bromide salt which could react with the indole nucleus to form bromonium ion XXVIII and could be intercepted with an internal or external nucleophile. We identify that such a process could be achieved with MgBr\(_2\) in an undivided cell with a graphite anode and a platinum-plated cathode with a constant cell potential of 5 V in a mixture of acetonitrile and water at room temperature without the need of an additional electrolyte (Scheme 20). Therefore, we achieved the conversion of tryptophol, tryptamine and tryptophan derivatives into bromofuranoindolines 67 and bromopyrroloindolines 68.\(^54,55\) Various electron-withdrawing groups on the indole nitrogen as well as halogens or donating groups on the benzene part of the indole permit the successful formation of the bromocyclized products. From tryptamines and tryptophans, different associations of orthogonal protecting groups of the indole and amine nitrogens were tolerated. Cyclization of tryptophan derivatives proceeds with an \(\textit{exo}\)-selectivity. The bromopyrroloindolines \(68\) obtained are important intermediates for the total synthesis of natural products of peptidic origin.
bond. For instance, we achieved the electrochemical double-bromocyclization of a diketopiperazine from two tryptophan units. We obtained a separable mixture of the cis and trans double-cyclized products 69a and 69b which are respectively intermediates for the synthesis of (-)-epi-samauromine and (+)-nooamauromine as described by Tokuyama.56

Shortly after our report, the group of Lei reported a related electrochemical halocyclization of tryptophol and tryptamine derivatives with lithium halides and Mn(OAc)₂ as catalyst.57 In an extension of this work,58 we showed that adding one carbon to the side chain at the C3-position, did not lead to the corresponding brominated-cyclized product. In an analogous manner with the direct oxidation approach (cf Scheme 18), 3-hydroxy-tetrahydropranoindolines 70 were formed from alcohols and carboxylic acids, probably via a SN1 process from the corresponding 3-bromo-tetrahydropranoindolines (Scheme 20). Inversion of regioselectivity was noticed from a pendant sulfonamide nucleophile with the synthesis of 2-hydroxy-3,3-spiroindolines 71. In these cases, only a substochiometric amount of MgBr₂, as a redox mediator, is necessary.

Starting from substrates without an internal nucleophilic entity, a dearomatized dihydroxilation is observed in these electrochemical conditions, most likely involving the double addition of water to bromonium bridge XVIII (Scheme 20). The diastereoselectivity of formation of 2,3-dihydroxyindolines 72 from 3-substituted indoles depends on the substituent of the indole nucleus: a tosyl group lead mainly to a cis-diastereoselectivity while an acetyl delivers the trans isomer as the major compound. Both electron-donating groups, halogens and electron-withdrawing groups on the benzene part of indole allowed the formation of dihydroxylindolines. Various substituents at the C3-position such as alkyl groups or the presence of a nitrile on the C3-allyl side chain are tolerated by this transformation. Interestingly, these mild conditions can be applied to tetrahydrocarbazoles to lead to cis-2,3-dihydroxyindolines 73 without the formation of α-hydroxyindoles as in it is the case for the direct anodic oxidation in methanol (cf Scheme 18).

Conclusion

The structural complexity as well as the biological importance of three-dimensional indoline derivatives have prompted chemists including our lab, to develop numerous elegant methods for their preparation. In this account, we wished to summarize our recent works related to dearomatization reactions of indole.

Our interest in this domain brought us to elaborate an original strategy based on the reversion of polarity of the indole nucleus or in other words: an "umpoling of indole". We have shown that the C3 position of N-Ac indoles, in the presence of FeCl₃ or TFOH, can be trapped by various π-nucleophiles, mainly electron-rich arynes but also allylsilanes. The ability of this mode of activation to be combined with other reactions was shown by developing a domino interrupted iso-nazarov/dearomative (3+2)-cycoaddition of electrophilic indoles leading to complex polyheterocyclic structures in a collaborative work. We are thankful to serendipity for the discovery of unexpected reactivities.

On the other hand, the generation of trifluoromethyl or phosphonyl radicals and their addition to indoles containing a pendant nucleophile led to the development of a diastereoselective dearrmatative 3,3-spirocyclization of indoles. This strategy should be amenable to various other radical sources and thus lead to the generation of scaffolds of potential interest for drug discovery.

Finally, in order to perform dearomatization reactions without the need to use an excess of oxidative reagents, we turned our attention towards electrochemistry. A first approach proceeds via direct anodic oxidation of the N-substituted indole into a radical cation and its reaction with alcohols or azides yielding three-dimensional indolines. In contrast, a second approach involves an indirect electrochemical oxidation of the indole nucleus mediated by the oxidation of MgBr₂ into a bromonium ion which is involved in the dihydroxylation, hydroxycyclization or bromocyclization of indole derivatives. For instance, we were able to convert tryptophol, tryptamine and tryptophan derivatives into 3a-bromofuranoinindolines and 3a-bromopyrroloindolines which are versatile building blocks.

In parallel to the work presented in this account, we also study oxidative couplings of indoles in the context of the total synthesis of natural products.59 We hope that this summary will provide a useful perspective of our approach in the field of indole dearomatization towards the synthesis of complex molecules with potential biological interest.

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Biosketches

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